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Heterogeneity in hyperkinetic disorder

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Declaration

I hereby declare that I am the sole author of this thesis. I have, unless otherwise stated, consulted all of the references cited in the thesis. Some of the work described in this thesis was conducted jointly with Dr Sinead Rhodes. Some of the work presented in Chapter 5 was accepted as part of Dr Rhodes' PhD. The rest of the work of which this thesis is a record was conducted by me and has not been previously accepted for a higher degree.

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Dr David Rockwell Coghill

Summary

It is increasingly recognised that the broadly defined behavioural phenotype of attention deficit – hyperactivity disorder (ADHD) is a heterogeneous condition and that this heterogeneity is seen across all levels of analysis from the genetic and environmental causes to the associated neuropsychological deficits, the clinical presentation and response to treatment.

This work investigated whether the more restrictive and clinically homogeneous hyperkinetic disorder (HKD) phenotype is associated with reduced neuropsychological heterogeneity compared with the broader ADHD phenotype. Using a well known, broad based battery of neuropsychological tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB) and a computerised Go/NoGo task in a large well described group of boys with rigorously diagnosed HKD who were stimulant medication naïve at baseline, it was demonstrated that the neuropsychological heterogeneity in the HKD boys was very similar to that seen previously in children with ADHD. Interestingly, and contrary to popular opinion, the strongest associations were with more simple recognition memory tasks with a low executive demand. Although there were significant associations between HKD and deficits on a range of tasks with high executive demands these were less strong.

Could this neuropsychological heterogeneity be a function of different developmental issues or comorbidity? With respect to development there was evidence that boys with HKD lagged behind the healthy boys with respect to the development of their neuropsychological performance. However the pattern of development was similar with the performance of the HKD boys paralleling that of the healthy boys, suggesting that the neuropsychological heterogeneity seen in HKD is not accounted for by developmental issues. With respect to the relationship between neuropsychological functioning and comorbidity, the impact of comorbid oppositional defiant disorder (ODD) and conduct

disorder (CD), it was found that all three clinical groups (pure HKD, HKD + ODD and HKD + CD) demonstrated deficits on several tasks compared with the healthy boys. Compared with healthy boys each of the three clinical groups was associated with at least one unique neuropsychological deficit. This suggests that comorbidity between HKD and both ODD and CD may contribute to the neuropsychological heterogeneity in the HKD boys.

Is there an association between clinical and neuropsychological responses to the treatment of HKD with the stimulant drug methylphenidate (MPH)? Detailed analyses were conducted to investigate heterogeneity of clinical and neuropsychological response in these boys to MPH. As predicted in previous studies there is evidence for clinical heterogeneity in response with between 68 and 78% of boys with HKD responding to MPH treatment at either one or both of the doses. The precise proportion responding was dependent on the scale and definition of response used. Clinical response was not predicted by age but was predicted to a degree by severity of symptoms at baseline and it was generally true that better response was predicted by lower (better) scores at baseline. Baseline performance on a component reflecting recognition memory performance at baseline predicted clinical response to the lower (0.3 mg/kg/dose), but not the higher (0.6, mg/kg/dose) dose of MPH with poorer baseline neuropsychological performance predicting a better clinical response. Whilst there was improvement on some neuropsychological measures following administration of MPH there was little association between clinical and neuropsychological responses to medication. Clinical response was only associated with neuropsychological response on a single measure from a single task (Go/NoGo Block 2 Errors to Distractors), a task that did not itself discriminate between the HKD boys and healthy Controls at baseline.

Abbreviations

5HTT	serotonin transporter
α	alpha
ADD	attention deficit disorder
ADDH	attention deficit disorder with hyperactivity
ADHD	attention deficit hyperactivity disorder
ADHD-C	attention deficit hyperactivity disorder – combined type
ADHD-HI	attention deficit hyperactivity disorder – hyperactive impulsive type
ADHD-I	attention deficit hyperactivity disorder – inattentive type
AD-HKD	attention deficit hyperactivity disorder / hyperkinetic disorder
ADRA2A	noradrenergic receptor 2A
ADRA2C	noradrenergic receptor 2C
AM	arithmetic mean
ANCOVA	analysis of covariance
ANOVE	analysis of variance
β	beta
BFCS	basal forebrain cholinergic system
BPVS	British Picture Vocabulary Scale
BSE	Between-search Error
BSEQ	Barkley side effect questionnaire
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBCL	Child Behaviour Checklist
CD	conduct disorder
CGI-I	Clinical Global Impressions-Improvement
CGI-P (-T)	Clinical Global Index-parent (-teacher)
CHRNA4	acetylcholine receptor A4
CHRNA7	acetylcholine receptor A7
CI	confidence interval
COMT	catechol-O-methyltransferase
CNS	central nervous system
CNV	contingent negative variation
CPRS-26	Revised Conners' Parent Rating Scale short version
CPT	continuous performance task
CTRS-28	Revised Conners' Teacher Rating Scale short version
∂	delta

d	Cohen's d (effect size)
D_1	dopamine 1 receptor (numbered 1 – 5)
DAT	dopamine transporter
DAT1	dopamine transporter gene
DDE	dichlorodiphenyldichloroethylene
DDT	dichlorodiphenyltrichloroethylene
DepCat	deprivation category
DEX	dexamfetamine
DF	DeFries & Fulker
dl	decilitre
DMtS	Delayed Matching to Sample task
DNA	deoxyribonucleic acid
DRD	dopamine receptor
DSM	Diagnostic and Statistical Manual of Mental Disorders
DZ	dizygotic
η^2_p	partial eta squared
E	environment
EEG	electroencephalography
EF	executive function
ES	effect size
ERD	errors to distractors
ERP	event-related potential
ERN	error-related negativity
fMRI	functional magnetic resonance imaging
F	F ratio
γ	gamma
g	grams
G	gene
(G)(E)	Gene-environment correlations
G x E	gene-environment interactions
GABA	γ-aminobutyric acid
GWAS	gene wide association scan
h^2	heritability
HKD	hyperkinetic Disorder
HOR	homogeneity of regression

HRNB	Halstead-Reitan Neuropsychological Battery
HTR1B	5-hydroxytryptamine (serotonin) receptor 1B
Hz	hertz
ICD-10	International Classification of Diseases 10th edition
ID/ED	Intradimensional/Extradimensional
IMAGE	International Multicenter ADHD Genetics
IQ	intelligence quotient
ITT	Initial Thinking Time
kg	kilogram
K-SADS-PL	Kiddie-schedule for affective disorders and schizophrenia - present and lifetime version
LOD	logarithm of the odds
LRP	lateralised readiness potential
ODD	oppositional defiant disorder
MAO	monoamine oxidase
MBD	minimal brain dysfunction
mcg	microgram
Met	methionine
mg	milligram
MOD	multipoint nonparametric LOD
MPH	methylphenidate
ms	milliseconds
MTA	Multimodal Treatment of ADHD
MZ	monozygotic
n	number
NICE	National Institute for Clinical Excellence
NMDA	n-methyl-d-aspartic acid
NS	non-significant
OR	odds ratio
p	probability
PAL	Paired Associate Learning
Pat Rec	Pattern Recognition
PBB	polybromated biphenyl
PCA	principal components analysis
PCB	polychlorinated biphenyl
PDD	pervasive developmental disorders

PET	positron emission tomography
PLA	placebo
POP	persistent organic pollutant
PSEQ	Pittsburgh side effect scale
r	correlation coefficient
RCI	reliable change index
RCT	randomised controlled trial
REM	rapid eye movement
RP	readiness potential
RT	reaction time
RTT	Reaction Time to Targets
SD	standard deviation
S_{diff}	standard error of the difference
se	standard error
sec	second
sim	simultaneous
SNAP-25	synaptosomal association protein of 25,000 Daltons
SNP	single nucleotide polymorphisms
Spat Rec	Spatial Recognition
SPSS	Statistical Package for Social Sciences
SQRT	square root
STin2	intron-2 polymorphism
strat	strategy
STT	Subsequent Thinking Time
SOC	Stockings of Cambridge
SWM	Spatial Working Memory
T 1-5	testing sessions 1 to 5
TDT	transmission disequilibrium test
t_{max}	time to peak blood drug concentration
UCI	University of California Irvine
UK	United Kingdom
US	United States (of America)
UTR	un-translated region
Val	Valine
VNTR	variable numbers of tandem repeats

vs.	versus
WISC-IV	Wechsler Intelligence Scale for Children ® - Fourth UK Edition
WCST	Wisconsin Card Sorting Test
WSE	Within Search Error

Chapter 1

Introduction and Background

In this first introductory Chapter I will concentrate on addressing two questions. What is attention deficit hyperactivity disorder / hyperkinetic disorder (AD-HKD) and how is it treated? The, often complex, answers to these questions are required in order to set the scene for an in-depth discussion of the causes of AD-HKD in Chapters 2 and 3, of previously reported data from my group's investigations into the neuropsychology and neuropsychopharmacology of hyperkinetic disorder in Chapter 4 and the new data and experimental findings on heterogeneity in hyperkinetic disorder in Chapters 5 to 9.

What is Attention Deficit Hyperactivity Disorder/Hyperkinetic Disorder?

Few childhood difficulties provoke as much concern and controversy within our society as the disorders of attention, impulse control and activity clinically known as Hyperkinetic Disorder (HKD: ICD-10, World Health Organisation 1992) and Attention Deficit Hyperactivity Disorder (ADHD: DSM-IV TR, American Psychiatric Association 2000). In view of continuing debate surrounding the nosology of these conditions, I have chosen to adopt the convention described by Schachar and Tannock (2002). Hence, I will refer to specific diagnostic terms, such as hyperkinetic disorder (HKD) or attention deficit hyperactivity disorder (ADHD) when addressing a particular diagnostic entity and set of criteria. I will use the acronym attention deficit/hyperkinetic disorder (AD-HKD) when referring to characteristics believed to be shared by ADHD and HKD.

Both disorders are characterised by pervasive, developmentally inappropriate and impairing levels of inattention, overactivity and impulsivity, which occur early in life and

frequently persist into adolescence and adulthood. In epidemiological samples the prevalence of the more restrictive hyperkinetic disorder is around 1.5% (Meltzer, Goodman, & Ford 2000) and of ADHD around 5% (Shaffer et al. 1996), in both cases there is a male preponderance in the order of 3:1 (Wolraich et al. 1998). Children with AD-HKD have a much higher prevalence of other psychiatric and developmental disorders than do children in the general population, in particular oppositional defiant disorder, conduct disorder, anxiety disorders, depressive disorder, specific learning disabilities and developmental coordination disorders (Biederman et al. 1992; Lahey et al. 1999; Lahey, McBurnett, & Loeber 2000). The presence of AD-HKD predicts a wide range of negative outcomes including increased accidental injury, poor performance at school and academic performance, difficulties with peer relationships and impaired family relationship patterns, and reduced social competence, self perception and self esteem (Hinshaw 2002). Importantly, the association with many of these outcomes remains significant even when comorbid problems are rigorously controlled (Lahey et al. 1998b). Both pharmacological and behavioural treatment strategies have been demonstrated to be effective in reducing the symptoms of AD-HKD and, at least in the short and medium term, in reducing impairment and improving outcome. The psychostimulant methylphenidate (MPH, often known by one of its trade names Ritalin) is the best studied and most frequently used pharmacological treatment for AD-HKD. In clinical trials it is effective in approximately 70% of subjects with an effect size (∂) of around 1.0. Unfortunately, the search for robust predictors of response to MPH treatment has been largely unsuccessful. As a consequence of the combined factors discussed above the accurate identification and management of AD-HKD is regarded as a major public health concern.

Historical Perspectives

The concept of AD-HKD has followed a long and, at times, tortuous path to reach its current position. Central to the difficulties in definition are the heterogeneity and diffuse nature of the behaviours, which are supposed to characterise the disorder. Different diagnostic systems have, at different times, attempted to embrace, account for, and reduce such heterogeneity in different ways and as a result it is often difficult to make comparisons between studies across either time or place. In view of the well publicised increased rate of recognition over the past 15 years , particularly in North America, it is often assumed that AD-HKD is a relatively recently described disorder and that it has been exported to the world by the United States. In fact the first published description of a child with impairing impulsive and overactive behaviour appeared as early as 1845 in an illustrated poem written by the German physician, Heinrich Hoffman. Hoffman describes the difficulties experienced by 'Fidgety Phillip' and his parents as a consequence of his inability to sit still at the dinner table (Hoffman 1845). Fifty six years later George Still was the first to formally describe the condition now recognised as AD-HKD in a series of lectures to the Royal College of Physicians in 1901, which were published a year later in the Lancet (Still 1902). Still described a case series of 20 children with overactivity, inattention, and poor "inhibitory volition" who also presented with aggressive and oppositional behaviours. In keeping with the thinking of the time he suggested that these children were suffering from "disorders of moral control", unable to control their primitive atavistic impulses. Despite several conceptual changes in thinking about AD-HKD since Still's initial description this notion of AD-HKD as a disorder of dyscontrol remained unchallenged until relatively recently when alternative hypotheses such as those suggesting that AD-HKD symptoms may alternatively reflect an attempt to alter behaviour rationally to control an altered motivational state (Sonuga-Barke et al. 1992). Although these early descriptions of the behaviours underlying AD-HKD remain recognisable today, a detailed look at the writings of

Still and others reveals that they also contain a great deal of descriptive information, which now seems naïve. It remains the case that in contrast to the clinical description of autism made by Kanner (1943) or Schneider's description of the first rank symptoms of schizophrenia (Schneider 1959), AD-HKD has never had a prototypical observational descriptive account. This is unfortunate as in contrast to these other conditions where the clinical description led to further systematic studies, which examined, for example, what it was that differentiated children with autism from those without and those with other types of difficulty, the constant theme in AD-HKD research has been that it is linked to specific but unknown brain lesions (Taylor 1998).

In the 1920s a pandemic of encephalitis left many children severely brain damaged and severely hyperkinetic. It was in this context that the notion of "minimal brain damage" was put forward to explain the symptoms of hyperactivity and inattention as a milder clinical consequence of a less severe brain insult. It was, however, never established that AD-HKD like symptoms were in fact a part of the spectrum of encephalitic injury and AD-HKD symptomatology does not appear to have become more common in post-encephalitic children than other children. As it became recognised that children with "minimal brain damage" did not show higher rates of damaging neurological events and as a consequence of a failure to locate the lesion or site of damage there was a shift of emphasis from brain damage to the conceptualisation of the disorder as 'minimal brain dysfunction' or MBD. This idea stemmed from a series of studies including those of; Strauss and colleagues (Strauss & Lehtinen 1947) who described behavioural syndromes, which they assumed to be a consequence of changes brain in brain function in individuals with mild learning difficulties; Pasamanick and colleagues studies, which suggested a link between a "continuum of reproductive causality" with hyperactive behaviour (Pasamanick & Knobloch 1966); and most significantly, Bradley's discovery that amphetamines improved the behavioural and educational symptoms in children with normal intelligence presenting with

"neurological and behaviour disorders"(Bradley 1937). Over time, the boundaries of MBD were being stretched to include a vast array of symptoms, which encompassed almost the whole of childhood psychopathology and learning difficulties (Clements & Peters 1962; Wender 1971). Clearly this descriptive system suffered from two major drawbacks: it was vastly over inclusive and presumed an unproven neural aetiology. Many of these arguments were based on circular reasoning and today it is clear that the hypothesis of a single characteristic MBD syndrome that takes the form of hyperactivity no longer warrants serious scientific consideration. As a response to these difficulties, and the broadening of the MBD concept, several authorities called for a narrower and more descriptive definition. Laufer, Denhoff and Solomons (1957) described "hyperkinetic disorder of childhood", which focused down on the dysregulated motor behaviour and the second edition of the Diagnostic and Statistical Manual (DSM: American Psychiatric Association 1968) adopted both this narrower conception and nomenclature. In addition to narrowing the focus this signalled a shift away from an assumption of causality to a descriptive account dependent upon adult informants' ratings of a child's behaviour and an attempt to empirically define syndromes of psychopathology.

By the late 1970s, based largely of the work of Virginia Douglas and colleagues, researchers in North America began to reconceptualise the core deficits of children considered to be "hyperkinetic" as related to deficits in sustained attention, response inhibition and self-modulation. When DSM-III was published (American Psychiatric Association 1980) the name of this syndrome was changed to attention deficit disorder (ADD) and motor hyperactivity was relegated to secondary importance. DSM-III described three symptom dimensions: inattention; overactivity and; impulsivity and two syndromes one with (ADDH) and one without hyperactivity (ADD), allowing the diagnosis of those with attention deficits and impulsivity but whose motor activity fell within the normal range. However, at least in part as a consequence of controversy over the increasing use of stimulant medications to

treat ADD and ADDH, the publication of DSM-IIIR (American Psychiatric Association 1987) reversed this situation somewhat, defining “attention deficit hyperactivity disorder” or ADHD as a combination of inattention, hyperactivity and impulsivity with these symptoms being again brought together in a single symptom list like they had been under the DSM-II definition. Whilst an additional category of “undifferentiated ADHD” was included, DSM-IIIR tacitly discouraged the diagnosis of what had been termed ADD without hyperactivity in DSM-III. This change from a three dimensional to a one dimensional definition of ADHD was controversial with both clinicians and researchers and led to more detailed investigation of the dimensional structure of symptoms underlying ADHD. Most studies (e.g. Bauermeister et al. 1992; Lahey et al. 1988; Lahey, Carlson, & Frick 1997; Pelham, Jr. et al. 1992) suggested that neither the three dimension structure of DSM-III, nor the single dimension of DSM-IIIR were consistent with the data. Rather, a two dimensional approach with one dimension reflecting parent and teacher ratings of inattention and the other reflecting ratings of hyperactivity and impulsivity was preferred. Based on these dimensions, the DSM-IV (American Psychiatric Association 1994) and the current DSM-IV TR (a minor revision that left the definitions of ADHD relatively unchanged: American Psychiatric Association 2000) definitions distinguish between those individuals who meet criteria for both dimensions (ADHD combined [C] type) and those who meet criteria for inattention only (ADHD predominantly inattentive [I] type) or for hyperactivity/impulsivity only (ADHD predominantly hyperactive-impulsive [H-I] type). Thus the distinction between those with and without hyperactivity (C and I types respectively) was restored and an additional type (H-I) included. A further important addition to the diagnostic criteria was the addition of criteria requiring the presence of both impairment and pervasiveness.

Compared with these developments in North America, the development of diagnostic criteria for AD-HKD in the UK and Europe has followed a more conservative and restrictive path. At the same time that the broader MBD concept was becoming popular in North

America, most European clinicians continued to apply these concepts infrequently and only to those children with obvious brain damage or dysfunction. Influential papers such as those of Ounstead (1955) and Ingram (1956) typified this narrower view and dominated British child psychiatric thinking and practice for many years. In Europe, the whole concept of MBD was strongly criticised by neurologists and paediatricians (Bax & MacKeith 1963) who believed that phenomena such as language delay and motor clumsiness were indicative of a serious rather than a mild condition. As a consequence, hyperkinesis remained an infrequent diagnosis in Britain and many European countries and was generally reserved for those for whom there was strong evidence of brain damage in the context of generalised intellectual retardation. Medical and educational researchers and practitioners sought to describe and emphasise the non-neurological causal explanations for failure at school, aggressive and disruptive behaviours and were therefore more likely to recommend psychotherapeutic interventions and less likely to use medications to manage these problems. "Hyperkinetic syndrome of childhood" was included in the World Health Organisation's International Classification of Disease 9th edition (ICD 9), which was published (World Health Organisation 1977) three years before DSM-III. Hyperkinetic syndrome of childhood described a group of children in which the essential features are short attention span and distractibility with early onset, disinhibited, poorly organised and poorly regulated *extreme* overactivity. Impulsiveness, marked mood fluctuations, aggression, delays in skills development and disturbed peer relationships were also noted to be common.

The essence of ICD 9 hyperkinesis and DSM-III ADDH were similar: both identified children with impaired concentration and overactivity. There were, however, several important discrepancies.

- The ICD system had a preference for there being a single diagnosis with the clinician matching the pattern that it most closely fits, whereas DSM is set within a multi diagnosis framework with less prominent exclusion criteria. Thus, whilst it was possible to diagnose both ADDH and an anxiety disorder under DSM-III, under ICD 9 the anxiety disorder is diagnosed and the hyperkinesis is not – assuming that the anxiety is considered the cause. This situation remains to a degree under DSM-IV and ICD-10 although it has been somewhat attenuated.

- Symptom requirements were less explicit under DSM-III, for example whist ICD 9 required "extreme" overactivity, under DSM-III the requirement is for "developmentally inappropriate" levels.

At this time (mid 1980s), compared with American colleagues, few British clinicians were diagnosing cases of hyperkinesis (Taylor 1985). However a formal assessment of the reasons for these differences found that researchers from the UK and US were in general agreement about the diagnostic status of children from both sides of the Atlantic when presented with standardised case histories. Each of the research teams was consistent in their approach with perfect agreement within the team on more than 80% of cases (kappa[1] of 0.69 within the DSM III team and 0.6 within the ICD 9 team). There were, however, differences between the children identified by each of the two systems. Out of 40 children drawn half from London and half from Washington, there was an agreement on a diagnosis of ICD 9 hyperkinetic syndrome in 22 cases and on DSM-III ADDH on 33 cases. For the US team, ICD 9 gave 27 cases (of hyperkinetic disorder) and DSM-III, 33 (of ADDH); for the UK

[1] Cohen's Kappa (often simply called Kappa) is a measure of agreement between two individuals or groups of individuals. Kappa is always less than or equal to 1 and a value of 1 would imply perfect agreement and values less than 1 imply less than perfect agreement. Different people have different interpretations as to what is a good level of agreement. However a generally accepted view would propose that; Kappa < .2 = poor agreement; between .2 - .4 = fair agreement; between .4 - .6 moderate agreement; between .6 - .8 = good agreement; and between .8 – 1.0 = very good agreement (Altman 1991).

team, ICD 9 gave 23 cases and DSM-III, 35. Panels of clinicians from the two countries were less reliable. The US clinicians' panel obtained a kappa of 0.32 for overall DSM-III diagnosis, 0.26 for ICD 9; the UK panel achieved 0.34 for DSM-III and 0.29 for ICD 9. Diagnostic rates were also more variable. The US panel generated a total of 398 diagnoses of ADDH in DSM-III and 335 of hyperkinetic syndrome in ICD 9; for the UK panel the corresponding figures were 425 and 251. Thus there was an interaction between the scheme used and the nationality of the clinician using it. In the main most difficulties concerned subjects with a mixed overactivity / conduct disorder pattern of symptoms (Prendergast et al. 1988).

Whilst the emphasis on a single diagnosis system was retained within the publication of ICD-10 (World Health Organisation 1992), there was, as there was with DSM-IV, an attempt to further operationalise symptoms, introduce criteria for pervasiveness and impairment and to close the gap between the two systems. Indeed the symptom criteria for DSM-IV TR ADHD and ICD-10 hyperkinetic disorder are now almost identical, although there remain important differences, which will be discussed in the next section.

Current Nosological Issues

As already mentioned, the two current diagnostic systems, ICD-10 and DSM-IV, are now much more similar in the way that they define individuals with AD-HKD than was the case with previous diagnostic systems. However there remain several important differences between the two systems. This section will review these differences and comment on their potential impact on prevalence, treatment response, and heterogeneity. However before looking at the differences between the two systems, it is necessary to comment on some issues relating to the ICD-10 system. There are two main versions of Chapter V (F) of ICD-10, the Chapter relating to the "Classification of Mental and Behavioural Disorders". The first to be published was the *Clinical Descriptions and Diagnostic Guidelines* Commonly known as "The Blue Book" (World Health Organisation 1992) . This version provided a

descriptive account of the criteria required for a diagnosis of HKD to be made and included diagnostic guidelines, comments on differential diagnosis written in a prose style. The *Diagnostic Criteria for Research* were published a year later (World Health Organisation 1993). These criteria gave clear opperationalised guidance regarding the required number of symptoms, age of onset, duration and impairment for a diagnosis to be made. Unfortunately in one respect, age of onset, the two descriptions are at slightly at variance to each other with the Blue Book suggesting onset must be before the age of 6 years and the research criteria (Green Book) specifying before age of 7 years. The research described in this thesis utilised the ICD-10 diagnostic criteria for research (World Health Organisation 1993) and all further discussion of the ICD-10 criteria will focus on this version. The features of ICD-10 Hyperkinetic disorder and DSM-IV ADHD are listed in table 1.1.

Both systems require not only an above threshold number of symptoms but also these symptoms to be;

1. Present from early in life
2. Present to a degree that is both maladaptive and developmentally inappropriate
3. Present in more than one situation (i.e. at home and at school, and often in a peer group setting or at work)
4. Functionally impairing

Table 1.1: The current diagnostic Criteria for Hyperkinetic Disorder as described in ICD-10 (World Health Organisation 1993) and for ADHD as described in DSM-IV TR (American Psychiatric Association 2000)

	Symptoms	
1	Fails to give close attention to details or makes careless mistakes in schoolwork, work, or other daily activities.	
2	Has difficulty sustaining attention on tasks or play activities.	**Subtypes**
3	Does not seem to listen to when spoken to directly.	ICD-10 Hyperkinetic Disorder: 6 items from 1 -9, plus 3 items from 10 – 14, plus 1 item from 16 – 18
4	Does not follow through on instructions and fails to finish schoolwork chores, or duties in the workplace (not due to oppositional behaviour or failure to understand instructions).	DSM-IV ADHD-Combined: 6 items from 1 -9, plus 6 items from 10 – 18 DSM-IV ADHD-Inattentive: 6 items from 1 -9 DSM-IV ADHD-Hyperactive/Impulsive: 6 items from 10 -18
5	Is often impaired in organising tasks (*DSM-IV: "Has difficulties organising tasks and activities"*).	
6	Avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort such as schoolwork or home work.	DSM-IV specifies a diagnosis of "in partial remission" for adolescents or adults who formerly met full criteria but now have some symptoms without meeting full criteria.
7	Looses things necessary for tasks or activities (e.g. toys, school assignments, pencils, books or tools).	
8	Is easily distracted by external stimuli (*DSM-IV: "by extraneous stimuli"*).	**Comorbidity**
9	Is forgetful in the course of daily activities (*DSM-IV:"In daily activities"*).	ICD-10: Specifies "do not diagnose" if child meets criteria for Pervasive Developmental Disorder, manic episode, depressive episode, or anxiety disorders. Hyperkinetic Conduct Disorder is given a separate diagnostic category.
10	Fidgets with hands or feet or squirms on seat (*DSM-IV: "in seat"*)	
11	Leaves seat in classroom or in other situations in which remaining seated is expected	DSM-IV: Specifies that symptoms should not be "better accounted for" by another mental disorder
12	Runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)	
13	Is often unduly noisy in playing or has difficulty in engaging quietly in leisure activities (*DSM-IV: "Has difficulty playing or engaging leisure activities quietly"*).	**Additional Criteria**
14	Exhibits a persistent pattern of excessive motor activity that is not substantially modified by social context or demands (*DSM-IV: "Is "on the go" or often acts as if "driven by a motor""*)	Onset: "Onset of the disorder" is no later than age 7 (ICD-10), or "Symptoms that caused impairment had to be present" before the age of 7 years of age (DSM-IV).
15	Talks excessively without appropriate response to social constraints (*DSM-IV: "Talks excessively"*).	Pervasiveness: "Criteria must be met" (ICD-10) or "impairment must be present" (DSM-IV) in two or more settings.
16	Blurts out answers before the questions have been completed.	Impairment: There must be clear evidence of clinically significant impairment or distress (ICD-10); or impairment of functioning (DSM-IV)
17	Fails to wait in lines or await turns in games or group situations (*DSM-IV: "Has difficulty awaiting turn"*)	
18	Interrupts or intrudes on others (e.g. butts into conversations or games)	
	Each behaviour must occur "often" and must persist for at least 6 months to a degree that is maladaptive and inconsistent with developmental level.	

The main differences between the two systems concern the ways that subtyping, pervasiveness, and comorbidity are handled. Although both systems use essentially the same list of symptoms, ICD-10 is a refined phenotype, which identifies only a subset of those recognised as meeting criteria for DSM-IV ADHD. ICD-10 requires that a minimum number of symptoms of inattention, hyperactivity and impulsivity each be present rather than treating hyperactivity/impulsivity as a single dimension and allowing for *either* inattentive *or* hyperactive/impulsive symptoms to be present. In addition ICD-10 requires that full diagnostic criteria be met independently according to both parent and teacher reports, including both symptomatology and impairment. In contrast DSM-IV only requires impairment to be present in two settings. With respect to HKD ICD-10, as discussed above, is a single diagnosis system and excludes cases with other diagnosable psychiatric conditions such as a depressive episode or anxiety disorder (comorbidity with conduct disorder and oppositional defiant disorder are treated as a special case and represents the main subdivision of hyperkinetic disorder with a separate diagnostic category: Hyperkinetic Conduct Disorder). DSM-IV permits multiple diagnoses and only insists that the ADHD symptoms are not "better accounted for" by another mental disorder. As a consequence of these differences the ICD-10 definition identifies a smaller number of children and adolescents than does the DSM-IV definition (Tripp et al. 1999).

Such differences can be thought about along the lines suggested by Cantwell (1996). Diagnoses are concepts, not objects, and therefore the important question is not which categorisation is the best (as is frequently debated by clinicians and academics from both sides of the Atlantic) but what are the different predictive powers inherent to each category. When extrapolating research findings or clinical experience between the two systems, it was assumed for many years that the differences in prevalence rates quoted for the two systems (ICD-10 hyperkinetic disorder: 1.5% (Meltzer, Goodman, & Ford 2000), DSM-IV ADHD: 5% (Shaffer, Fisher, Dulcan, Davies, Piacentini, Schwab-Stone, Lahey,

Bourdon, Jensen, Bird, Canino, & Regier 1996) could be accounted for by the exclusion of the ADHD Inattentive (ADHD-I) and ADHD Hyperactive/Impulsive (ADHD-HI) types by ICD-10 and that those children meeting criteria for hyperkinetic disorder are very similar to those meeting criteria for ADHD-Combined (ADHD-C) type. Whilst it is certainly true that almost all children meeting ICD-10 criteria for hyperkinetic disorder will belong to a subset of those with ADHD-C, it has recently been demonstrated that the converse is not true; i.e. many children identified as ADHD-C do not meet criteria for hyperkinetic disorder. Santosh and colleagues (Santosh et al. 2005) recently reanalysed a large and well characterised data set of children diagnosed as suffering from ADHD-C, from the Multimodal Treatment of ADHD study (MTA study; MTA Cooperative Group 1999). They applied a series of filters to the original diagnostic information to assess which of the original 579 ADHD-C cases met criteria for ICD-10 hyperkinetic disorder. The filters were applied in the following order;

Comorbidity filter: If a research diagnosis of anxiety or depression was present, the hyperkinetic disorder diagnosis was excluded.

Symptom Domain Filter: If the ICD-10 symptom count criteria were not met in all three domains (inattentiveness, hyperactivity, and impulsiveness) in either school or home, the hyperkinetic disorder diagnosis was excluded

Pervasiveness Filter: If the symptom count were not met in one of the two settings, the hyperkinetic disorder diagnosis was excluded.

Impairment Filter: If overall impairment was not endorsed at interview, the hyperkinetic disorder diagnosis was excluded.

The results of this filtering process are shown in table 1.2.

Table 1.2: The re-diagnosis of the MTA sample (n = 579, all of whom were originally diagnosed as having DSM-IV diagnosis of ADHD combined type) using a series of filters designed to impose the ICD-10 criteria for hyperkinetic disorder (Santosh et al. 2005)

ICD-10 filters	Number of cases excluded following application of each ICD-10 filter (% of total MTA sample)	Number of cases passing successive ICD-10 filters (% of total MTA sample)
1 Comorbidity	147 (25.4)	432 (74.6)
2 Symptom Domain	71 (12.3)	361 (62.3)
3 Pervasiveness	200 (34.5)	161 (27.8)
4 Impairment	16 (2.8)	145 (25.0)
ICD-10 diagnosis of hyperkinetic disorder		145 (25.0)

In summary only 25% (n = 145) of the original sample passed though all of the filters. A further 11.1% of cases (n = 64) would have met ICD-10 criteria for hyperkinetic disorder if they had not been suffering from a comorbid anxiety or depressive disorder. Thus it appears that individuals with hyperkinetic disorder form only a small subset of those children with ADHD-C and that caution must be exercised when extrapolating results from one group to the other. Indeed the Santosh reanalysis demonstrated that, when compared with ADHD-C, a diagnosis of hyperkinetic disorder has a strong positive moderating effect on response to stimulant treatment.

Whilst such comparative studies are extremely rare in the literature there are several other published studies, which suggest that pervasive ADHD symptoms may moderate presentation. For example, a cluster analysis of a group of clinic referred children with overactivity suggested a subgroup of these children with the pervasive presence of all symptom domains of AD-HKD who ,when compared with other groups characterised by either milder or situation-specific difficulties, had the clearest deficits in tests of executive and inhibitory functioning and motor control (Taylor et al. 1986). Also, an epidemiological study demonstrated that hyperkinetic disorder, but not ADHD, (once cases of hyperkinetic disorder were removed) was predictive of neurodevelopmental delays (Taylor et al. 1991). Each of these studies provides important evidence that can be interpreted as supporting the validity of hyperkinetic disorder as a refined phenotype of AD-HKD with additional predictive powers.

It is clear from the preceding discussion that, at a behavioural level of analysis, AD-HKD is a heterogeneous disorder with a wide range of possible presentations. The impact of the different classification systems on heterogeneity remains unclear. From one perspective the more restrictive and refined criteria of ICD-10 hyperkinetic disorder seem likely to identify a more homogeneous group of individuals than the DSM-IV ADHD-C criteria.

However it may also be the case that those with hyperkinetic disorder represent a group at the extreme end of the AD-HKD spectrum resulting as a consequence of several distinct and less common causal agents with subsequent increased heterogeneity. Similarly the consequence of the subdivision of ADHD into the -C, -I and -HI subtypes on heterogeneity is unclear. Despite the supposition that the ADHD-I subtype is qualitatively distinct from the ADHD-C and –HI subtypes (Milich, Balentine, & Lynam 2001) empirical data do not always support this position (Hinshaw 2001; Lahey 2001).

Validity, Comorbidity and Contextual Issues

Validity

Despite the heterogeneity of the AD-HKD behavioural phenotype and continuing doubts concerning the validity of AD-HKD, voiced principally by the mass media, but also within some quarters of the professional literature (e.g. Searight & McLaren 1998), there is now an extensive literature supporting the validity of AD-HKD as a distinct and important psychiatric disorder. Robins and Guze (1970) proposed criteria to assess the evidence on the validity of psychiatric disorders. They suggested that validity derives not from any single study or line of evidence, but from a pattern of consistent data across a range of areas including; clinical correlates, course and outcome, family history, laboratory studies and treatment response.

Clinical correlates

With respect to clinical correlates, Robins and Guze suggest that a valid disorder needs to be reliably identified through a consistent pattern of symptoms demarcating it from other disorders and psychiatric wellbeing. This has been demonstrated on many occasions for AD-HKD in both clinic referred cases and within epidemiological studies (Szatmari 1982). For example, a series of systematic field trials conducted as a part of the development of the DSM-IV criteria demonstrated substantial agreement amongst clinicians (Frick et al.

1994; Lahey et al. 1994). Reliability studies of AD-HKD rating scales and diagnostic interviews, reviewed by Faraone (2005), show high levels of reliability as measured by Cronbach's alpha (0.66 – 0.95) and Cohen's kappa (0.82 – 0.95). Measures of sensitivity were around 95%, specificity: 97%, positive predictive power: 98% and negative predictive power: 95%. The AD-HKD symptom clusters have consistently been associated with high levels of functional impairment across a wide range of settings including the development of social skills (Greene et al. 2001; Rucklidge & Tannock 2001), peer and family relationships (Barkley et al. 1990a), and the school (Barkley et al. 2006a) and justice systems (Satterfield & Schell 1997). Those with AD-HKD are also at greater risk than those without for substance misuse (Wilens et al. 1997) and accidental injury. Further, when injured they are more likely to sustain severe injuries (DiScala et al. 1998).

Clearly a diagnosis cannot be considered valid if its clinical features and impairments could be accounted for by another disorder. ICD-10 attempts to deal with this through its single diagnosis philosophy and DSM-IV by explicitly stating that symptoms should not be "better accounted for" by another mental disorder. However, at least in the case of DSM-IV ADHD, comorbidity is the rule rather than the exception and thus it is important to demonstrate that patterns of comorbidity are not simply an artefact of overlapping diagnostic criteria. In fact there is considerable symptom overlap between AD-HKD and several other diagnostic groups. Depression is associated with psychomotor disturbance and poor concentration, bipolar disorder with overactivity, impulsivity and distractibility and generalised anxiety disorder with restlessness and difficulty concentrating. However when Milberger and colleagues (1995) carefully assessed a group of children with ADHD and removed overlapping symptomatic criteria from the diagnostic algorithm, the majority of children retained their previous diagnoses. Further studies have demonstrated that whilst the outcomes of children with ADHD and comorbid psychiatric conditions are worse than those

with ADHD alone, the comorbid conditions do not account for all the outcomes and impairments seen with ADHD (Fischer et al. 2002; Szatmari, Boyle, & Offord 1989).

Course and outcome

It is generally agreed that a valid disorder should have a characteristic course. There are several lines of evidence to suggest that AD-HKD meets this criterion. Longitudinal studies following children with AD-HKD into adulthood have demonstrated considerable continuity and very similar patterns of correlates across multiple domains of assessment including psychosocial adversity and comorbidity with conduct, depressive, and anxiety disorders (Biederman et al. 1998a; Kessler et al. 2006). Biederman and colleagues (2000) reported that, at the age of 19 years, 38% of children previously diagnosed with ADHD continued to meet full diagnostic criteria, 72% showed persistence of at least one third of the symptoms required for the diagnosis and 90% showed evidence of clinically significant impairment associated with their ADHD. Other studies have demonstrated that the chronic course of AD-HKD is associated with continuing impairments including academic underachievement (Murphy & Barkley 1996), poor occupational functioning and lower occupational status (Mannuzza et al. 1997), increased risk of motor vehicle accidents (Barkley, Murphy, & Kwasnik 1996) and substance misuse (Biederman et al. 1998b). Indeed “adult AD-HKD”, a much more contentious clinical entity than ADAD-HKD in children and adolescents, itself meets many of the Robins and Guze criteria for validity (Coghill 2004).

The validity of AD-HKD is also supported by evidence from ***family history***, ***laboratory studies,*** and ***treatment studies***. The data relating to family history and laboratory studies is reviewed in detail in Chapter 2 and will therefore not be discussed further at this point. Evidence relating to treatment response is discussed below.

Critics of the of concept of AD-HKD as a disorder point out that children meeting the diagnostic criteria merely represent an extreme of normal variation, rather than a distinct

diagnostic group. It is true that the actual boundary between case and non-case is, to some degree, arbitrary and requires a clinician to make a series of decisions based on experience of what is and what is not “normal” on the one hand and “impairing” on the other. However the problem with using this argument to criticise the concept of AD-HKD is that it fails to acknowledge that even normal variation can become a disorder if those at the extremes suffer distress, impairment and disability. This is demonstrated in the field of physical medicine by the cases of increased blood pressure and serum cholesterol. Both represent the extreme end of a normal variation; yet clearly represent significant and valid medical disorders.

Comorbidity

Comorbidity with other types of psychiatric and non-psychiatric problems represents an important source of heterogeneity in AD-HKD. Uncomplicated AD-HKD is rarely seen in a clinical setting, over half of all children diagnosed with ADHD also meet criteria for a comorbid psychiatric diagnosis and many children who would otherwise meet criteria for hyperkinetic disorder are only excluded from this diagnosis by virtue of meeting the criteria for hyperkinetic conduct disorder or for another psychiatric disorder (Biederman, Faraone, & Lapey 1992; Biederman, Newcorn, & Sprich 1991; Gillberg et al. 2004; Jensen, Martin, & Cantwell 1997; Sprich-Buckminster et al. 1993; Taylor et al. 2004). Although it is almost certain that higher rates of comorbidity are found in those children who are referred to clinics than in the group that can be identified in epidemiological studies (the so called "Berkson's bias", Berkson 1946) increased rates of comorbidity are also found in community samples (Anderson et al. 1987; Bird et al. 1988; Bird, Gould, & Staghezza 1993; Kadesjo & Gillberg 2001; Meltzer, Goodman, & Ford 2000).

The most commonly diagnosed comorbid conditions are the disruptive behavioural disorders such as Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) with

reported rates of ODD of between 50 – 60% of all children with DSM-IV ADHD and even higher rates for those with combined type ADHD (Gillberg, Gillberg, Rasmussen, Kadesjo, Soderstrom, Rastam, Johnson, Rothenberger, & Niklasson 2004). The rates of coexisting CD are less well studied but appear to be around 14% (MTA Cooperative Group 1999). The rates of co-existing anxiety (≈ 12%) and depressive disorders (16 – 26%) are also higher than would be expected by chance (Gillberg 1983; Gillberg, Gillberg, & Rasmussen 1983). About half of those with chronic tics or Tourette's syndrome also meet criteria for ADHD (Gillberg, Gillberg, Rasmussen, Kadesjo, Soderstrom, Rastam, Johnson, Rothenberger, & Niklasson 2004). Adolescents and young adults with AD-HKD are around two times more likely than those without AD-HKD to have a co-existing substance misuse disorder. Whilst controlling for comorbid disorders (particularly conduct disorder) substantially weakens, and in some samples completely accounts for this association (Lynskey & Hall 2001), there is some evidence that non-comorbid ADHD in adults does act as an independent risk factor for substance misuse (Wilens, Biederman, Mick, Faraone, & Spencer 1997).

Although currently considered as an exclusion criteria for a diagnosis of AD-HKD, many children with pervasive developmental disorders (PDD: autism, Asperger's syndrome, autism spectrum disorders) show symptoms of AD-HKD. Estimates of the numbers of children affected vary greatly. One community based study suggested that 80% of those meeting criteria for Asperger's also met criteria for DSM-III-R ADHD (Ehlers & Gillberg 1993), whilst another more recent study using DSM-IV criteria in a group of children with rigorously diagnosed autism spectrum disorders found that 28% of this group also met criteria for ADHD (Simonoff et al. 2008). Whilst the true rates are likely to be nearer to this lower more recent estimate it is certainly the case that children with PDD often show hyperactive behaviour and that autistic symptoms are sometimes seen in the hyperactive. The DSM-V committee is currently considering whether a diagnosis of PDD should continue

to preclude a diagnosis of ADHD (Rohde 2008). Further research is currently underway to clarify the relationship between the two disorders.

Other developmental disorders are also commonly associated with AD-HKD. AD-HKD is often accompanied by problems in sensory motor coordination, especially seen as poor handwriting, clumsiness, poor performance in sports and marked delays in achieving motor milestones (Gillberg 2003; Kadesjo & Gillberg 2001). Reading Disorder, delayed language development and other specific learning disabilities are also common (Hinshaw 1992; Taylor, Sandberg, Thorley, & Giles 1991).

The reasons for these increased levels of coexisting problems appear to be different in different situations. Of particular relevance to this discussion is the relationship between AD-HKD, ODD and CD and the overlap between impulsiveness and oppositionality (Taylor 1998). Scientific investigations are currently divided as to the meaning of this comorbidity. There is evidence to suggest that CD is not so much a differential diagnosis or comorbid condition, but that it arises as a secondary complication of ADHD (Taylor et al., 1991). By this account ADHD is a risk factor for CD, with the appearance of CD in some children with AD-HKD, including those who showed “pure” AD-HKD at the beginning of their problems, and an assumption that CD does not give rise to hyperactivity in the same way. Others have described studies in which children with AD-HKD and co-existing CD differed from those with AD-HKD alone in that the AD-HKD/CD group presented with lower levels of impulsiveness suggesting that this indicated an alternative route to AD-HKD for children with CD rather than a route by which AD-HKD leads to CD (Halperin et al. 1990). Similar discussions have resulted from analysis of neuropsychological data pertaining to AD-HKD and CD, which will be discussed in detail in Chapter 9 (Willcutt et al. 2008).

Clearly these co-existing disorders, when present, add to the overall impairments, result in greater levels of suffering and add another level of complication to an already difficult life

situation. Hence the assessment of co-existing psychiatric and developmental problems is key to both the clinical management and academic study of AD-HKD as they will impact on both the clinical course, and the analysis and interpretation of research data.

Contextual Issues

There is now considerable and compelling data supporting the notion of AD-HKD as a global problem which, if measured using the same tools, appears to be equally prevalent across the world (Faraone et al. 2003) and stable across time (Meltzer, Goodman, & Ford 2000; Taylor, Sandberg, Thorley, & Giles 1991). The administrative prevalence of AD-HKD – the rate at which the disorders are in practice recognised – has risen sharply in the past 20 years across the globe but continues to vary greatly between different countries. Identification rates are much higher in the US than in Europe (Swanson et al. 1998). In the US where most assessment and treatment is carried out within a primary care setting, and few patients ever have contact with specialist services, there are concerns over the quality of diagnosis and care (Wolraich 2003). As a consequence there are large variations in practice across the US whereby only 1 in 8 children with ADHD are treated with stimulant medication, yet 50% of those being treated do not meet criteria for ADHD (Jensen et al. 1999). In Europe, where most AD-HKD care is given within a secondary care setting, although this varies by country, there is also considerable variation in administrative prevalence between countries from almost zero to 2.5% (Koster et al. 2004). Within the UK, the National Institute for Clinical Excellence (NICE), using a very conservative approach to treatment decision making, reported that in England and Wales only 30% of those with hyperkinetic disorder, the most severe form of ADHD, were receiving stimulant medication (National Institute for Clinical Excellence 2000). In Scotland the administrative prevalence of AD-HKD is currently in the region of 0.6% (NHS Quality Improvement Scotland 2008). Thus the worrying “explosion” in the diagnosis of AD-HKD, as is often depicted in the

popular press, is actually likely to a move towards, but not yet achieving, a more appropriate recognition and treatment of a serious childhood disorder.

Interestingly, the same secular changes, which have resulted in a vastly increased recognition and diagnosis of AD-HKD in Europe in recent years (e.g. changes in marketing practices by the pharmaceutical industry that initially reintroduced and then heavily marked stimulant and non-stimulant drug treatments for AD-HKD) may have also altered the diagnostic practices of European physicians. In an ongoing pan-European observational study of 1500 children with AD-HKD 43% of cases were diagnosed using DSM-IV criteria, 32% using ICD-10 and 12% using both (Preuss et al. 2006). European guidelines, however, have continued to stress the importance of retaining both criteria, particularly in view of the moderating effect of hyperkinetic disorder on response to medication treatments (Taylor, Dopfner, Sergeant, Asherson, Banaschewski, Buitelaar, Coghill, Danckaerts, Rothenberger, Sonuga-Barke, Steinhausen, & Zuddas 2004).

The Treatment of AD-HKD

Psychological interventions, educational change and medication have all been demonstrated to be effective interventions for AD-HKD. They should all be available, and their use should be guided by a treatment plan drawn up for the individual. Most children with AD-HKD have a broad array of problems and difficulties, and multimodal intervention is usually indicated.

As MPH – a stimulant medication – was the treatment used in the study described here, this discussion will focus on the evidence surrounding its use and only briefly mention other treatment modalities.

Non-pharmacological approaches

Psychoeducational measures

Education and advice for patients and their parents or carers should be universally applied and form the base from which all other treatment is given. It is important to assess health beliefs as well as causal and control attributions; and inform all concerned about AD-HKD – especially symptoms, aetiology, clinical course, prognosis and treatment. Consultation with parents and school, on appropriate class or school placement and management, is nearly always needed. Children who are old enough should be educated about self-observation and self-management. Evidence from the Multimodal Treatment of ADHD study (MTA study) suggests that such approaches may improve the effectiveness of medication interventions (Vitiello et al. 2001).

Parent training and behavioural interventions in the family

Parent training and behavioural interventions in the family have been shown to be effective by random allocation trials (Pelham, Wheeler, & Chronis 1998). There are many approaches, most of which include: instruction on monitoring and identifying problem situations and behaviours; enhancing parent attending and communication skills; increasing positive interactions; rewarding positive behaviours; the use of appropriate negative consequences and the use of time out from reinforcement.

Behavioural interventions in preschool and school situations

Behavioural interventions in the kindergarten, the preschool or the school are known to be effective in reducing hyperactive behaviour and promoting social adjustment (DuPaul & Eckert 1997). No one scheme has been shown to be superior to others, but most validated approaches include: maintaining appropriate classroom structure and task demands; assisting the teacher to identify and monitor specific problem situations and behaviours;

the enhancement of differential attending skills and positive attending of the teacher; the use of token reward, response cost and time out systems.

Cognitive behaviour therapy of the child

Summer treatment programmes with social skills training and contingency management have also been proven to be effective (Pelham & Waschbusch 1999). Isolated self-instructional approaches have not yet been shown to be effective by controlled trial (Abikoff 1991) but experience suggests they may be helpful in individuals in combination with other behavioural approaches.

Pharmacological approaches

The three main medications used in the treatment of AD-HKD are the stimulant drugs MPH and dexamfetamine and the non-stimulant atomoxetine. As the focus of this study is on the clinical and neuropsychopharmacological effects of MPH, which is also the best studied and most frequently prescribed of the three, it will be discussed in the greatest detail. Several other medications have demonstrated superiority in random-allocation, double blind trials of variable quality and methodology including clonidine, tricyclic anti-depressants such as imipramine, bupropion, modafanil and neuroleptic antidopaminergic drugs (thioridazine and haloperidol), however these are now much less frequently used in clinical practice and will not be discussed further.

Methylphenidate (MPH)

Pharmacokinetics and Pharmacodynamics

Absorption of MPH is essentially complete and rapid (Gualtieri et al. 1982). The time to peak blood drug concentrations (t_{max}) following the oral administration of immediate release MPH is between 1 and 3 hours (Kimko, Cross, & Abernethy 1999). There is considerable inter-individual variability in MPH absorption rate in hyperactive children. The plasma binding of MPH is low (approx 15%) (Hungund et al. 1979). The drug penetrates the

blood brain barrier readily (Ding et al. 1994). MPH undergoes stereo-selective metabolism with the inactive *l-threo*-MPH undergoing rapid metabolism and clearance (Kimko, Cross, & Abernethy 1999). Most of the metabolism of MPH occurs extra-cellularly. The main metabolic pathway is de-esterification, via the enzyme carboxylesterase 1, to form the carboxylic acid metabolite, commonly known as ritalinic acid, which is pharmacologically inactive. About 70% of a dose of MPH is converted to ritalinic acid and excreted in urine. Minor pathways (less than 2%) involving aromatic hydroxylation, microsomal oxidation and conjugation have been reported to form the p-hydroxy-, oxo- and conjugated metabolites, respectively. There is no evidence that any of these MPH metabolites contribute substantially to the pharmacological activity. Volkow and colleagues have carried out a series of functional neuroimaging studies using PET and radio labelled MPH in both humans and primates to study the pharmacokinetic properties of intravenous and oral MPH and levels of dopamine transporter (DAT) blockade (reviewed in Swanson & Volkow 2001). These studies demonstrated that;

1. After oral doses of MPH, peak brain levels occur between 1 and 2 hours after dosing, which is about the same time as the peak pharmacokinetic and pharmacodynamic (behavioural) effects of clinical doses.

2. After oral administration of MPH, while relatively high concentrations are maintained at the site of action in the brain, some behavioural effects dissipate suggesting acute tolerance, possibly due to adaptation responses at the synaptic level in response to DAT blockade.

3. At commonly used clinical doses, MPH blocks >50% of the DAT and maximum MPH blockade of DAT (about 80% occupancy) occurs at a serum concentration of about 8 to 10 ng/ml suggesting that higher concentrations are not likely to be very effective in further blocking DAT or increasing efficacy due to this site of action (NB

> although there is great inter-individual variation a 5mg dose of oral immediate release MPH results in a serum peak concentration of approximately 5 ng/ml, a 10 mg dose approximately 10 ng/ml and a 20 mg dose approximately 16/ng/ml).

These findings are interesting in view of the fact that several studies have now demonstrated that there appears to be a ceiling effect with MPH where increasing dose does not lead to increased effect.

The relationship between the pharmacokinetics and pharmacodynamics of MPH is complex, and incompletely understood. Several early studies suggested that pharmacokinetic and pharmacodynamic measures for MPH are highly correlated (Kupietz et al. 1980; Shaywitz et al. 1982). This linear relationship was questioned by further studies which concluded that MPH concentrations are not related to clinical response (Gualtieri, Wargin, Kanoy, Patrick, Shen, Youngblood, Mueller, & Breese 1982; Gualtieri et al. 1984). Other early studies suggested a complex relationship whereby, whilst the pharmacodynamic effects of MPH on measures of attention parallels the pharmacokinetic serum concentrations (peak at 1 hour, half-life of 3 hours), the effects on activity peak at the same time followed by a longer half-life, or even continued increases in efficacy over time after high doses (Solanto & Conners 1982). Using laboratory classroom settings Swanson and colleagues confirmed the rapid onset (1.5 hrs) and short duration (4.0 hours) of action of MPH on both academic and behavioural ratings (Swanson & Volkow 2001). Recent studies using the standardised UCI laboratory school protocol have again suggested that the clinical effects of MPH closely follow the predicted pharmacokinetic profiles (Sonuga-Barke et al. 2004; Swanson et al. 2004).

In another series of well conducted pharmacokinetic/pharmacodynamic studies Swanson and Volkow (2001) have suggested that when MPH is given across the day there is a close relationship between drug levels and clinical response in the mornings but that the relationship is coloured in the afternoon due to the onset of an acute tolerance effect (see below). There is also some evidence, which suggests that during the initial 45 minutes following a dose of MPH patients may experience a transient worsening of symptoms (Swanson et al. 1999).

Whilst it has often been argued that there is no evidence that individuals taking MPH over a prolonged period of time develop chronic tolerance (Gualtieri et al. 1981; Safer & Allen 1989; Satterfield, Cantwell, & Satterfield 1979; Satterfield, Satterfield, & Cantwell 1980), evidence from more recent clinical trials has suggested that individual dose requirements do, in fact, increase over time, suggesting the possibility of a degree of chronic tolerance (Vitiello, Severe, Greenhill, Arnold, Abikoff, Bukstein, Elliott, Hechtman, Jensen, Hinshaw, March, Newcorn, Swanson, & Cantwell 2001). There is also evidence to suggest that acute tolerance to MPH occurs. Swanson and colleagues conducted a series of well-designed studies utilising the UCI laboratory school protocol to assess the complex interactions between the pharmacokinetics and pharmacodynamics of MPH. They found evidence for the development of a rapid onset (and offset) of acute tolerance to MPH (Swanson, Gupta, Guinta, Flynn, Agler, Lerner, Williams, Shoulson, & Wigal 1999). As a consequence higher levels of MPH are required in the second half of the day to produce a similar pharmacodynamic effect to that produced by the first dose in a day. This tolerance is reported to be short lived, completely wearing off by the next day.

Sensitisation to stimulants has been typically described in animal studies. However these studies typically used intra-peritoneal or intravenous administration of high doses of drug. There are several descriptions of cross sensitisation to MPH occurring in animals with

several drugs, most notably CNS stimulants such as amphetamine and cocaine. Whilst there is currently no evidence for sensitisation to MPH occurring in human subjects (Greenhill 2001) this is an area that requires further study.

Clinical Effects

There is a substantial evidence base for the effect of MPH over treatment periods up to a year and in doses up to 60 mg daily. Systematic reviews and meta-analyses of the numerous randomised placebo-controlled trials, which have investigated the effects of MPH in AD-HKD comment on the poor design of early many studies but also confirm the substantial short-term benefit with an effect size of approximately 1.0 for teacher ratings and 0.86 for parent ratings (Banaschewski et al. 2006; Jadad et al. 1998; King et al. 2006; Scottish Intercollegiate Guidelines Network 2001). MPH has been demonstrated to markedly and rapidly reduce the overt clinical manifestations of restlessness, inattentiveness and impulsiveness; improve classroom behaviour (Abikoff & Gittelman 1985) and academic productivity in experimental settings (Carlson & Thomeer 1991); improve the quality of social interactions with peers (Whalen et al. 1989), siblings (Schachar et al. 1987) and parents (Barkley et al. 1984), and to decrease aggression and increase behavioural compliance (Gadow et al. 1990; Klein et al. 1997).

Clinically meaningful benefits are seen in approximately 70% of patients (Elia et al. 1991) although children with ADHD receiving MPH may still display more behavioural problems than healthy children. MPH seems to be more effective at treating the behavioural difficulties associated with ADHD (effect size 0.8 – 1.0) than the cognitive deficits (effect size 0.6 – 0.8)(Spencer et al. 1996).

The evidence for the long-term efficacy is much weaker than for short-term use. There are no truly long-term trials of stimulant treatment of ADHD. There are however a handful of controlled trials that have extended over a year (Gillberg et al. 1997; MTA Cooperative

Group 1999; Schachar, Taylor, Wieselberg, Thorley, & Rutter 1987) and open-label extensions of industry sponsored studies are starting to appear (Wilens et al. 2003; Wilens et al. 2005). Together these studies suggest that the clinical perception of persistence of effect over time is accurate. Discontinuation of medication also seems to lead to a recurrence of symptoms in a majority of cases. Whilst it would be preferable to have evidence from placebo-controlled trials conducted over long periods of time it is unlikely that such trials can ethically be run. There is a need, however, for an investment into research in this area as many questions and concerns remain unanswered. For example the effects of MPH on longer-term academic performance and other health related quality of life parameters remain uncertain (Greenhill 2001).

Stimulant medications such as MPH also have limitations. Some children and families do not view them as an acceptable treatment option. Many families believe that their child's problems reside in the context of key relationships or in the child's school and are thus reluctant to accept medication on this basis. Lack of adherence limits the effectiveness of MPH, as it does with any medical treatment. Although generally safe, MPH does have side-effects in a proportion of recipients that, in some cases, result in the termination of treatment (see below).

As described previously the decision about which individuals with AD-HKD should be offered drug treatment is also complex. However there is increasing consensus that those with ICD-10 hyperkinetic disorder should usually be considered for treatment with MPH as a first line treatment and that those with the broader DSM-IV ADHD phenotype may require a drug treatment if behavioural treatments are either unacceptable or ineffective within a reasonable time frame (around 3 months) (Taylor, Dopfner, Sergeant, Asherson, Banaschewski, Buitelaar, Coghill, Danckaerts, Rothenberger, Sonuga-Barke, Steinhausen, & Zuddas 2004).

Predictors of Response to MPH

It is not yet possible to predict MPH response in the individual AD-HKD child. Most research has failed to identify any clinically useful neurological, physiological or psychological measures of functioning that are reliable predictors of response (Pelham, Jr. & Milich 1991; Zametkin & Rapoport 1987). Those few studies that have reported clinically significant predictors have reported contradictory findings. Both Taylor (1987) and Buitelaar (1995) found younger age to be a positive predictor of clinical response to MPH, but whilst Taylor observed greater pre-treatment attentional impairment, hyperactivity and lower IQ scores in 'responders', Buitelaar found the opposite pattern. Denney and Rapport (1999) applied a range of theoretical and statistical models to assess predictors of teacher-rated response to MPH. They identified numerous weaknesses in previous studies and failed to replicate many previously reported findings. They concluded that a comprehensive model of MPH response will be dependent upon a wide range of factors, which cannot reasonably be reduced down to any single measure.

MPH Adverse Effects

In general the most common adverse effects associated with MPH are decreased appetite and insomnia. These are generally mild in nature and in most cases do not require discontinuation of treatment. The adverse effects of MPH and other AD-HKD treatments have recently been reviewed in detail (Graham & Coghill 2008) and the evidence from the main trials describing the common adverse effects of immediate release MPH preparations are described in Table 1.3.

Table 1.3: Randomised Controlled Clinical Trials generating basic adverse effect data for immediate release MPH in the treatment of AD-HKD in children and adolescents

Authors	Trial Type	N	Duration	Intervention	Measure	Results
Barkley et al. (1990b)	RCT	83	1 week	MPH vs. Placebo	BSEQ	↓appetite, insomnia, stomach ache and headache. Most in the 'mild' range. 3.6% discontinuation rate. Note high incidence of baseline ratings, e.g. insomnia in 40% and irritability in 72%.
Ahmann et al. (1993)	RCT	206	1 week	MPH vs. Placebo	BSEQ	↓appetite, insomnia, stomach ache, headache and dizziness. 2% discontinuation rate.
Efron et al. (1997b)	RCT (cross over)	125	2 weeks	MPH vs. Dex	BSEQ	MPH vs. baseline:↓appetite only. Dex vs. baseline: ↓appetite and insomnia. MPH vs. Dex: insomnia, irritability, prone to crying, anxiousness, sadness and nightmares in Dex relative to MPH. 1.6% discontinuation rate on each stimulant
Schachar et al. (1997)	RCT	91	16 weeks	MPH vs. Placebo	BSEQ	↓appetite, stomach ache, reduced weight gain rate, affective symptoms. Adverse effects generally persisted over 4 month period 10% discontinuation rate
Charach et al. (2004)	RCT (plus follow-up)	91 (79)	12 months (5 years)	MPH vs. Placebo	BSEQ	↓appetite, and others unspecified persisting over trial period
MTA Cooperative Group (1999)	RCT	580	14 months	MPH vs. behavioural intervention	PSES	Mild, moderate or severe side effects were reported by approximately 50%, 10% and 3% respectively at the end of the trial. Effect type not specified

RCT = Randomised controlled trial, MPH = Methylphenidate, Dex = Dexamfetamine, BSEQ= Barkley side effect questionnaire (derived from a review of prior anecdotal studies in which adverse events were mentioned), PSES= Pittsburgh side effect scale

Mechanism of Action of MPH

The precise mechanism of action of MPH is not known. Even some of the most fundamental issues continue to be debated. Much of the research into the mechanism of action of MPH is brought together in a recent publication (Solanto, Arnsten, & Castellanos 2001).

It has often been assumed that the main actions of MPH come from actions on dopamine transmission in the prefrontal cortex. In this context AD-HKD symptoms are hypothesised to arise from a dopamine insufficiency in the prefrontal cortex and that MPH acts to increase dopamine concentrations, thus normalising function. Whilst this assumption is rarely challenged there has been until recently little data using low dose oral MPH to either support or refute it. MPH probably acts, at least in part, through its binding to and inhibition of the dopamine transporter (DAT). DAT is located on the plasma membrane of dopaminergic neurons, where it controls the concentration of dopamine by rapidly removing the transmitter from the extracellular space and localising it into the cytoplasm (Amara & Kuhar 1993). Data from PET studies have demonstrated MPH preferentially binds to DAT in the striatum rather than in the prefrontal cortex (Volkow et al. 1998) and it may be the case that the clinical effects of MPH are dependent on effects in both the striatum and cortex.

Various more detailed theories regarding the effects of MPH have been proposed. Recent psychopharmacological studies have demonstrated the complex nature of the regulation of dopamine transmission and have highlighted the importance of both tonic and phasic dopamine release. Grace (2001) has proposed that children with ADHD may have low tonic dopamine levels in the nucleus accumbens, possibly due to insufficient stimulation from an under active or underdeveloped prefrontal cortex, and that these low levels of tonic dopamine lead to elevated levels of phasic dopamine release. By blocking dopamine

reuptake in the striatum, low dose oral MPH may exert some of its effects by causing an accumulation of dopamine in the synaptic space, which then diffuses into the extrasynaptic spaces. These increased levels of extrasynaptic dopamine may then stimulate impulse regulating dopamine autoreceptors resulting in a decrease in phasic dopamine release. Thus the net effect is a reduction in phasic dopamine levels and an increase in tonic dopamine levels.

Volkow and colleagues (2001) have proposed that the blocked DAT overcomes the inhibitory effects from activation of the autoreceptors, leading to a net effect of dopamine accumulation in the synapse and amplification of dopamine signals, which result from tonic as well as phasic dopamine cell firing. They demonstrated that oral MPH leads to increased levels of dopamine in the striatum, which they believe is due both to the blockade of DAT and increased rates of dopamine release. In an extension of this argument Pucak and Grace (1994) have suggested that the high levels of variability in the doses necessary to elicit clinical responses to MPH among individuals with AD-HKD may be related to individual differences in dopamine cell firing and by environmental stimulation, and that low levels of dopamine cell activity may account for non-response to MPH in some individuals. Further studies have demonstrated that these increases in dopamine are, at least to some extent, dependent on a pairing with a salient event or stimulus, thus suggesting that the effects of MPH occur by increasing the salience of stimuli (Volkow et al. 2002; Volkow et al. 2004).

It now also seems likely that both dopaminergic and noradrenergic transmission are involved in both the pathogenesis of ADHD and in the mechanism of action of MPH (Arnsten 2006b). Both dopamine and noradrenaline have marked effects on prefrontal cortex function, a brain region of particular relevance in AD-HKD (see Chapter 2). MPH has been demonstrated to block both the dopamine and noradrenaline transporters and, although its effects on dopamine are the best recognised, recent pre-clinical studies in rats

suggest that low, oral doses of MPH, similar to those used to treat AD-HKD may have a greater effect on noradrenaline neurotransmission than they do on dopamine (Kuczenski & Segal 2002). Arnsten and Dudley (2005) have demonstrated that similarly low doses of oral MPH can improve performance of prefrontal cortex tasks and that this improvement is, in part, dependent on α-2A adrenoceptor stimulation. Such studies support the hypothesis that the actions of MPH are mediated by both dopamine and noradrenaline.

All of the alterations in catacholaminergic neurotransmission described above would be predicted to enhance a range of cognitive functions including: working memory, behavioural inhibition, planning and attentional set-shifting that have been implicated in causal models of AD-HKD and thus may be expected to improve the symptoms of AD-HKD. The neuropsychology and neuropsychopharmacology of AD-HKD will be discussed in Chapters 2 and 3. In summary, whilst there is still much to learn about the mechanism of action of MPH, current evidence provides strongly convergent support for behavioural effects, which are mediated by alterations in catacholaminergic neurotransmission in the striatum and prefrontal cortex, and that these alterations in neurotransmission may result in improved cognitive performance across a range of tasks, including those higher cognitive abilities, which are dependent on the prefrontal cortex and which, have been demonstrated to be deficient in AD-HKD.

Summary and Conclusions

In this Chapter I have summarised the literature relating to the history, nosology, phenomenology, validity, comorbidity, contextual and treatment issues relating to AD-HKD. AH-HKD is a complex disorder with core symptom domains of inattention, overactivity and impulsivity, begin early in life, are persistent and result in pervasive impairments across many aspects of daily life. Clinically there is considerable heterogeneity with respect to the degree that each of the core symptom domains impacts on and causes impairment for any one individual, the course and outcome of the disorder and the degree to which the AD-HKD is associated with other coexisting disorders.

The definition of what constitutes AD-HKD has changed considerably over time and there are currently two distinct, but closely related, diagnostic criteria. The American Psychiatric Association's DSM-IV criteria use the term attention deficit hyperactivity disorder (ADHD) to define a disorder, which can present as either the combined, inattentive or hyperactive/impulsive type. The World Health Organisation's ICD-10 criteria use the term hyperkinetic disorder (HKD) to describe a more restrictive diagnostic grouping, which does not allow either for subtyping or the presence of comorbidity. Whilst all of those meeting the more restrictive HKD criteria are likely to also meet criteria for combined type ADHD the reverse is not true. It is possible that those with HKD will represent a more homogeneous population than those with ADHD.

Importantly, clinical heterogeneity is not restricted to the initial presentation, course and comorbidity of AD-HKD but is also found with respect to response to treatment. Although it has proved difficult to identify factors, which consistently predict a positive response to treatment, there is some recent evidence to suggest that diagnostic status (ADHD vs. HKD) may be one such moderator of treatment response. When compared with children with non HKD combined type ADHD, children with HKD had a more strongly positive response to

stimulant medication. This finding further strengthens the possibility that the differences between the DSM-IV and ICD-10 criteria may have a bearing on heterogeneity within AD-HKD.

In Chapter 2, I will explore the various strands of evidence relating to causality in ADHD with particular reference to evidence suggestive that heterogeneity exists not only at a clinical level but across all of the various levels of analysis.

Chapter 2

What causes AD-HKD?

From the discussion in Chapter 1 it will be clear that the AD-HKD phenotype is heterogeneous. As it is likely that this phenotypic heterogeneity is associated with an underlying causal heterogeneity, this Chapter will address current knowledge (and limitations) regarding the causes of AD-HKD. The discussion will be divided into two main sections addressing causal and mediating factors. The section considering causal factors will be subdivided into sections dealing with genetic and environmental factors and the section on mediating factors will be divided into sections addressing neuroanatomical, pathophysiological and neuropsychological factors.

Aetiology – Causal Factors

Genetic Factors

Behavioural Genetics

There is now considerable evidence from family, adoption and twin studies that AD-HKD is highly heritable (Thapar, O'Donovan, & Owen 2005). Estimates of heritability from parental ratings range from around 0.6 – 0.95 (Thapar et al. 1999; Thapar, O'Donovan, & Owen 2005) with a mean of 0.76 (Faraone et al. 2005) suggesting that AD-HKD is one of the most heritable psychiatric disorders. Almost all of the environmental impact appears to be a consequence of non-shared effects with a negligible contribution from shared environment. Interestingly the heritability estimates for teacher ratings are somewhat lower than those for parent ratings (Goodman & Stevenson 1989; Sherman, McGue, & Iacono 1997). It is not yet clear whether this is due to teachers and parents observing and

rating different behaviours, which have differing heritabilities, or as a consequence of various types of differential rater biases.

Levy, Hay and colleagues used a methodology originally described by DeFries & Fulker (DF method: 1985), which was developed to assess whether a variable should be seen as continuous or categorical to analyse data from a large twin Australian sample (Levy et al. 1997). The DF method involves asking three basic questions of the data: Can the score of one twin be predicted from that of the other (a measure of familiality)?; Is the accuracy of the prediction influenced by knowing whether the twin pair are identical or not (a measure of genetic effects)?; Is the heritability of the disorder the same as that of the trait (the category/continuum debate)? They concluded that the heritability of the disorder (0.91 ±0.12) and that of the trait (0.75 ±0.21) are not significantly different from each other, and that the heritability remains stable across the entire distribution of the trait. These results clearly suggest that AD-HKD should be considered the extreme end of a continuum rather than as a discrete entity. This has implications both for our conceptualisation of AD-HKD as a disorder and also for the predictions we will make regarding those aspects of the causal model, which sit between the genetic causes and the behavioural phenotype, as these would also be expected to be quantitatively rather than qualitatively different from the general population.

Hudziak and colleagues extended these findings (Hudziak et al. 1998). They conducted a latent class and factor analysis on a large (n = 1549) sample of female twins, which suggested the presence of three separate continuous domains; inattention, overactivity-impulsivity and combined inattention and overactivity-hyperactivity thus supporting the DSM-IV subtypes of AD-HKD and suggesting that each subtype may exist on a separate continuum.

Although comorbidity with a wide range of other disorders is frequent in children with AD-HKD, relatively few studies have investigated the potential genetic contributions to these various comorbidities. There is however data for some specific associations. Two groups have presented independent data, which suggests that shared genetic factors may account for at least some of the overlap between AD-HKD and reading disorder (Levy et al. 1995; Stevenson et al. 1993). There is also fairly strong evidence to suggest that the majority (93%) of the overlap between AD-HKD and oppositional defiant disorder and conduct disorder is due to common genetic influences with the remaining 7% being due to non shared environmental factors (Waldman et al. 2001).

Unsurprisingly, as a consequence of these behavioural genetic findings, there has been a fairly intensive interest in the molecular genetics of AD-HKD.

Molecular Genetics

Whilst the behavioural genetic approach can give indirect support for a genetic influence on a particular trait or disorder, molecular methods are required to provide direct evidence of genetic involvement. A range of methods are available, each of which tests for relationships between specific variations in DNA sequences and a phenotypic presentation. Unlike much of the other evidence discussed in this Chapter, these methods test for causality rather than association and address the hypothesis that a particular part of the genome causes at least a part of the phenotypic variation. The molecular genetics of AD-HKD has recently been reviewed (Coghill & Banaschewski 2009).

Molecular genetics methods can be broadly divided into tests of linkage and tests of association. Linkage methods are usually applied first to screen the genome broadly and identify loci that are exerting influence on a trait. Association methods are then applied, once the approximate locations of candidate loci are known, to identify the actual genes associated with the disorder. In AD-HKD research, however, the targets for association

studies have generally been chosen based on hypotheses and/or assumptions of the neurobiology of AD-HKD rather than as a consequence of the findings from linkage studies. This has led to a situation whereby replicated positive findings from the association studies are not always supported by the available data from linkage studies.

Linkage studies

Genetic linkage is said to occur when particular genetic loci or alleles for genes are inherited jointly with each other. Whilst the genetic material within the same chromosome tends to stay together during meiosis, and are therefore described as being genetically linked, there is however some crossing over of DNA within a chromosome, which occurs when the chromosomes segregate, and which can result in alleles on the same chromosome being separated and going to different daughter cells. The likelihood of a cross-over occurring depends on the distance between two alleles and is more likely to occur if the alleles are far apart on the chromosome. Linkage studies are used to broadly screen the genome to identify loci that influence a trait and thereby to identify which chromosomal regions contain the risk genes for a particular disorder. Linkage studies achieve this by using genetic markers, which are distributed as evenly as possible over the entire genome, and then identifying patterns of co-segregation between these markers and the disorder. If certain markers, which importantly are not necessarily either functional polymorphisms or etiologically relevant, are found to co-segregate with a disorder more often than would be expected by chance, it may be assumed that risk genes for that disorder are to be found somewhere within that chromosomal region. Although more powerful genetic techniques and larger studies are making it possible to use more, and therefore closer packed markers, it is still usual for each region to contain several hundred individual genes. These studies depend on powerful statistical techniques through which deviations from the expected probability for linkage are calculated as Logarithm of the

Odds (LOD Score) and which supply a reference to the strength of the linkage of a particular region with a particular disorder. LOD Scores larger than 3.3 are indicative of a clear linkage with LOD Scores between 2.2 and 3.29 being seen as suggestive for linkage (Schimmelmann et al. 2006). Unfortunately linkage studies are only useful at identifying genes that possess a substantial effect, i.e. usually genes, which account for more than 15% of the variance of the disorder and this limits their applicability to complex disorders like AD-HKD where the genetic effects are thought to be carried by several genes acting together, each of which is only contributing a small proportion of the variance.

To date seven whole genome linkage studies have been conducted in AD-HKD. Four affected sib pair linkage studies; two from the US (Faraone et al. 2008; Ogdie et al. 2003; Ogdie et al. 2004) one from the Netherlands (Bakker et al. 2003) one from Germany (Hebebrand et al. 2006) and one from across Europe (Asherson et al. 2008), one multiplex family study from Columbia (Arcos-Burgos et al. 2004) and one of eight, non-related, German origin extended family pedigrees (Romanos et al. 2008). Positive findings have been reported for some chromosomal regions (e.g. 5p13, 11q22-25, 17p11) across several independent studies. These replicated findings suggest that these regions may contain susceptibility genes for AD-HKD and that they should now be further fine-mapped in future studies. However no single region has been consistently identified in all of these studies and the majority of the positive findings have not yet been replicated. One interpretation of these results is that there are no single genes with strong effects for AD-HKD. These differing results could also be a consequence of the heterogeneity across the samples, which were recruited in different ways and from communities with very different ethnic backgrounds. However they could just as easily be accounted for by heterogeneity within the AD-HKD phenotype. This last hypothesis receives some support from the study of Bakker and colleagues (Bakker, van der Meulen, Buitelaar, Sandkuijl, Pauls, Monsuur, van

't, Minderaa, Gunning, Pearson, & Sinke 2003) who reported different results for groups with narrow and broadly defined AD-HKD. However these differences may have been somewhat exaggerated by relatively small sample sizes, which would reduce the probability of any particular sub-group of subjects, however defined, being adequately represented within the study population.

A recent meta-analysis of all seven AD-HKD linkage studies identified a region on chromosome 16 as having the most consistent linkage evidence (Zhou et al. 2008b). This region had the maximum rank in two scans with multipoint nonparametric LOD (MOD) = 3.1 in the Asherson et al. (2008) study and MOD global = 3.2 in the Romanos et al. (2008) study. Nine other regions (bins 5.3, 6.3, 6.4, 7.3, 8.1, 9.4, 15.1, 16.3, 17.1) were identified as having nominal linkage signals (P_{SR} <0.05) suggesting that at least some of these regions may contain genes for AD-HKD.

Furthermore, a region within the short arm of the chromosome 5, identified in the meta-analysis, is close to a region (5p13) identified by two of the linkage studies (Hebebrand, Dempfle, Saar, Thiele, Herpertz-Dahlmann, Linder, Kiefl, Remschmidt, Hemminger, Warnke, Knolker, Heiser, Friedel, Hinney, Schafer, Nurnberg, & Konrad 2006; Ogdie et al. 2006). Whilst it is unlikely that these two regions are the same, the finding is of interest as they contain the dopamine transporter gene (DAT1), which has been identified through association studies as being of potential importance in AD-HKD, and fine mapping of the DAT1 region has suggested that genetic variation in this gene could account for the linkage signal (Friedel et al. 2007; Ogdie, Bakker, Fisher, Francks, Yang, Cantor, Loo, van der, Pearson, Buitelaar, Monaco, Nelson, Sinke, & Smalley 2006).

Several of the AD-HKD linkage studies have suggested linkage in chromosomal regions, previously identified as potentially containing risk genes for autism, [16p, 15q (Bakker et al.

2005; Ogdie, MacPhie, Minassian, Yang, Fisher, Francks, Cantor, McCracken, McGough, Nelson, Monaco, & Smalley 2003; Smalley et al. 2002)] and/or for dyslexia [e.g. 1p, 14q, 13q, 15q, 16p, 17q, 20q (Bakker, van der Meulen, Buitelaar, Sandkuijl, Pauls, Monsuur, van 't, Minderaa, Gunning, Pearson, & Sinke 2003; Gayan et al. 2005; Loo et al. 2004; Zhou et al. 2008a)]. These findings raise the possibility that some risk alleles may have pleiotropic effects, i.e. are involved not only in the aetiology of the AD-HKD, but also that of other disorders (Jain et al. 2007).

Association Studies

Until now most of the molecular genetics research in AD-HKD has been based on association studies. In contrast to the explorative strategy inherent to linkage studies, association studies are designed to investigate whether specific allelic variants of putative candidate genes are associated with AD-HKD. Various types of allelic variants can be studied including those whereby individual nucleotides are exchanged (single nucleotide polymorphisms; SNPs) and those where a variable number of nucleotide sequences are repeated within the gene (variable numbers of tandem repeats; VNTRs). One advantage of the association study over the linkage studies is that they can identify genes with much smaller effects, which would not be possible to detect in a linkage study unless an often unrealistically large sample was collected. In general association studies need substantially more markers than for linkage studies (in the region of 500,000-1,000,000 single nucleotide polymorphisms (SNPs), if the whole genome is examined). This has the unfortunate additional effect of increasing the amount of multiple testing and the subsequent need for statistical adjustment (a p value of around 10^{-7} is required for gene wide significance). As a consequence multiple replication studies and meta-analyses are required to confirm novel association findings.

Traditionally candidate genes have been selected as a consequence of their having been suggested via linkage studies. However in AD-HKD an alternative strategy has predominated whereby candidate genes have been chosen due to their potential biochemical, physiological or pharmacological relevance. This approach to choosing candidate genes can be criticised from at least two perspectives. First the low prior probability for the involvement of any particular gene in a particular disorder has been likened to trying to find a needle in a haystack. In fact those warning against the "needle in a haystack" approach have been surprised by the success of studies to date. Second it has been argued that by choosing to focus on only one or two of the many potential genes of interest this approach could, if "successful", lead to an inappropriately rapid over-focusing on these genes at the expense of other, potentially more important, genes. Association studies on AD-HKD have focused so far particularly on genes involved in the monoamine neurotransmission (dopamine, serotonin and noradrenaline) and on genes involved in brain development maturation or in the modulation of neurotransmission and it is true that, even though this approach has had a degree of success, it may have resulted in other potential candidate genes being somewhat neglected. With the recent appearance of new technologies and gene wide association scans (GWAS) there is potential for a broadening out of focus to occur.

Gene wide association scans

Gene wide association scans (GWAS) extend the traditional candidate gene approach by scanning very large samples using either a case-control cohorts or family trio design, and utilising hundreds of thousands of SNP markers located throughout the human genome. Therefore in contrast to the candidate gene approach, a GWAS permits a comprehensive scan of the genome in an unbiased fashion and has the potential to identify novel susceptibility factors whilst retaining the benefits of association over linkage designs. Neale

et al. (2008) published the first GWAS for AD-HKD using families collected by the International Multicenter ADHD Genetics (IMAGE) project. They genotyped approximately 600,000 SNPs in 958 AD-HKD affected family trios. After data was cleaned a total of 438,784 SNPs were analysed using the transmission disequilibrium test (TDT[2]) in 2,803 individuals (909 complete trios), using the AD-HKD diagnosis as the phenotype. Unfortunately none of the SNP association tests achieved a genome-wide significance. This suggests that any risk variants for AD-HKD must have very small average effects at the population level with maximum odds ratios of around 1.3 – 1.4 and probably much smaller, and that much larger sample sizes are required. The authors suggest that sample sizes of between 10,000 and 20,000 will be required to accurately detect novel genes for AD-HKD using GWAS studies (Neale et al. 2008).

Candidate gene approaches

AD-HKD genetics is a rapidly developing field and it is therefore difficult to keep up with the expanding literature. However as independent replication is the key to demonstrating a clear effect it is possible to summarise current knowledge with respect to candidate gene approaches to a degree. The current literature is supportive of a small but significant effect for several genes and in particular those coding for the dopamine receptors DRD4 and DRD5, the dopamine transporter (DAT1), the serotonin HTR1B receptor, the serotonin transporter and synaptosomal association protein of 25,000 Daltons (SNAP-25), all of which have been examined in three or more studies and supported by meta-analyses. The odds ratios for these associations range between 1.1 and 1.5 (Coghill & Banaschewski 2009; Thapar, O'Donovan, & Owen 2005). The pooled odds ratios for these gene variants and

[2] The transmission disequilibrium test (TDT) provides a mechanism for avoiding population stratification biases that can occur in cases control genetic studies. In the TDT parents are used as the controls. Data is examined to see whether a particular allele is transmitted together with the disorder/trait more frequently than would be expected by chance. As it is guaranteed that cases and controls have originated from the same populations the stratification effects are avoided.

Dopamine β-Hydroxylase, for which there has been no meta-analysis but for which association has been shown in several independent studies, are shown in table 2.1. All of these odds ratios were significantly different from 1.0.

Table 2.1: Gene variants associated with AD-HKD. Pooled odds ratios for those gene variants for which there is evidence of a significant association with AD-HKD, which are supported by positive findings from a meta-analysis and/or three or more case-control or family-based candidate gene studies of AD-HKD.

Gene	Study Design	Pooled OR	95% CI
Dopamine D4 Receptor (exon III VNTR, 7 repeat)	Family	1.16	1.03-1.31
Dopamine D4 Receptor (exon III VNTR, 7 repeat)	Case-control	1.45	1.27-1.65
Dopamine D5 Receptor (CA repeat, 148bp)	Family	1.24	1.12-1.38
Dopamine Transporter (VNTR, 10-repeat)	Family	1.13	1.03-1.24
Dopamine β-Hydroxylase (Taql A)	Case-control	1.33	1.11-1.59
SNAP-25 (T1065G)	Family	1.19	1.03-1.38
Serotonin Transporter (5-HTTLPRlong)	Case-control	1.31	1.09-1.59
Serotonin HTR1B Receptor (G861C)	Family	1.44	1.14-1.83

OR, odds ratio; CI confidence interval; VNTR, variable number of tandem repeats
Redrawn from Faraone, Perlis, Doyle, Smoller, Goralnick, Holmgren, & Sklar 2005

DRD4 is the most studied of gene in AD-HKD and the one for which there is the strongest evidence for an association. Meta-analysis suggests that the 7 repeat allele is associated with an increased risk with an odds ratio (OR) of around 1.45 (95% CI 1.27 – 1.65; $p < 10^{-7}$) in case control studies and 1.16 (95% CI 1.03 – 1.31; p = 0.02) in family based studies (Faraone et al. 2001). It has been proposed that the 7 repeat allele is less effective at reducing cyclic AMP than the more common 4 repeat allele and this suggests a possible mechanism by which this gene variability can interfere with optimal dopaminergic neurotransmission (Asghari et al. 1995).

There is also strong evidence for an association between the 148 base pair allele of DRD5 and AD-HKD. Meta-analysis suggests an OR of 1.24 (95% CI 1.12 –1.38;$p < 10^{-4}$)(Lowe et al. 2004) however there is no evidence to support this allelic variation having any obvious functional significance, which mutes the significance of these findings somewhat.

There have been three meta-analyses of data relating to the 10 repeat allele in a VNTR in the 3'-UTR of the DAT 1 gene. The first two, based on 9 and 11 studies respectively, were suggestive of heterogeneity within samples but only trends for an association (Faraone, Perlis, Doyle, Smoller, Goralnick, Holmgren, & Sklar 2005; Maher et al. 2002). The most recent meta-analysis was based on an extension of the previous samples and reported a small but significant association odds ratio of 1.13 (95% CI 1.03 – 1.24)(Faraone, Perlis, Doyle, Smoller, Goralnick, Holmgren, & Sklar 2005). There is some evidence from a single study that the 10 repeat allele may be associated with increased amounts of DAT1 protein (Heinz et al. 2000), which would be compatible with increased dopamine clearance and therefore be of potential importance in the pathophysiology of AD-HKD.

SNAP-25 is a membrane bound protein that plays an important role in the development of axons, synaptic plasticity and the release of neurotransmitters from neural vesicles into the

synaptic gap. Variations in the SNAP 25 gene have been reported to be associated with AD-HKD in several studies. A meta-analysis of family based studies conducted in 2005 reported a slightly increased risk (pooled odds ratio: 1.19) (Faraone, Perlis, Doyle, Smoller, Goralnick, Holmgren, & Sklar 2005). Since then several further studies, both supporting (Choi et al. 2007; Kim et al. 2007) and not supporting (Renner et al. 2008) an association, have been reported in family based studies.

Meta-analysis has also supported an association between AD-HKD and a 44-base-pair insertion/deletion (5-HTTLPR) in the promoter region of the serotonin transporter gene (5HTT); this insertion/deletion causes long or short alleles, whereby the long variant is coding a functionally more active transporter (pooled odds ratio: 1.3) (Faraone, Perlis, Doyle, Smoller, Goralnick, Holmgren, & Sklar 2005). However, although there have been further replications since this meta-analysis (Kopeckova et al. 2008; Li et al. 2007; Retz et al. 2008), several studies have failed to replicate these (Brookes et al. 2006a; Grevet et al. 2007; Mick & Faraone 2008; Wigg et al. 2006; Xu et al. 2008) and others have found a reversed association (Li, Wang, Zhou, Zhang, Yang, Wang, & Faraone 2007) or that the association for 5-HTTLPR was only significant when paired with an intron-2 (STin2) polymorphism (Banerjee et al. 2006), whilst the intron-2 (STin2) polymorphism was associated with AD-HKD.

There are also contradictory findings with respect to the serotonin HTR1B receptor. A meta-analysis supported an association between the HTR1B-receptor gene and AD-HKD (pooled odds ratio: 1.44; (Faraone, Perlis, Doyle, Smoller, Goralnick, Holmgren, & Sklar 2005)) and, whilst there are subsequent replications for HTR1B (Hawi et al. 2002; Quist et al. 2003), there are also negative findings (Brookes, Xu, Chen, Zhou, Neale, Lowe, Anney, Franke, Gill, Ebstein, Buitelaar, Sham, Campbell, Knight, Andreou, Altink, Arnold, Boer, Buschgens, Butler, Christiansen, Feldman, Fleischman, Fliers, Howe-Forbes, Goldfarb,

Heise, Gabriels, Korn-Lubetzki, Johansson, Marco, Medad, Minderaa, Mulas, Muller, Mulligan, Rabin, Rommelse, Sethna, Sorohan, Uebel, Psychogiou, Weeks, Barrett, Craig, Banaschewski, Sonuga-Barke, Eisenberg, Kuntsi, Manor, McGuffin, Miranda, Oades, Plomin, Roeyers, Rothenberger, Sergeant, Steinhausen, Taylor, Thompson, Faraone, & Asherson 2006a; Ickowicz et al. 2007).

Whilst there is no meta-analysis for the dopamine β-hydroxylase gene, there are independent replicated findings. Dopamine β-hydroxylase is the primary enzyme responsible for the conversion of dopamine to noradrenaline. Several case-control and family studies have found a significant association between the Taq1 A polymorphism of the dopamine β-hydroxylase gene and AD-HKD (Barkley et al. 2006b; Bellgrove et al. 2006; Daly et al. 1999; Roman et al. 2002; Smith et al. 2003). However, there were differences between studies, with increased risk being associated in some studies with the A2 allele, and in others with the A1 allele (Mick & Faraone 2008; Waldman & Gizer 2006). The functional significance of these polymorphisms is not known.

It is unlikely that the genes already identified are the complete picture. There are current reports supporting the involvement of a wide range of other genes including the noradrenergic receptors ADRA2A and 2C (Comings et al. 1999; Comings et al. 2003), the noradrenaline transporter (Comings et al. 2000b), tryptophan hydroxylase (Li et al. 2003), the acetylcholine receptors CHRNA4 and A7 (Comings et al. 2000a; Kent et al. 2001; Todd et al. 2003) and the NMDA receptor (Turic et al. 2004). These findings are all currently un-replicated, and for some, attempts at replication have been unsuccessful. However, in this fast moving field it is likely that some of these will soon find replications and also that other genes will soon be implicated.

Taken together, these findings of small but significant increased odds ratios for several genes are consistent with the hypothesis that AD-HKD is a heterogeneous disorder and suggest that the genetic causality of AD-HKD is likely to be polygenic in nature i.e. AD-HKD is mediated by several genes each of relatively small effect (Faraone, Perlis, Doyle, Smoller, Goralnick, Holmgren, & Sklar 2005). This may help to explain the frequent failure to replicate findings that have dogged this area of investigation. Genetic studies already require very large samples to ensure that they are adequately statistically powered. Such heterogeneity alongside a polygenic causality will clearly require even larger studies than would be the case for a disorder where only a few genes are involved, each of which has a large effect. As a consequence there has been a move towards pooling data sets, conducting meta-analyses and designing large collaborative studies to ensure that sample sizes are large enough to test hypotheses (Faraone 2003; Kuntsi et al. 2006; Manolio et al. 2007).

In addition, and relevant to the topic of this thesis, the utilisation of sampling techniques, which can reduce heterogeneity and result in a more refined phenotype or endophenotypes, may be helpful. Although subgroups for such analyses have not been defined, promising delineations may include subtypes defined by symptom profiles, comorbidity, course and persistence, brain imaging findings or patterns of neuropsychological deficit, each of which could potentially reduce the required sample size significantly. To this end there is increased interest in the use of endophenotypes in molecular genetic studies. These are discussed in greater detail in Chapter 3.

Gene Environment Interplay

It is often assumed that the heritability of around 0.76, taken together with an almost negligible level of shared environmental effects, implies that the only environmental effects to be accounted for in the causality of AD-HKD are the non-shared environmental

effects that make up the remaining 24% of the risk. Such an account, however, fails to acknowledge the potentially large contribution likely to be made by gene - environment interplay, a considerable proportion of which may be "hidden" within the estimate of heritability. There are two main mechanisms by which genes and the environment interplay; gene environment interactions and gene environment correlations. Both may play a part in the causality of AD-HKD.

Gene-Environment Interactions

Gene-environment interactions (often abbreviated to G x E interactions) occur when there is a genetic sensitivity to a particular environmental effect or when an environmental factor activates a genetic effect, which would otherwise remain dormant. Non AD-HKD examples include the now classic findings of Caspi and colleagues (2002b), which is referred to again in Chapter 9. They studied a large sample of boys from birth to adulthood and investigated why some children who are maltreated grow up to develop antisocial behaviour, whilst others do not. They identified that a functional polymorphism in the gene encoding monoamine oxidase A (MAOA) moderated the effects of maltreatment. Those maltreated children with a genotype that conferred high levels of MAOA expression were less likely to develop antisocial problems than those with a genotype resulting in low MAOA expression. The same group also identified a similar G X E interaction between stressful life experiences, a functional polymorphism of the gene encoding for the serotonin transporter (5-HT-T) and the risk of developing depression. Individuals with either one or two copies of the short allele of the 5-HT T promoter polymorphism exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than individuals homozygous for the long allele (Caspi et al. 2003).

As both of these examples involve relatively uncommon environmental factors these effects would, in behavioural genetic studies, probably have appeared within the model as

non-shared environmental effects However where the interaction is between a genotype and a relatively common environmental risk factor the effects will be “hidden” in the heritable effects (Purcell 2002). For example, if one assumes that an almost ubiquitous environmental factor such as pollen interacts with a specific genetic variant to cause an effect, e.g. hay fever, then monozygotic twins would tend to both be affected together more frequently than dizygotic twins and in the context of a twin study this effect would be hidden in the heritable portion of the variance.

Clearly, such interactions are important when interpreting the estimates for heritability and environmental effects for AD-HKD derived from twin studies and incorporating these into the development of potential causal models. Without this information, the potential impact of environmental factors can be seriously underestimated, as many are prone to do with respect to AD-HKD.

It is very likely that there are G x E interactions in AD-HKD similar to those described above, and whilst some of these will involve uncommon environmental risk factors, others will involve more common environmental factors with their impact being hidden within the heritability estimates. Whilst G x E research in AD-HKD is still in its infancy, several G x E interactions have received some research attention.

Maternal smoking during pregnancy: Several groups have identified interactions between dopaminergic genes and parental smoking. Kahn et al. (2003) found that children who were both exposed prenatally to smoke and who were homozygous for the 480-bp DAT allele (DAT +/+) had significantly elevated hyperactive-impulsive scores compared with children with no smoke exposure and who were either DAT +/- or -/-. Neither prenatal smoke exposure alone nor DAT +/+ genotype alone was significantly associated with increased scores (Kahn et al. 2003). Neuman et al (2007) assessed the relationship between ADHD subtypes, DAT1 and DRD4 polymorphisms, and prenatal substance exposures in a birth-

record sample of male and female twin pairs, aged 7-19 years. They reported interactions between prenatal exposure to smoking and variations in both DAT1 and DRD4 loci in children with either the DSM-IV or population-defined ADHD combined subtypes. The odds of a diagnosis of DSM-IV combined subtype ADHD was 2.9 times greater in twins who had inherited the DAT1 440 allele and who were exposed, than it was in unexposed twins without the risk allele. The Odds ratio for the DRD4 seven-repeat allele was 3.0. The Odds ratio for exposed children with both alleles was 9.0 (Neuman et al. 2007). Langley et al. (2008) investigated the interactions between various gene variants (DRD4, DAT1, DRD5 and 5HTT) and several environmental factors (smoking and alcohol use during pregnancy, and birth weight). Maternal smoking was found to interact with DRD5 (but not DRD4) and antisocial behaviour but not ADHD itself (Langley et al. 2008). Todd et al. (2007) found that an exon 5 polymorphism in the CHRNA4 gene interacted with prenatal smoking to increase the risk for severe combined type ADHD.

Maternal alcohol use during pregnancy: Brookes et al. (2006b) reported an association between AD-HKD, the intron 8 polymorphism of the DAT1 gene, and a specific risk haplotype in both English and Taiwanese samples, which showed significant interactions with maternal use of alcohol during pregnancy. Langley et al (2008) were unable to replicate these findings in an independent sample and did not find an interaction between alcohol use during pregnancy and the other three gene variants studied (DRD4, DRD5 and 5HTT) (Langley, Turic, Rice, Holmans, Van den Bree, Craddock, Kent, Owen, O'Donovan, & Thapar 2008).

Low birth weight: In the study described above Langley et al. (2008) did find an interaction between birth weight and both DRD5 and DAT1 with respect to antisocial behaviour but not ADHD itself (Langley, Turic, Rice, Holmans, Van den Bree, Craddock, Kent, Owen, O'Donovan, & Thapar 2008). Thapar et al. (2005) investigated the interactions between

COMT Val108/158Met gene and birth weight with respect to the presence of antisocial behaviours in a group of individuals with AD-HKD. They found main effects of the COMT gene variant and birth weight and also a significant G x E (COMT x birth weight) interaction such that those possessing the Val/Val genotype were more susceptible to the adverse effects of low birth weight. Sengupta et al. (2006) were unable to replicate these findings in an independent sample.

Psychosocial adversity: Laucht et al. (2007) reported that adolescents homozygous for the 10-repeat allele of the 40-bp VNTR polymorphism of the DAT1 gene who also grew up in greater psychosocial adversity exhibited significantly more inattention and hyperactivity-impulsivity than adolescents with other genotypes or who lived in less adverse family conditions. This G x E interaction was also observed in individuals homozygous for the 6-repeat allele of the 30-bp VNTR polymorphism of DAT1 and in the haplotype comprising both markers (Laucht et al. 2007). Two groups have investigated the interaction between serotonin transporter polymorphisms and adversity in AD-HKD populations. Retz et al. (2008) found that carriers of at least one 5HTTLPR short allele are more sensitive to the effects of childhood adversity than those carrying the LL-genotype. These effects were supported by those of Muller et al. (2008) who also found the short allele to be associated with increased vulnerability to early stressors in an adult sample.

Sonuga-Barke et al. (2008) investigated the moderation of genetic effects in AD-HKD by maternal expressed emotion using data from the gene wide association scan conducted on the IMAGE sample. Although none of the G x E interactions reached genome wide significance, several nominal effect were found both with and without genetic main effects. The observed interactions between both the solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), member 1gene (SLC1A1) and the NRG3 gene and conduct disorder symptoms were felt to represent the most likely candidate

genes for further study (Sonuga-Barke et al. 2008). Waldman (2007) investigated the relationship between the mother's marital stability and the variants of DRD2 gene. Significant interactions were found between the child's DRD2 genotype and the mother's marital status and number of marriages or cohabiting relationships.

These studies clearly need to be replicated in independent, and larger, samples. However they do suggest that at least some of the heritability of AD-HKD may be attributable to G x E interactions, although how much of the observed heritability is the result of "pure" genetic effects and how much to common environmental factors operating through G x E interactions is still unclear. Other potentially important environmental risk factors and genes still need to be investigated.

Gene Environment Correlations

The second type of gene – environment interplay is the gene environment correlation (abbreviated to (G)(E) correlations). This takes into account the fact that parents pass on both genes and environment to their children and that these two factors are often correlated with each other, making their impact on the child difficult to separate. Here, the misattribution of causal effects is in the opposite direction to those seen with G x E interactions. Where there is a correlation between genes and shared environment the genetic effects are "hidden" within the shared environment term derived from behavioural genetic studies and where there is a correlation between genes and non-shared environment, the environmental effects will be subsumed within the heritability term (Purcell 2002).

Scarr and McCartney (1983) proposed three different types of (G)(E) correlations.

- "Passive" (G)(E) correlations; where parents pass on both genes and environment to their children (e.g. the children of intelligent parents are likely to receive both

the genes associated with higher intellectual abilities and an environment conducive to learning)

- "Evocative" (G)(E) correlations; Where the child's genetic makeup leads to them eliciting a particular type of response from others thus creating a particular type of environment around themselves (e.g. a loud demanding child is likely to elicit more negative responses from others than a more passive quiet child)

- "Active" (G)(E) correlations; Individuals select their environments according to their temperaments (e.g. the impulsive, risk-taking child may be drawn to a more risk-taking peer group and therefore be exposed to more dangerous situations than would the more fearful child)

Whilst it is easy to predict that many such (G)(E) correlations may occur for children with AD-HKD there has been little formal study and associations remain speculative. (G)(E) correlation studies are complex, difficult to design and execute, and require large sample sizes (Eaves & Erkanli 2003; Turkheimer et al. 2005). Both evocative and passive (G)(E) correlations can be expressed through a child's interpersonal relationships and social experiences (Nigg 2006, page 213). It is possible that the resulting sub-optimal parent-child interactions could then influence the development of self control, executive functioning and emotional reactivity and thus the development of AD-HKD. These effects, if occurring through (G)(E) correlations, would not be expected to impact on the estimates of heritability from behavioural genetic studies.

Whilst (G)(E) correlations have not yet been clearly demonstrated in AD-HKD there is evidence to suggest that the child's behaviour does impact on the type of parenting that is delivered (i.e. a potential evocative (G)(E) correlation). Barkley and Cunningham (1979) demonstrated that when children were successfully treated with stimulant medication, and

their AD-HKD symptoms were less apparent, their parents were more effective caregivers than they had been previously when the children were unmedicated.

Environmental Factors

Environmental factors constitute the other class of potentially causative agents. It is clear from the above discussion that not only should we look at which environmental factors contribute to the 24% of the propensity to develop AD-HKD, which the behavioural genetic studies have attributed to non-shared environmental factors, but also those environmental factors, which may contribute to both G x E interactions and (G)(E) correlations.

Johnston and Mash (2001b) suggested several potential avenues of enquiry requiring further study in AD-HKD with respect to their impact on child development, including parenting styles, parent –child conflict, marital / couple conflict and parental psychopathology. As there is little evidence to evaluate these at present, they will not be considered further in this thesis.

Nigg (2006) has separated potential environmental factors into two groups, common and uncommon. The uncommon environmental risk factors could potentially have either direct effects as non-shared environmental factors or be involved in G x E interactions (in which case the genetic component would be hidden in the non-shared environmental risk). The common environmental risk factors are unlikely to appear as non-shared risks, and therefore, as there are negligible shared environmental effects, they are more likely to be acting via G x E interactions and their effects hidden within the heritability estimates.

Relatively uncommon environmental risks for which there is at least some supportive evidence include; low birth weight, prenatal exposure to teratogens such as alcohol and nicotine, high levels of exposure to lead and other toxic substances, and exposure to serious psychological trauma or severe early deprivation.

Relatively common environmental risk factors include dietary factors including food additives, omega-3 fatty acid deficiency and organophosphate pesticides, low level exposures to lead and other heavy metals and environmental toxins such as persistent organic pollutants such as polychlorinated biphenyls.

Low Birth Weight

As antenatal care has improved over time the risk of being born with a "very low" (<1,500 grams) or an "extremely low" (< 1,000 grams) birth weight has increased considerably. This group of children are at risk for a broad range of difficulties including cerebral palsy, low IQ and various neurological and neuropsychological problems including spatial, motor and verbal deficits (Hack et al. 2004). Several studies suggest that even when these other negative outcomes are controlled for, low birth weight children remain at increased risk for AD-HKD, that this risk is greater than the risk for other psychiatric disorders (e.g. Mick et al. 2002; Pinto-Martin et al. 2004) and that the increased risk does not diminish when genetic effects are controlled for (Hultman et al. 2007; Lehn et al. 2007). Together these findings suggest that low birth weight represents a modest but consistent environmental influence on the development of AD-HKD. Nigg (Nigg 2006; pages 228 - 229) has calculated that as many as 12.8% of AD-HKD cases could be a consequence of low birth weight.

Low birth weight is, of course, itself multiply determined with causes including poor maternal health and nutrition, significant maternal stress during pregnancy, nicotine or cigarette use, and alcohol, or other substance misuse during pregnancy (Chomitz, Cheung, & Lieberman 1995). Chomitz and colleagues estimated that, of these, smoking during pregnancy is both the greatest known risk factor and the most preventable cause of low birth weight in developed countries. They suggested that around 20% of all low birth weight could be avoided if women did not smoke during pregnancy. Low birth weight is also associated with motor control problems (Hack, Klein, & Taylor 1995) and it is possible

that these cases account, at least in part, for the motor control problems noted in samples of children with AD-HKD. Low birth weight does not account for some of the other neuropsychological deficits found in AD-HKD samples, such as problems with alerting (Potgieter, Vervisch, & Lagae 2003). However, this is an area in which there has been relatively little research interest and requires further study.

Prenatal Exposure to Alcohol

Heavy alcohol use during pregnancy has well recognised teratogenic effects (Stratton, Howe, & Battaglia 1996). First described in the early 1970s, foetal alcohol syndrome is defined by the characteristic facial dysmorphologies and is accompanied by a range of neurological signs, language and cognitive delays and increased levels of hyperactivity and impulsivity. Even though there may be an association between foetal alcohol syndrome and some cases of AD-HKD, the two are distinct conditions. Foetal alcohol syndrome is relatively uncommon with an incidence of between 0.3-1.4 per 1000 live births (Meaney & Miller 2003) and most cases of AD-HKD do not meet criteria for foetal alcohol syndrome. More recent study has concentrated on the potential effects of lower-level effects that fall short of full blown foetal alcohol syndrome. These have been termed foetal alcohol effects or more recently foetal alcohol spectrum disorders (Stratton, Howe, & Battaglia 1996). These continue to require heavy maternal drinking during pregnancy (> 5 units of alcohol per day, or heavy weekend binge drinking) but include those who do not have any physical abnormalities. Five categories have been defined ranging from category 1; classic foetal alcohol syndrome to category 5; foetal alcohol syndrome with alcohol related neurodevelopmental disorder where there are no physical abnormalities but there is either CNS abnormalities (e.g. language, motor, cognition) or complex behavioural/cognitive problems (Stratton, Howe, & Battaglia 1996). This clearly represents a much broader group and the prevalence of all five categories together is estimated at just under 1% of live births (Sampson et al. 1997). It has been speculated that around 40% of these children may

develop AD-HKD (Koren et al. 2003). Taking other factors into account, Nigg estimates that this would equate to between 2 – 3% of all AD-HKD cases (Nigg 2006, page 232).

Links between AD-HKD and lower levels of drinking during pregnancy have been much more difficult to establish. Linnet and colleagues systematically reviewed the literature on maternal lifestyle factors during pregnancy and risk of developing AD-HKD (Linnet et al. 2003). They identified 9 studies that investigated relationships between alcohol use during pregnancy and AD-HKD, five of which failed to find an association. Relatively few studies have directly compared the neuropsychological performance of children exposed to alcohol during pregnancy with that of children with AD-HKD. There are however, some studies, which suggest similarities between the two groups (e.g. Burden et al. 2005; Coles et al. 2002), but differences have also been reported (e.g. Coles et al. 1997).

It therefore remains unclear what proportion of children whose mothers consumed low to moderate amounts of alcohol during pregnancy develop behaviour problems, which are severe enough to call AD-HKD, and whether the neuropsychological deficits caused by alcohol intake during pregnancy are similar enough to AD-HKD to create a phenocopy. It is, however, possible that where exposure to alcohol during pregnancy does contribute to the development of AD-HKD, that these children will have a different profile of neuropsychological deficits to those whose AD-HKD is caused by other factors and as such, alcohol exposure may make some contribution to the heterogeneity found within AD-HKD samples.

Prenatal Exposure to Nicotine

Prenatal exposure to nicotine is a well established risk factor for a range of childhood developmental problems (Ernst, Moolchan, & Robinson 2001) and there have been many suggestions that it may play a role in the development of AD-HKD. Smoking during pregnancy is still relatively common with most recent survey findings in the UK suggesting that just over a third of mothers (34%) in the United Kingdom smoked before or during their pregnancy, with a fifth (20%) continuing to smoke throughout their pregnancy (Hamlyn et al. 2002). It follows that if smoking was found to be causal in the development of AD-HKD it would represent a significant preventable risk factor. Further, if the pattern of AD-HKD consequent to prenatal nicotine exposure differs to that associated with other causal factors, it could contribute to the heterogeneity within AD-HKD samples. As prenatal nicotine exposure has been found to be associated with a range of adverse developmental outcomes including low birth weight and aggressive behaviours it is important to first account for these potentially confounding factors when assessing the evidence for a link between maternal smoking and AD-HKD. Similarly, it is possible that maternal smoking itself may be a consequence of certain maternal characteristics such as socioeconomic status, depression, alcohol and drug misuse and, maybe most importantly, maternal AD-HKD, each of which could also be a cause of increased rates of AD-HKD in the child. The results described below also need to be considered in light of the positive findings for G x E interactions described previously.

Linnet and colleagues (2003) reviewed 24 studies of maternal smoking and child AD-HKD and concluded that a link between maternal smoking and AD-HKD was likely on the basis of several well controlled replications, including both prospective population studies and retrospective case controlled studies. This is an association, which holds even when low socioeconomic status, maternal IQ, low birth weight, and some aspects of maternal mental illness are controlled for. However, they were unable to comment on the potential role of

maternal AD-HKD, which had not been measured. In their own study the same group used a nested case-control design to investigate the contribution of maternal smoking to the development of AD-HKD in a sample of 170 Danish children with hyperkinetic disorder and 3765 population-based control subjects (Linnet, Dalsgaard, Obel, Wisborg, Henriksen, Rodriguez, Kotimaa, Moilanen, Thomsen, Olsen, & Jarvelin 2003). Women who smoked during pregnancy had a 3-fold increased risk for having offspring with hyperkinetic disorder (HKD) compared with non-smokers. Socioeconomic factors and history of mental disorder (maternal AD-HKD was not measured) in the parents or siblings seemed to confound the result to some extent (adjusted relative risk: 1.9; 95% confidence interval: 1.3-2.8). Adjustment for parental age or exclusion of children with low birth weight (<2500 g), preterm delivery (<37 weeks completed gestation) and Apgar scores <7 at 5 minutes did not alter the findings. Neither did excluding children with conduct disorders or comorbid disorders.

It is unfortunate that few studies have specifically controlled for the confounding of this association by parental AD-HKD. Such interactions could be mediated in several ways. For example women with AD-HKD could tend to smoke more often which could increase the risk of AD-HKD in the child, thus contributing to the observed familial nature of AD-HKD. Alternatively, smoking could act as a non-causative correlate of the genetic transmission of AD-HKD, as seems to be the case for the association between parental smoking during pregnancy and antisocial behaviour in the child where increased risk seems to be accounted for by the child's genetic inheritance of the mother's antisocial traits rather than as an effect of the smoking (Silberg et al. 2003). Whilst studies investigating the role of AD-HKD as a risk factor for smoking are not conclusive, they do seem to suggest that smoking is predicted to a far greater extent by antisocial behaviours than AD-HKD symptoms, but that AD-HKD does have an independent impact even when antisocial behaviours are controlled

for (Milberger et al. 1997). Taken together it would seem that, whilst AD-HKD does contribute to smoking in parents, it is not the main driver. Even so it is important to consider evidence from genetically informative studies that control for both parental AD-HKD and antisocial behaviours, which can verify that the effects noted above are not a consequence of gene environment correlations by which AD-HKD or AD-HKD and antisocial traits in parents are passed on to children with both parents and children more likely to smoke.

Unfortunately very few such studies have been reported. Milberger and colleagues described a clinical series (Milberger et al. 1996) and a series of siblings of AD-HKD boys (Milberger et al. 1998). In both samples maternal smoking predicted AD-HKD even when maternal AD-HKD was controlled for (Odds ratios AD-HKD boys study = 2.7, Sibs of AD-HKD boys study = 4.4). These studies did not however control for maternal antisocial behaviour or alcohol use and were not genetically informative. Thapar and colleagues studied 1,452 twin pairs in a UK sample (Thapar et al. 2003). Whilst genetic factors explained most of the AD-HKD symptom variance, maternal smoking during pregnancy continued to make an independent contribution after these genetic effects and other environmental confounds were controlled for. Smoking independently contributed about 1% of the risk and may have made additional contributions through its effect on low birth weight. Unfortunately this study did not measure maternal AD-HKD.

In conclusion, a link between maternal smoking during pregnancy and AD-HKD in the offspring of that pregnancy has withstood scrutiny to date, there is evidence supporting G x E interactions and a small independent environmental effect. Whether this effect is differentially mediated by any particular neuropsychological effects is not yet known.

Prenatal Maternal Stress

The possibility that prenatal maternal stress levels could contribute to the development of AD-HKD has not been well studied. However a recent systematic review, which included four studies addressing AD-HKD symptoms, found a robust association between prenatal maternal stress and AD-HKD symptoms (Talge, Neal, & Glover 2007). These effects were independent of postnatal depression and anxiety. Unfortunately most studies have failed to control for other important factors such as maternal smoking and alcohol use during pregnancy or parental AD-HKD (Linnet, Dalsgaard, Obel, Wisborg, Henriksen, Rodriguez, Kotimaa, Moilanen, Thomsen, Olsen, & Jarvelin 2003). However, when these factors were controlled for, O'Conner et al. (2002) still found an association between self reported maternal prenatal stress and maternal reported AD-HKD symptoms at 4 years of age. Van den Bergh and colleagues found that even after controls for postnatal anxiety, cigarette use during pregnancy and birth weight, high levels of prenatal anxiety predicted AD-HKD symptoms at 8-9 years of age (Van den Bergh & Marcoen 2004) and performance on a continuous performance task, an objective measure of sustained attention/self-regulation, at age 15 years (Van den Bergh et al. 2006). Therefore despite a relative lack of data these promising early findings suggest that this is an area which requires further investigation. The proposed mechanism would be for maternal stress to result in the developing foetus being exposed to increased levels of cortisol, which in turn could alter neurotransmission and influence brain development. This is supported by both animal and human studies, which suggest a link between the stress-responsive hypothalamic-pituitary-adrenal axis and its hormonal end-product cortisol, which can affect the serotonergic system and interfere with neurone development (Talge, Neal, & Glover 2007).

Pre and Postnatal Exposure to Heavy Metals

Exposure to high levels of lead, mercury or other heavy metals have been known to result in a range of cognitive, motor and sensory impairments for many years (Needleman et al. 1979; Rice et al. 1996).

Lead

Although lead poisoning due to exposure has decreased considerably in many developed countries in recent years, high level exposure remains very common in children in developing countries (Fewtrell et al. 2004). Animal studies have identified a causal role for high lead exposure in the development of several cognitive deficits, including the management of reward delay (Brockel & Cory-Slechta 1998), attentional processes (Bellinger et al. 1994), poor impulse control and temporal management (Cory-Slechta 2003). Interestingly, in the same study Cory-Slechta (2003) noted that neither memory nor vigilance task performance were impaired by high exposure to lead. These findings suggest the possibility that the AD-HKD associated with exposure to high lead levels may be expected to be associated with impulsivity and problems with reinforcement learning rather than memory or executive functioning deficits. Notwithstanding these findings, most of the studies that have investigated behavioural outcomes of high lead exposure have focused on antisocial behaviour rather than AD-HKD symptoms and specific data on the association with AD-HKD is sparse. However, it has become clear over time that serious negative consequences can actually arise secondary to much lower levels of exposure to lead than had originally been thought. This has led to a series of studies that have investigated the consequences of exposure to "low level" lead, with each level that is studied (starting with levels < 10mcg/dl and decreasing from this) having been found to be associated with neural damage. This has increased the urgency to understand the relationship between such low level exposure and neurological and behavioural consequences as many children are currently exposed to such levels. For example, if a level

of 5mcg/dl is taken as a cut-off, 25% of children between the ages of 1 and 5 years are above the cut-off. This proportion reaches almost 50% in some ethnic and cultural groups such as African Americans and those living in older housing (Bernard & McGeehin 2003).

There is evidence to suggest cognitive deficits including executive functioning problems and impulsivity, as well as AD-HKD, increase with exposures to lead, even at these lower levels. Thomson and colleagues (1989) reported a dose relationship between blood lead levels and teacher rated hyperactivity in a general population sample of Edinburgh schoolchildren. Tuthill (1996) showed a dose response relationship between hair lead levels (from 1 – 11.3 parts per million) and both an AD-HKD diagnosis and teacher rated attention problems. More recently associations have been reported between low level lead exposure and a range of laboratory measures, including impulse control and reinforcement learning (but not set-shifting) (Canfield et al. 2003), the spatial working memory, attention set-shifting and planning tasks of the Cambridge Neuropsychological Testing Automated Battery (CANTAB) (Canfield, Gendle, & Cory-Slechta 2004) and reaction time and set-shifting (Minder et al. 1994). Chiodo and colleagues (2004) studied a group of children with very low lead levels (mean 5mcg/dl) and found an association between lead levels and inattentive but not hyperactive impulsive symptoms. They also found an association between lead levels and visual-motor ability and short term non working memory (digit span) but not on set-shifting or commission errors on a continuous performance task. Further analysis of the data suggested that there was no safe lower limit for these effects. Again, these findings both support a possible association between AD-HKD, neuropsychological deficits and low lead exposure and suggest low lead exposure as a potential causal candidate for the heterogeneity within AD-HKD samples. It is possible that different levels of exposure are related to different neuropsychological deficits, however this hypothesis has not been fully tested It is also possible that subsets of children, possibly

those with a particular genetic profile, would be more sensitive to the effects of low level lead than others. Nigg has calculated that if a twofold risk of AD-HKD was associated with lead levels above 5mcg/dl, low level lead exposure could account for 25% of the cases of AD-HKD in the United States. Even a more conservative increase in risk of between 25-50% could still account for between 6 and 12% of cases, which would be potentially preventable (Nigg 2006, page 250).

Mercury

Mercury is amongst the most common chemical toxins that children are exposed to. Although it is no longer widely dispersed by car exhaust fumes, it is still present in the waste gasses expelled by coal-fired power plants and waste incinerators. From here it settles in soil and water and can therefore reach children through the air, water and food, especially fish. Mercury has been demonstrated to have neurotoxic effects following exposure, both pre- and postnatally (Myers & Davidson 2000; Williams & Ross 2007). As with lead the "safe" exposure limits for mercury have been brought down considerably over time. In the 1970s postnatal levels below 34mcg/kg/day were considered safe however now the published safe levels range between 0.1 and 1.0 mcg/kg/day (Stein et al. 2002). Prenatal exposures in the range of 0.8mcg/day appear to result in deficits in language, memory and attention (Grandjean et al. 1997). Data specifically linking mercury to AD-HKD are lacking. However, a link is plausible and as in the United States 7% of women of childbearing age and 20% of children are estimated to be above the recommended safe limits (Schettler 2001), mercury exposure could potentially make a significant contribution to the incidence of AD-HKD.

Manganese

Manganese, at high exposure levels in rodents, results in damage to the striatum with an initial hyperactivity and subsequent Parkinson's like motor problems (Centonze et al. 2001).

Exposure at lower levels can lead to more subtle effects with a reduction in striatal dopamine levels, reduced working memory and deficits in avoidance learning (Tran et al. 2002). Exposure is generally through exhaust fumes and soy based infant milk formula, which can contain 50x greater levels of manganese compared to breast milk. However, at the current time any link between manganese and AD-HKD remains theoretical and awaits further study.

Persistent Organic Pollutants

The persistent organic pollutants (POPs) compromise a group of industrial compounds including more than 200 different polychlorinated biphenyls (PCBs) and related compounds such as polybromated biphenyls (PBBs), dichlorodiphenyldichloroethylene (DDE), dichlorodiphenyltrichloroethylene (DDT) and many other chemicals. The production of these compounds has been banned since the 1970s. However, as they are characterised by their extreme persistence, they remain present in significant quantities in the environment and they tend to move from the soil and water into aquatic life and from here pass through the food chain increasing in concentration as they do. They are lipophilic with long half-lives and once they enter the body, they remain for considerable lengths of time (Matthews & Dedrick 1984). Significant quantities of PCBs have been found in several human tissues including adipose tissue, blood, the placenta and breast milk (Longnecker, Rogan, & Lucier 1997). It is well established that high exposure to POPs can result in cognitive delays. However, it also possible that low level background exposures at levels that would make exposure almost ubiquitous in modern society, may also result in more subtle cognitive and behavioural deficits (Rice 1997b). One postulated mechanism of action suggests that occupation of the oestrogen receptor by POPs disrupts endocrine activity, which in turn impacts negatively on brain development (Bonefeld-Jorgensen et al. 2001). If true, this may provide a partial explanation for the gender differences in AD-HKD. Another

potential mechanism involves disruption of the thyroid during foetal development (Osius et al. 1999), which may have neurotoxic and neurodevelopmental consequences.

Animal studies have confirmed a causal link between exposure to moderate levels of the POPs and a range of cognitive deficits, in particular, deficits have been identified in working memory and reinforcement learning (Rice 1997a; Rice & Hayward 1997). These findings are consistent with a preferential impact of POPs on dopamine dependent prefrontal cognitive abilities. As was suggested by Rice in her review of the literature, these findings are consistent with the POPs having a potential causal role in AD-HKD (Rice 2000). Studies in humans have confirmed that even a low level exposure to PCBs prenatally is associated with neuropsychological deficits including problems with selective attention, response organisation, set-shifting and inhibition (Jacobson & Jacobson 2003; Kofman et al. 2006; Schantz, Widholm, & Rice 2003). Interestingly, these same studies suggested that the POPs do not lead to hyperactivity and that sustained attention and visual-spatial functioning are similarly not affected by the POPs. There also seems to be a possible interaction between prenatal exposure to POPs and breast feeding whereby breast feeding is protective against the deleterious cognitive effects. Notwithstanding these interesting findings, a direct link between exposure to POPs and AD-HKD has still to be demonstrated. However, we can say that whilst the POPs do not seem to have a direct effect on hyperactivity they do appear to be related to aspects of inattention and impulsivity and may therefore contribute both to the development of AD-HKD and the heterogeneity seen within AD-HKD samples.

Thyroid Hormone

Thyroid hormones are essential for normal brain development and both over- or under availability of thyroxin have been demonstrated to influence both behaviour and cognitive function in children and adults. In a prospective screening study the prevalence of thyroid abnormalities was found to be higher in a group of 277 children with AD-HKD (5.4%) than in

a comparable group of children from the normal population (< 1%) (Weiss et al. 1993). A cross-sectional study of preschoolers found high concentrations of thyroid stimulating hormone and a low free thyroxin index was associated with AD-HKD symptoms in otherwise healthy preschoolers (Alvarez-Pedrerol et al. 2007). AD-HKD has also been associated with a generalised resistance to thyroid hormone, a condition with reduced responsiveness of both peripheral and pituitary tissues to thyroid hormones (Hauser et al. 1993), although other studies have failed to detect such an effect (Spencer et al. 1995). A recent study has suggested that abnormalities in thyroid function in AD-HKD could potentially be mediated by the POPs (Alvarez-Pedrerol et al. 2008).

Dietary Factors

Over the years, many dietary factors have been put forward as potential causative agents for AD-HKD. For many of these there is either little scientific rational or evidence or there is evidence from failed controlled clinical trials, which does not support causality (Barkley 2006). For example, a meta-analysis of 23 controlled studies did not support the notion, prevalent in the 1980s, that dietary sugar causes AD-HKD (Wolraich, Wilson, & White 1995). There are however several interesting, as yet neither proven nor discredited, possibilities, which warrant brief discussion.

Zinc and Iron Deficiencies

Several controlled studies have reported zinc deficiencies in children with AD-HKD compared with control children and that zinc sulphate supplements may be beneficial in reducing AD-HKD symptoms (see Arnold & Disilvestro 2005 for a review). It should, however, be noted that most studies have been conducted in countries traditionally associated with low levels of dietary zinc (e.g. Turkey and Iran).

Iron deficiency has been suggested as a possible risk factor for AD-HKD but there is no firm evidence to support these claims (Millichap, Yee, & Davidson 2006).

Food Additives

Food additives in various forms, such as salicylates, dyes and preservatives have been linked with AD-HKD since the 1970s (Feingold 1975). Although there has been considerable study into these possible associations, the literature remains somewhat inconclusive with many contradictory findings. It is, however, interesting to note that whilst early meta-analyses failed to support an association (Kavale & Forness 1983; National Advisory Committee on Hyperkinesis and Food Additives 1980), more recent reviews, based on better designed studies, have been more positive and concluded that further study is required (Arnold 2001; Schab & Trinh 2004). A recently completed study (McCann et al. 2007) utilised a randomised, double-blinded, placebo-controlled, crossover design to test whether intake of artificial food colour and additives affected childhood behaviour in a UK population sample. Whilst they found that artificial colours and/or a sodium benzoate preservative in the diet did result in increased hyperactivity in 3-year-old and 8/9-year-old children in their sample, the study's authors were careful to point out that they did not assess for the presence of AD-HKD and that their results do not equate to evidence that these additives are a cause of AD-HKD. It does, however, seem plausible that certain food additives could be impacting on the heterogeneity found within AD-HKD samples. As these additives are now fairly ubiquitous in most developed and many developing countries, the most likely causal pathway for these effects would be via a G x E interactions.

Omega-3 fatty acid deficiency

The highly unsaturated omega-3 fatty acids have been hypothesised to play a role in the development of a range of psychiatric disorders and learning difficulties including schizophrenia and AD-HKD. They are most commonly found in fish oils, certain plant oils such as olive and canola oils and certain types of nuts and seeds including walnuts and flax seeds. These fatty acids have been demonstrated to play an active role in maintaining neuronal membrane health, signal transduction and neural development. There is

reasonable evidence to suggest that the vast majority of the US population suffer from a dietary shortage of these fatty acids (Holman 1998) and it is likely that this is true for many developed countries. It is therefore possible that this, again probably in interaction with genetic factors, may lead to disruptions in neural development and subsequent behavioural problems including AD-HKD (Horrobin, Glen, & Hudson 1995).

Delion and colleagues (1996) demonstrated that α-Linolenic acid dietary deficiency disrupted dopaminergic and serotonergic neurotransmission in the rat frontal cortex and appeared to result in decreased dopamine availability. Both findings are consistent with what is known about the pathophysiology of AD-HKD.

The results of preliminary studies in humans are mixed. Two studies have found that, compared with age and sex matched controls, children with AD-HKD had lower serum free fatty acid levels (Bekaroglu et al. 1996; Stevens et al. 1995). However, it is equally as possible that AD-HKD has led to these decreased levels as it is that the AD-HKD was caused by the decreased levels. Initial attempts to decrease AD-HKD symptoms by dietary omega-3 supplementation were largely unsuccessful (Voigt et al. 2001). Richardson and Puri (2000) criticised these studies for not including a full range of fatty acids. In their own 12 week randomised double blind placebo controlled trial, conducted with a group of 41 children with specific learning difficulties and increased AD-HKD symptoms, but not necessarily an AD-HKD diagnosis (Richardson & Puri 2002), they reported improvements in the secondary measures of AD-HKD symptoms, but not in the primary measures of learning disability symptoms, for the group treated with fatty acids compared with the control group. Unfortunately blood levels were not measured and persistence of response was not measured over time. In summary, it remains possible that dietary fatty acid deficiency could contribute to the heterogeneity found in AD-HKD samples but further study is required before any strong arguments can be made.

Organophosphate pesticides

Organophosphate pesticides are very heavily used in modern agriculture and include several chemical entities, which have been identified as having adverse effects on the developing nervous system (Koger, Schettler, & Weiss 2005). Whilst the effects of relatively high levels of exposure of these chemicals on those who work with them and their families have been well documented, the impact of a more generalised, lower-level exposure in the general population and in children in particular, has received far less attention. The organophosphates have been demonstrated to have cholinergic actions and although understudied, there are several lines of evidence suggesting that altered cholinergic neurotransmission could be relevant to the pathophysiology of AD-HKD (Rhodes, Coghill, & Matthews 2004; Wilens et al. 2000; Wilens et al. 2006). Children may be at particular risk from these agents due both to the large amounts of food they eat per kg of body weight and their relative proximity to the ground, where levels are reported to be highest (Weiss 2000). Evidence from the US (Schettler 2001) and Europe (Heudorf, Angerer, & Drexler 2004) suggests that most children are indeed exposed to these chemicals. Whilst the levels detected in these studies are lower than current published “safe” levels, there is little empirical evidence to support the safety of these designated levels and it may be the case, as was seen with lead and mercury, that the true safe levels for these pollutants are actually much lower than originally considered acceptable. Few studies have investigated the possible links between these chemicals and behavioural disturbances and most of those that have, only reported on the consequences of high levels of exposure. There are, however, several animal studies, which have linked a low level of exposure to organophosphates to altered behavioural patterns, including overactivity, and cognitive effects including working memory deficits, similar to those that would be expected in AD-HKD (Ahlbom, Fredriksson, & Eriksson 1995; Icenogle et al. 2004; Winrow et al. 2003).

Exposure to serious psychological trauma or severe early deprivation

Many children with AD-HKD live within chaotic family situations and many parents struggle to effectively manage their AD-HKD child's behaviour. As a result it is often suggested that AD-HKD is simply the behavioural consequence of poor parenting techniques (Cook 2003). Such claims continue to be made despite longstanding evidence that , in the case of AD-HKD type behaviours, it is the child's behaviours that drive the parenting effects rather than the other way around (Barkley & Cunningham 1979). Parenting style does, however, have an impact on the course of AD-HKD. Children whose parents have less effective parenting skills are more likely to have persistent AD-HKD symptoms than those with more effective parents (Campbell 2002). Children who receive higher levels of hostile and critical parenting are more likely to develop oppositional and aggressive behaviours (Taylor et al. 1996). Thus, whilst these parenting factors do not contribute causally to AD-HKD, they may still account for some of the heterogeneity within samples. It also remains possible that more extreme levels of trauma or deprivation prenatal stress, could contribute to the causes of AD-HKD.

Teicher and colleagues (2003) have demonstrated that early psychological abuse and maltreatment can alter the development of the hippocampus, amygdale, frontal cortex and cerebellar vermis and that children who have been sexually abused can, in addition to PTSD and depression, also present with overactivity and impulsivity (Glod & Teicher 1996). Recent studies have also investigated the outcomes of extreme disruptions of parenting, particularly that experienced by some institutionally reared children. The most detailed study has compared children adopted after an early period of institutional care in England to a group adopted into similar families after a period of institutional care in a Romanian orphanage during a period of extreme social unrest and dislocation (Kreppner, O'Connor, & Rutter 2001; O'Connor et al. 2000; O'Connor & Rutter 2000; Rutter, Kreppner, & O'Connor 2001). Compared with the children adopted from English institutions, whose care had been

fairly sound prior to adoption, the children from the Romanian orphanages had experienced severe deprivation prior to adoption. The Romanian children presented with significantly higher levels of inattention and overactivity and these symptoms were more likely to be pervasive than they were in the English group. These differences remained after the effects of low birth weight, IQ and nutritional status were controlled for. It must be stressed that these findings are not going to be informative about most cases of AD-HKD as the deprivation suffered by the Romanian children was extreme. However they do suggest that severe deprivation and abuse may be one route to AD-HKD in a small proportion of cases.

Aetiology – Mediating Factors

These are factors, which sit between genetic and environmental causative agents, and mediate their impact on the development of AD-HKD symptoms. They sit across several levels of analysis and will be discussed under several headings; brain mechanisms, pathophysiology and electrophysiology, and neuropsychology. Of course, these levels are interrelated and there is a degree of interdependence between them. These issues will be discussed in detail in Chapter 3.

Brain Mechanisms

Structural Imaging findings

Whilst structural imaging studies have consistently reported differences between the brains of those with and without AD-HKD, a detailed comparison of studies indicates inconsistencies across studies with some non-replication of findings (Seidman, Valera, & Makris 2005), particularly with reference to the splenium of the corpus callosum (Giedd et al. 1994; Semrud-Clikeman et al. 1994) and the caudate, where studies have found AD-HKD individuals to have the same sized (Hill et al. 2003), larger (Mataro et al. 1997) or smaller (Hynd et al. 1993) caudate nuclei than control subjects. In order to address these issues

Valera et al. (2007) conducted a meta-analysis of structural imaging studies in AD-HKD. They identified 22 separate studies and conducted their primary analysis on regions of interest that had been assessed in at least 3 studies. They reported differences for total and right cerebral volume, right and left cerebellum, the cerebellar vermis, lobules VIII-X of the posterior vermis, the splenium of the corpus callosum and the right caudate (Valera et al. 2007). Other regions, which were less frequently studied, but, which also showed large significant differences included; the frontal lobes, the prefrontal cortex and deep frontal white matter (total and right and left). When all regions across all studies were compared there were global reductions for the AD-HKD subjects compared with normal controls with a standardised mean difference of 0.408, which was statistically significant ($p < 0.001$). The authors note that these results, particularly those for regions that have been less well studied, need to be interpreted with caution, and that further studies are required to further clarify these results. A further caveat concerns not only the areas chosen by researchers to measure, but also the ways that results are reported and interpreted. For example, in the largest structural imaging study reported to date, whilst Castellanos and colleagues reported in the results section that the largest differences between AD-HKD subjects and controls were seen in the temporal lobes (Castellanos et al. 2002e), these differences were not considered in the discussion.

Longitudinal data from the National Institute of Mental Health Study Group suggest that these differences are present early in development and are not caused by stimulant treatment (Castellanos et al. 2002d; Shaw et al. 2006). Further longitudinal data from the same group, published too late to be included in Valera's meta-analysis, addresses the issue of whether AD-HKD results from a delay in brain maturation or whether it represents a complete deviation from the template of typical development (Shaw et al. 2007). Using computational neuroanatomical techniques, they estimated cortical thickness at more than

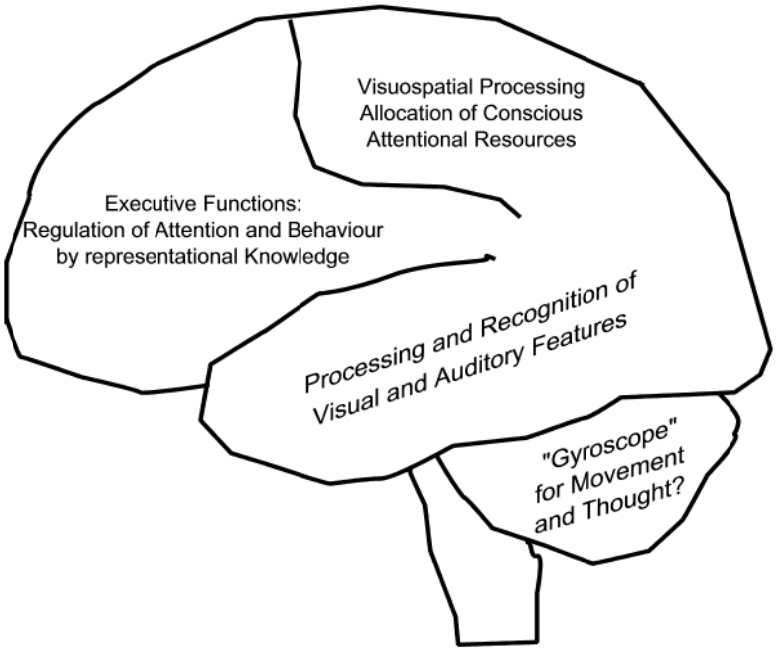
40,000 points from a total of 824 magnetic resonance scans, which had been acquired prospectively on a cohort of 223 children with AD-HKD and 223 typically developing normal controls. They were able to define the growth trajectory of each cortical point, and demonstrate a phase of childhood increase in cortical thickness followed by a period of adolescent decrease. They found that maturation progressed in a similar manner in both children with and without AD-HKD. There was, however, a marked delay in these changes in the AD-HKD subjects such that the median age by which 50% of the cortical points attained peak thickness for the AD-HKD group was 10.5 years, which was significantly older than that for the control group (median age of 7.5 years). This delay was most prominent in prefrontal regions, which are important for control of cognitive processes, including attention and motor planning.

The same group have also reported that children with AD-HKD show relative cortical thinning in regions important for attentional control, and children with worse clinical outcome had a thinner left medial prefrontal cortex at baseline than both the better outcome group and the controls (Shaw, Lerch, Greenstein, Sharp, Clasen, Evans, Giedd, Castellanos, & Rapoport 2006). They also found that, whilst cortical thickness developmental trajectories did not generally differ significantly between the AD-HKD and control groups, the right parietal cortex was the one exception, and for this region the two trajectories converged, but only in the better outcome group. Thus those children with a worse outcome seemed to have "fixed" thinning of the left medial prefrontal cortex, which the authors hypothesise may compromise the anterior attentional network and encumber clinical improvement (Shaw, Lerch, Greenstein, Sharp, Clasen, Evans, Giedd, Castellanos, & Rapoport 2006). In a separate analysis of the same study, they also report that possession of the DRD4 7-repeat allele was associated with a thinner right orbitofrontal/inferior prefrontal and posterior parietal cortex regions, which overlapped with those regions

found to be thinner in subjects with AD-HKD compared with controls. Participants with AD-HKD carrying the DRD4 7-repeat allele also had a better clinical outcome and the distinct trajectory of cortical development previously linked with better clinical outcome. By contrast, there were no significant effects of the DRD1 or DAT1 polymorphisms on clinical outcome or cortical development (Shaw, Eckstrand, Sharp, Blumenthal, Lerch, Greenstein, Clasen, Evans, Giedd, & Rapoport 2007).

Although much less suited to structural analysis studies using electrophysiological techniques (Barry, Johnstone, & Clarke 2003)and transcranial magnetic stimulation (Garvey et al. 2005) have tended to support the findings of the structural imaging studies.

Figure 2.1: The brain regions involved in the regulation of attention as seen from the left lateral surface [a] (Redrawn from Arnsten (2006)



[a] The basal ganglia circuits are not shown in this view. They are however thought to contribute to the automatic planning, selection, initiation and execution of complex movements and thoughts.

Functional Imaging Studies

Based on our understanding of the brains functioning several areas stand out as potentially important in the development of AD-HKD (Figure 2.1).

Inferior temporal cortex

The inferior temporal cortex is involved in visual memory and its neurones process visual features and determine "what" things are based on colour and shape. Activity in these neurones can be modulated up or down depending on sensory conditions and internal directions (Desimone 1996; Kastner et al. 1998). The activity of these neurones is increased by salient stimuli but continued experience with the same stimuli leads to decreased responding and may account for the boredom seen with repetition. Visual stimulus processing is also diminished by interference from nearby stimuli in the same visual field. Both of these suppressive effects can be prevented by "top down" projections imputing from the prefrontal cortex, which allow for directed selective attention of visual feature processing.

Posterior Parietal Association Cortex

The parietal association cortex is critical to the process of "paying attention". It plays a specialist role in analysing movement and spatial relationships, analyzing quantity and constructing spatial maps, and orientating in time and space (Coull & Nobre 1998). Lesions of the right posterior parietal cortex are associated with contralateral neglect. Recordings from parietal neurones in monkeys are consistent with a role in allocating attentional resources and it would appear that this brain region is therefore critical to conscious attention (Crowe et al. 2004). Parietal neurones also appear be involved in mapping space, projecting this information to the prefrontal cortex, which uses it to guide behaviour during various activities, including the completion of spatial working memory tasks (Snyder et al. 1998).

Prefrontal Cortex

The prefrontal cortex has been held in special regard in AD-HKD due to a range of convergent evidence from imaging, electrophysiological and neuropsychological studies implicating it in AD-HKD pathophysiology. The prefrontal cortex acts as an active filter using representational knowledge to guide both overt and covert responses, thus allowing an individual to inhibit inappropriate responses and gate the processing of irrelevant stimuli (Godefroy & Rousseaux 1996; Goldman-Rakic 1996; Knight et al. 1999; Robbins 1996). Subjects with prefrontal lesions are easily distracted, poorly organised and have difficulties in set-shifting tasks, and they can also be impulsive, especially when the lesion is in the right hemisphere (Aron, Robbins, & Poldrack 2004). Such lesions also impair the ability to sustain attention over a delay and reduce the ability to filter and gate sensory input (Wilkins, Shallice, & McCarthy 1987). Prefrontal cortex lesions also impair divided and focused attention, particularly when they occur in the left superior prefrontal cortex (Godefroy & Rousseaux 1996). Prefrontal cortex neurones have been demonstrated to have the ability to hold information “on-line” over a delay in the absence of incoming stimuli and, importantly, in the presence of distracters (Miller, Li, & Desimone 1993). This ability underlies the ability to inhibit a pre-potent response, a deficit thought to be central to AD-HKD by certain authors (Barkley 1997a).

Cortical Projections to the Basal Ganglia and Cerebellum

Both the basal ganglia and the cerebellum receive projections from the association cortices. These are organised as a series of parallel, closed loop circuits (Dum, Li, & Strick 2002). Although the roles of the basal ganglia and cerebellum in the regulation of movement have been known for some considerable time, it is only now being recognised that they appear to play important parallel roles in the coordination of higher cognitive processes. It is hypothesised that the basal ganglia may play an important role in planning, and the selection, initiation and execution of thoughts, and that the cerebellum may serve

as what Arnsten terms a “biological gyroscope”, constantly making micro corrections on a range of cognitive functions (Arnsten 2006a).

Functional Imaging Studies

Initial functional imaging studies in AD-HKD focused largely on top-down cortical control systems involving the prefrontal cortex with less attention given to bottom-up studies investigating the neural systems implicated in AD-HKD (Casey, Nigg, & Durston 2007). However, when looked at together, recent studies demonstrate not only a consistent pattern of frontal hypofunction and altered activity patterns in the anterior cingulate, prefrontal cortices, but also in the associated temporal, parietal, striatal, and cerebellar regions (Bush, Valera, & Seidman 2005; Dickstein et al. 2006; Durston et al. 2006; Epstein et al. 2007; Konrad et al. 2006; Pliszka et al. 2006; Smith et al. 2006; Tamm, Menon, & Reiss 2006). Each of these last four regions form a part of unique circuits, which project both to and from the prefrontal cortex, and provide a means for alerting prefrontal regions when their top-down control needs to be imposed. Altered functioning in any one of these regions could lead to dysregulated behaviours, however there would be likely to be subtle differences, depending on the system involved or the task used. This hypoactivation appears to normalise with MPH (Epstein, Casey, Tonev, Davidson, Reiss, Garrett, Hinshaw, Greenhill, Glover, Shafritz, Vitolo, Kotler, Jarrett, & Spicer 2007; Vaidya et al. 1998). A recent systematic review of functional MRI (fMRI) studies in AD-HKD identified group differences in activation across several brain regions (Paloyelis et al. 2007). In addition to frontal lobe hypoactivation during tasks of inhibitory control, the reviewers noted that AD-HKD was associated with hypofunction in temporal and parietal areas in attentional tasks, and over frontal areas in motor tasks. Data from subjects who had not used AD-HKD medications suggests that these patterns of altered brain activation are not due to the effects of treatment (Paloyelis, Mehta, Kuntsi, & Asherson 2007). Patterns of hypoactivation of the ventral prefrontal and inferior parietal regions related to attentional

networks also appear to be present in the unaffected siblings of children with AD-HKD (Durston, Mulder, Casey, Ziermans, & van Engeland 2006).

Individuals with AD-HKD have also been shown to demonstrate greater activation in regions associated with motor and visual, spatial processing, when engaged in tasks requiring higher cognitive functioning, when compared with controls (Fassbender & Schweitzer 2006). It is not clear whether these findings are indicative of primary abnormalities or whether they are identifying correlates of the AD-HKD subject's use of specific compensatory strategies. Individuals with AD-HKD are found to generally activate more diffuse, wider neural systems in order to perform tasks than control subjects (Durston et al. 2003). Functional MRI findings have shown reduced accumbens activity in anticipation of large reward in adolescents with AD-HKD (Scheres et al. 2007).

The broad nature of these results does not support those older models of AD-HKD, which emphasised dysfunction in only one particular sub-region of the brain or another. They are much more consistent with the notions that AD-HKD is the consequence of widespread alterations in brain activity and that there is considerable heterogeneity within the AD-HKD population.

The introduction of newer technologies, such as diffusion tensor imaging, have allowed researchers to move on from identifying discrete regions of dysfunction and to start investigating the role of alterations in connectivity between these structures. An initial study investigated white matter abnormalities in 18 patients with AD-HKD and 15 age- and gender-matched controls. When fractional anisotropy maps (an index of white matter tract myelination and regularity) of white matter were compared between groups it was found that, as predicted, children with AD-HKD had decreased fractional anisotropy in areas previously implicated in the pathophysiology of AD-HKD: right premotor, right striatal, right cerebral peduncle, left middle cerebellar peduncle, left cerebellum, and left parieto-

occipital areas, supporting the hypothesis that alterations in brain white matter integrity in frontal and cerebellar regions may contribute to the pathophysiology of AD-HKD (Ashtari et al. 2005).

Casey et al. (2007)used functional imaging maps from a group of parent-child dyads with AD-HKD who performed a Go/NoGo task to identify which regions of the ventral prefrontal cortex and striatum are involved when suppressing an inappropriate action. An automated fibre-tracking algorithm was then used to delineate white matter fibres adjacent to these functionally defined regions based on diffusion tensor images, and fractional anisotropy was calculated to characterise the associations between white matter tracts and function. Fractional anisotropy in right prefrontal fibre tracts was correlated with both functional activity in the inferior frontal gyrus and the caudate nucleus, and performance on the Go/NoGo task. The prefrontal fibre tract measures were found to be tightly associated between AD-HKD parents and their children. These findings support the suggestion that disruption in frontostriatal white matter tracts is one possible pathway to the development of AD-HKD. They also support the heritability of frontostriatal structures among individuals with AD-HKD. Collectively, these early findings from connectivity studies suggest that variability in the myelination and regularity of right prefrontal fibres may contribute to cognitive deficits in AD-HKD.

Looked at as a whole, the evidence from these functional imaging studies supports the hypothesis that disruption of various frontostriatal circuits at different loci may result in similar functional consequences. It also supports the notion that this altered functioning of fronto-striatal circuits is itself affected by dysfunctions of the posterior cortical regions, the cerebellum and/or ascending arousal systems, all of which are known to closely interact with the prefrontal cortex and have also been implicated in AD-HKD. However it is important to note that these findings do not preclude the involvement of other brain

structures in the development of AD-HKD. As noted previously, researchers have tended to only look for abnormalities in a small subset of brain regions and there are still many potential areas of importance, such as, but not restricted to, the temporal lobes, amygdale and hippocampus that have to date received little attention.

Pathophysiology

In view of the effectiveness of the stimulant medications in reducing AD-HKD symptoms, it has for a long time been assumed that the dopaminergic and noradrenergic neurotransmitter systems play a key role in the pathophysiology of AD-HKD (Arnsten 2006a). Converging evidence from molecular genetics findings (summarised earlier in the chapter), animal models (Sagvolden et al. 2005), and functional imaging studies (Durston et al. 2005) supports this position. There is, however, still considerable controversy regarding the precise nature of these alterations in dopaminergic and noradrenergic functioning. Arnsten (2006a) has recently reviewed the potential mechanisms by which these neurotransmitters could modulate the relevant cortical circuits.

Catacholaminergic modulation of cortical circuits

Dopamine

Dopamine acts at both the D_1 ($D_{1\text{ and }}D_5$) and D_2 (D_2, D_3, and D_4) families of receptors. In actual fact, the D_4 receptor should probably be thought of as a catacholaminergic receptor as it also has a high affinity for noradrenaline. The $D_{1\text{ and }}D_5$ seem to be functionally identical and are therefore normally discussed together. Little is known about the actions of the D_3 receptor in the prefrontal cortex.

D1 receptor actions

Stimulation of this family of receptors in the prefrontal cortex produces an inverted U-shaped dose response effect on working memory and attentional regulation (Arnsten et al. 1994; Granon et al. 2000). Thus whilst moderate levels of D_1 stimulation are required for

accurate performance higher levels, such as those occuring as a response to stress, impair performance. In humans a genetic variant of the catechol O-metyltransferase enzyme results in those with the methionone for valine substitution having weaker enzyme activity and therefore higher than expected levels of dopamine. Whilst under basal conditions these subjects have better working memory performance and a more efficient prefrontal cortex activation, their performance deteriorates significantly following the administration of amfetamine or exposure to stress, whilst the performance of those without the substitution improve under the same conditions (Mattay et al. 2003). These effects are mediated by the D_1 receptor.

D_2 receptor actions

There has been much less study of D_2 stimulation on prefrontal cortical functioning. There is however some evidence to suggest that excessive D_2 stimulation impairs working memory in rats (Druzin et al. 2000) and that D_2 receptors may be localised on cells thatproject to areas guiding movement in monkeys (Wang, Vijayraghavan, & Goldman-Rakic 2004). D_2 autoreceptors are situated pre-synaptically and have neuromodulatory functions providing negative feedback and thus limiting the release of dopamine.

D_4 receptor actions

The D_4 receptors are concentrated on the γ-aminobutyric acid (GABA) interneurons and appear to inhibit GABA transmission (Mrzljak et al. 1996; Wang, Zhong, & Yan 2002). Thus weaker D_4 activity results in greater GABA neurotransmission and a subsequent suppression of pyramidal cell firing. The 7 repeat polymorphism of the D_4 receptor gene, which is associated with AD-HKD is also associated with weaker D_4 efficacy (Sunohara et al. 2000; Tahir et al. 2000), which would suggest that these individuals will have poor D_4 inhibition of GABA and that this would result in insufficient prefrontal cortex pyramidal cell firing. Stimulant medication may increase the levels of dopamine and noradrenaline

stimulation of D_4 receptors, reversing this process. However, the picture is not entirely clear as there is some evidence that D_4 receptor stimulation can also inhibit pyramidal cell firing (Wang, Zhong, & Yan 2002)

Noradrenaline

Noradrenaline acts at α_1 – , α_2 -, β_1 - , β_2 - and β_3 –adrenoceptors. Of these, the α_1 – , α_2 - and β_1 – adrenoceptors are the most important modulators of cortical function.

α_{2A} – adrenoceptor actions

Noradrenaline improves prefrontal cortical functioning through actions at the postsynaptic α_{2A} – adrenoceptors. (Franowicz et al. 2002). Guanfacine, an α_{2A} – agonist effective in reducing AD-HKD symptoms, improves working memory, and attentional regulation in rodents (Franowicz, Kessler, Borja, Kobilka, Limbird, & Arnsten 2002), monkeys (Li et al. 1999b)and humans (Jakala et al. 1999a) (although, interestingly, neither it nor clonidine improved performance on a delayed matching to sample memory task in humans (Jakala et al. 1999b)). Conversely α_{2A} – blockade with Yohombine infusions in monkeys resulted in reduced delay-related cell firing (Li et al. 1999a), impaired working memory performance (Berns, Song, & Mao 1999; Li & Mei 1994)and locomotor hyperactivity (Ma, Arnsten, & Li 2005). Dopamine β-hydroxylase, the enzyme that synthesises noradrenaline, has been implicated as a potential causal agent in AD-HKD. A weak dopamine β-hydroxylase may lead to suboptimal stimulation of the α_{2A} – adrenoceptors in the prefrontal cortex, which may result in a similar profile of actions as is seen with Yohimbine.

α_1 – adrenoceptor actions

In direct contrast to its actions at the α_{2A} – adrenoceptors, increased noradrenaline levels can impair prefrontal cortical functions, including working memory, through actions at the α_1 – adrenoceptors (Arnsten et al. 1999). Thus α_1-agonists such as phenylephrine impair

(Mao, Arnsten, & Li 1999) and α_1-antagonists such as urapidil and prazosin improve (Birnbaum et al. 1999) prefrontal cortical functioning.

β_1 – and β_2-adrenoceptor actions

Recent studies have suggested that stimulation of the β_1 – adrenoceptors impairs prefrontal cortical functioning and working memory (Ramos et al. 2005), and that stimulation of the β_2 – adrenoceptors improves prefrontal cortical functioning and working memory in aging animals (Ramos et al. 2007)

Catacholaminergic modulation of basal ganglia and cerebellum

The basal ganglia are powerfully modulated by dopamine and the cerebellum by noradrenaline (Arnsten 2006a). Dopamine increased thalamocortical stimulation of movement and thought via direct actions of D_1 receptors and indirect, inhibitory actions of the D_2 receptors in the basal ganglia (Steiner & Gerfen 1998). Noradrenaline modulates cerebellar processing through β-adrenoceptor mechanisms with increased stimulation promoting cognition (Cartford et al. 2004). It is therefore possible that genetic variations affecting either dopaminergic or noradrenergic neurotransmission will impact on basal ganglia and cerebellar functioning, in addition to cortical functioning.

Cholinergic neurotransmission

Whilst theories of the neurobiological basis of AD-HKD have largely focused on dysregulation of central dopaminergic function, recent studies have started to explore the potential roles of other neurotransmitter systems. Of these there is most support for the involvement of the central nicotinic cholinergic system in AD-HKD (Potter, Newhouse, & Bucci 2006).

Those with AD-HKD smoke at significantly higher rates than comparable people in a community sample and also appear to have more difficulty stopping smoking (Pomerleau

et al. 1995). Unlike the findings for several drugs of abuse, these findings remain after controlling for the effects of conduct disorder (Disney et al. 1999). Several nicotinic agonists have also been shown to be effective in reducing the core symptoms of AD-HKD (Levin et al. 1996; Potter & Newhouse 2004; Shytle et al. 2002; Wilens et al. 1999; Wilens, Verlinden, Adler, Wozniak, & West 2006). There is also evidence that modulation of the central cholinergic system impacts on task performance on a range of cognitive tasks on which children with AD-HKD perform poorly when compared with healthy controls. Potter and Newhouse (2004) found that nicotine (as well as MPH) improved performance in AD-HKD subjects on a Stop Signal Task and, in a separate study, on the Stroop Task (discussed in, Potter, Newhouse, & Bucci 2006). Nicotine also resulted in improvements in AD-HKD subjects on the Choice Delay Task, a measure of delay aversion (discussed in, Potter, Newhouse, & Bucci 2006), and the Continuous Performance Task, a measure of sustained attention (Shytle, Silver, Wilkinson, & Sanberg 2002). Cholinergic systems are also thought to play an important role in working memory function. In animal studies both $\alpha 4\beta 2$ and $\alpha 7$ nicotinic agonists have been demonstrated to improve working memory and nicotinic antagonists disrupt working memory (Levin 2002), and the nicotinic agonists ABT-418 and ABT-089 improved performance in monkeys on a delayed-recall task by increasing accuracy particularly when a distracter was present. Scopolamine, a muscarinic antagonist, impairs performance of healthy subjects on the CANTAB Delayed Matching to Sample task (Robbins et al. 1997) in a similar delay dependent manner to that reported by Rhodes et al (2004) in boys with AD-HKD. Nicotine enhances working memory in cigarette deprived healthy smokers (Foulds et al. 1996). Unfortunately there are not yet any studies investigating the effects of nicotinic agonists on working memory in subjects with AD-HKD.

There are several mechanisms by which stimulation of central cholinergic systems may affect cognition. The beneficial effects of nicotine on cognition could arise from direct

effects on cognitive functions known to be mediated by central cholinergic systems, such as the basal forebrain cholinergic system (BFCS). The BFCS has often been divided into two main projection pathways, a medial and a lateral pathway (Rye et al. 1984; Saper 1984). The neurons that constitute the medial pathway primarily innervate the hippocampus, cingulate and retrosplenial cortex. In contrast, most neurons comprising the lateral pathway provide widespread innervation of the cortex. These components of the BFCS are critically involved in various aspects of attentional function, including sustained attention, selective attention, and the ability to increase and decrease attention to stimuli (Sarter et al. 2005; Sarter, Bruno, & Givens 2003). Recruitment of the system appears to increase with increasing cognitive demands and may reflect effortful processing. Impairments in cholinergic system functioning are likely to result in impairments on tasks that have high attentional demands, such as tasks that are difficult, require task or context switching, or require searching for targets (Potter, Newhouse, & Bucci 2006).

Cholinergic systems may also modulate dopaminergic systems and dopamine-mediated functions. There are a variety of mechanisms and anatomical loci where dopaminergic and cholinergic systems may directly interact, possibly mediating the positive effects of nicotine on cognition and in AD-HKD. At least three of the cholinergic systems, originating in various brainstem nuclei (e.g., pedunculopontine and laterodorsal tegmental nuclei), provide direct input to dopaminergic cell groups in the substantia nigra (Wainer & Mesulam 1990). There is also evidence to confirm a direct synaptic connection between cholinergic terminals and dopaminergic cell bodies in the ventral tegmental area (Garzon et al. 1999) and nicotine has been shown to increase the release of dopamine in both striatal and mesolimbic dopaminergic pathways (Rapier, Lunt, & Wonnacott 1990). Levin et al. (1997) also found that activation of nicotinic receptors and dopamine receptors is additive, and possibly synergistic. Other data indicate that interactions between brainstem cholinergic systems

and dopaminergic pathways may have a significant role in reward mechanisms (Ikemoto & Wise 2002; Merlo, Chiamulera, & Carboni 1999). Whilst there clearly needs to be more AD-HKD specific work in this field this evidence, when taken together, makes a plausible argument for the potential involvement of central cholinergic systems in AD-HKD and serves as a further reminder that, when searching for the causes of AD-HKD, one needs to cast a broader net than has traditionally been the case.

Neurophysiology

Electroencephalography (EEG) can provide valuable information about brain function, with high temporal, but poor spatial, resolution. In many senses the information from EEG is complimentary to that from functional imaging studies where there is excellent spatial but poor temporal resolution. The EEG is able to provide useful information about the background state of the brain, and assist in indexing the substrates of cognition and behaviour. It can also be used to derive the event-related potential (ERP) signature of the processing of a stimulus. It is unfortunate that despite an obvious interdependence between EEGs and ERPs, the electrophysiological investigation of AD-HKD has largely examined these aspects in isolation.

Qualitative and Quantitative EEG studies.

To aid analysis, EEG data is often clustered into bands based on the frequency of the waveforms, each of which has been found to have particular topographic, developmental and functional characteristics (Table 2.2). The initial EEG studies of subjects who would now be recognised as having AD-HKD were qualitative in nature, relying on the visual interpretation of EEG traces, which were then classified into normal or abnormal. In general

Table 2.2: An overview of the various EEG frequency bands, their topography, developmental and functional characteristics, and exemplary findings

EEG					
Frequency bands	Delta (<4 Hz)	Theta (4–7 Hz)	Alpha (8 – 12 Hz)	Beta (13–30 Hz)	Gamma (30–70 Hz)
Topography			Posterior	Frontal	
Developmental characteristics	Predominant during neonatal period & early childhood		Increases until early adolescence	Continues to mature until adulthood	
Examples of functional states where predominantly seen	sleep, decreased vigilance		relaxation	concentration, neuronal excitability	Feature binding
Exemplary findings	AD-HKD: increased slow wave activity Cholinergic muscarinic receptor gene related to theta and delta event-related oscillations Considerable heritability			Associated with GABA-A receptor polymorphism Risk for alcohol dependence associated with increased beta AD-HKD: EEG subtype with increased beta	

these studies reported that a relatively high proportion (around 50 – 60%), but not all, of these subjects had “abnormal” EEGs and that these abnormalities were predominantly related to an increase in slow wave activity (around 2 – 6 Hz) (see Barry, Clarke, & Johnstone 2003 for a full review of this data). These data are in general agreement with the more recent findings from quantitative EEG studies.

Advances in computer-aided spectral analysis have facilitated the development of several new approaches to EEG analysis. These include;

- The measurement of waveform amplitude using either absolute measures whereby the amplitude of every wave in a given frequency band is averaged, or relative amplitude, which is calculated by dividing the absolute amplitude of one frequency band by the sum of the absolute amplitudes of all the calculated frequency bands

- The calculation of absolute and relative power estimates. These provide an easily-interpreted and reliable method of quantifying changes in the EEG under a range of different conditions, and also the differences between various clinical and normal groups. These methods have been shown to have good test retest reliability(John et al. 1980).

- The power ratios between different frequency bands have been used to evaluate changes in the EEG that occur due to normal maturation and as a measure of cortical arousal.

Data from studies using these techniques has painted a fairly consistent picture which, again, suggests that compared with healthy children those with AD-HKD have elevated levels of slow wave activity. The most reliable measure of this has been the relative theta power. Reduced amounts of relative alpha and beta have also been found in most power studies, while absolute alpha and beta seem to be less reliable discriminators. Increased

delta activity in both absolute and relative measures has also been found in AD-HKD, but with far less consistency (Barry, Clarke, & Johnstone 2003).

In general, anomalies are found in both combined and inattentive AD-HKD but are more pronounced in those with the combined type. The theta/alpha and theta/beta ratios appear to be fairly reliable at differentiating AD-HKD and healthy subjects, and between the DSM-IV types of the disorder. Although neither measure has greater sensitivity than the other, the theta/beta ratio is preferred by some researchers (e.g. Lubar 1991).

EEG defined subtypes of AD-HKD have been described by several groups, perhaps reflecting the heterogeneity that seen at other levels of analysis. Clarke et al. (1998; 2001b; 2001c) found that between 15 and 20% of children with combined subtype AD-HKD had significantly elevated levels of beta activity in their EEG. This group was also found to have a somewhat different behavioural profile from the other children with the combined subtype AD-HKD, with an increased rate of temper tantrums and moody behaviours.

Clarke et al. (2001a) used cluster analysis to further explore EEG defined subtypes in a large sample (n = 184) of boys with combined subtype AD-HKD. They identified 3 distinct EEG-defined subtypes. One cluster had increased total power, relative theta and theta/beta ratio, and decreased relative delta and beta across all regions, a pattern considered indicative of cortical hypoarousal. Another was characterised by increased slow wave and deficiencies of fast wave activity. This is broadly indicative of a maturational lag in CNS development, although the theta levels were slightly higher than expected, suggesting an additional dysfunction. The third cluster had excess beta activity, and was labelled an over-aroused group. The same group conducted a similar analysis of a group of children with inattentive subtype AD-HKD (Clarke et al. 2002). They identified two clusters. The first was characterised by reduced frontal relative delta, increased relative theta, and a reciprocal decrease in relative beta across the scalp. Alpha activity was at normal levels, suggesting a

primary deficit associated with cortical hypoarousal. The second cluster had increased frontal and decreased posterior total power, increased centro-posterior relative delta, increased relative theta and decreased relative alpha across the scalp, and a decrease in fronto-central relative beta activity, indicative of a maturational lag. Comparison of the data from the two studies suggested that the clusters in the combined type may have had some degree of cortical hypoarousal above those in the inattentive group. From this research Clarke et al (2002) proposed a model of AD-HKD focusing on the underlying dysfunction rather than the behavioural profile. Their model proposes 3 distinct subtypes within the AD-HKD diagnosis, which are largely independent of the DSM-IV diagnostic category. These consist of a cortical-hypoarousal subtype and a maturational-lag subtype, both of which are found in groups of children with either combined or inattentive types of AD-HKD. The third EEG subtype, with excess beta activity, is proposed to be exclusively found in combined type.

Loo and Smalley have recently published preliminary data examining the familiality EEG measures among affected sibling pairs with AD-HKD (Loo & Smalley 2008). EEG was recorded during the resting state and cognitive activation with a continuous performance task. Sibling correlation for EEG measures was moderate during baseline conditions and significantly higher for the cognitive activation condition. Familial clustering of frontal and parietal alpha power was only evident during the cognitive activation condition and cognitive task performance did not exhibit familial clustering. Theta and alpha power correlated significantly with continuous performance task (CPT) response variability and omission errors, respectively. It was therefore suggested that alpha power recorded during cognitive activation may be regarded as a putative endophenotype for AD-HKD.

Event Related Potentials

Event related potentials (ERP) are changes in the ongoing EEG that are time-locked (i.e., stimulus- or response locked) and phase-locked (i.e., time-locked and with the same polarities) to perceptual, cognitive, and motor processes. They are typically extracted from the ongoing electroencephalogram by means of signal averaging, which not only eliminates the spontaneous background EEG, but also those event-related EEG modulations which are not phase-locked as 'noise'. ERPs consist of characteristic sequences of components or 'microstates' (i.e., time segments with a stable topographical distribution of brain electrical activity). These span a continuum between early activity, primarily determined by the physical characteristics of the eliciting stimulus (latency range <250 ms), and later components (latency range >250 ms) dominated by cognitive rather than physical characteristics of the stimuli (Brandeis & Lehmann, 1986; Picton & Hillyard, 1988). These components are characterised by their topography, polarity and amplitude, by their latency and their functional significance (Banaschewski & Brandeis 2007). Their properties are summarised in Tables 2.3 and 2.4.

Table 2.3: An overview of exemplary early Event Related Potential (ERP) components, their topography, developmental latency, functional significance, generators, corresponding exemplary findings in AD-HKD and their specificity (reproduced with permission from Banaschewski and Brandeis (2007))

Early ERPs				
Component (modality)	P50 (auditory)	N1, N170 (visual)	N2	Mismatch negativity (MMN)
Topography	Central	Posterior temporal	Frontal	Frontocentral
Latency (msec)	40–80 post-stimulus	140–200 post-stimulus	200–400 post-stimulus	120–250 post-stimulus
Functional significance	Refractory reduction of P50 amplitude in a paired auditory stimuli paradigm⇒pre-attentive sensory inhibition of irrelevant inputs	Early attentional orienting &stimulus evaluation Face processing, expertise	Response monitoring & response inhibition	Pre-attentive auditory discrimination & sensory memory. Elicited by deviants in an unattended repetitive auditory sequence
Generators		Visual N1: extrastriate visual cortices, ventral occipitotemporal cortices		Frontal & supratemporal auditory cortices
Exemplary findings in AD-HKD		AD-HKD: increased in CPT⇒ deviant orienting	reduced in Stop task ⇒impaired inhibition	
Specificity	Low	Low	Low	Low

Tables 2.3 and 2.4 also summarise the main findings from ERP studies in AD-HKD. These include differences in preparatory responses with alterations in the automatic information processing stages related to the initial orienting and stimulus evaluation (Brandeis et al. 1998). Children with AD-HKD exhibit increased early attentional orienting before failing to allocate sufficient attentional resources in further processing stages (Banaschewski & Brandeis 2007). Importantly, these attentional deficits occur without concomitant response or performance deficits, temporally precede inhibitory or executive control, and predict subsequent performance. While inhibitory control deficits are also found in children with AD-HKD they are preceded by state regulation deficits or accompanied by executive control deficits, particularly at slow event rates (Banaschewski & Brandeis 2007).

In one sense these ERP findings appear to contradict some of the behavioural studies which reported that neither a reduced-capacity (Schachar & Tannock 1993) nor a dysfunctional (Radosh & Gittelman 1981; van der Meere & Sergeant 1987; van der Meere & Sergeant 1988) attention system are the major cause of AD-HKD symptoms/ behaviours. These ERP studies suggest various stages of sensory and cognitive processing are atypical. This apparent discrepancy may represent basic differences in methodology and focus, with behavioural studies analyzing the outcome of internal cognitive processes, and ERP studies examining electrical correlates of these brain processes. Indeed, several ERP studies report differences in stages of information processing (via group differences in ERP amplitude and latency) in conjunction with no differences in performance measures such as reaction time and errors.

In summary, when the combined EEG and ERP research on AD-HKD is looked at, it suggests the presence of a sequence of multiple activation deficits of posterior and anterior attention networks within a sub-second range, causally preceding inhibitory or executive control.

Table 2.4: Overview of exemplary late Event Related Potential (ERP) components, their topography, developmental latency, functional significance, generators, corresponding exemplary findings in AD-HKD and their specificity

Late ERPs					
Component (modality)	Error-related negativity(ERN)	P300	Readiness potential (RP); lateralised RP (LRP)	Contingent negative variation (CNV)	N400
Topography	Frontocentral	P3a, Nogo-P3: frontocentral; Cue-P3, oddball P3: centroparietal	Initial bilaterally centrally symmetric, then lateralised over motor cortex		Centroparietal
Latency (msec)	100 after error	300–800 post-stimulus	RP starts 1000, LRP 200–500 prior to movement		400 post-stimulus
Functional significance	Error evaluation &conflict monitoring Sensitive to mood and personality variables	Oddball-P3, Cue P3: attentional allocation, stimulus evaluation & context updating Nogo-P300 amplitude, anteriorisation: response control P3a: novelty orienting	Motor preparation	Cognitive preparation, time estimation and working memory	Semantic language processing, contextual integration
Generators	Anterior cingulate cortex; modulated by Dorsolateral prefrontal cortex & dopamine	NogoP3: Anterior cingulate cortex, Dorsolateral prefrontal cortex, parietal cortices cue P300: posterior attention networks P3a: inferior parietal & prefrontal regions; reflects phasic noradrenergic activity	supplementary motor area, motor cortices	supplementary motor area, motor cortices	Anterior medial temporal lobes
Exemplary findings in AD-HKD	Reduced ERN ⇒attenuated anterior cingulate cortex activity and reduced control; Diminished sensitivity to internal feedback, enhanced sensitivity to external negative feedback	Reduced target P300 amplitude and Nogo-P300 anteriorisation Reduced cue P3 ⇒attentional problems More pronounced deficits in NoGo P3 ⇒inhibitory problems	LRP attenuations	Reduced CNV	
Specificity	Low	None (except topography)	Low	Low	Low

Neuropsychology

The neuropsychology of AD-HKD has been extensively studied. Much of the early interest was in identifying the "attention deficit" in AD-HKD and more recently, there has been a focus on behavioural inhibition and other executive functioning deficits. It is, however, becoming increasingly clear that a broader approach is required (Castellanos et al. 2006; Coghill, Nigg, Rothenberger, Sonuga-Barke, & Tannock 2005; Nigg 2006). In a similar vein, whilst initial studies sought to identify the "core deficit" associated with AD-HKD, it is now agreed that causality is much more complex than previously thought and causal models will need to accommodate multiple deficits (Coghill, Nigg, Rothenberger, Sonuga-Barke, & Tannock 2005; Sonuga-Barke 2003). As there are more than 200 publications assessing the neuropsychological deficits associated with AD-HKD, it is necessary to structure any review of this data. Here, I will broadly follow the structure outlined by Nigg (2006), which organises the most relevant neuropsychological processes into functional domains and sub-domains. I shall use a modified version of this structure to discuss the relevant findings for neuropsychological deficits in AD-HKD (Table 2.5).

Table 2.5: The key functional neuropsychological candidate systems and subsystems that have been proposed as being potentially important in the development of AD-HKD (after Nigg (2006) page 66)

1. Attention and arousal
   - A) Posterior attention system
     - i) Reflexive spatial orientating (where do I look)
     - ii) Perceptual selection (what do I look at)
     - iii) Other bottom-up selection processes
   - B) Vigilance system
     - i) Alerting or Arousal: Readiness for new or unexpected stimuli
     - ii) Sustained attention (vigilance) to ongoing or expected stimuli
2. Executive functioning ("Cognitive control", "effortful control")
   - A) Control of Attention
     - i) Conflict detection
     - ii) Control of interfering information / responses
     - iii) Set-shifting
   - B) Control of motor response and behaviour
     - i) Suppressing or interrupting a prepotent (prepared) response
     - ii) Delaying any and all responses
   - C) Working memory
     - i) Auditory working memory
     - ii) Spatial working memory
     - iii) Location working memory
   - D) Planning / organisation
   - E) State regulation / activation
3. Motivation
   - A) Reward system: Excitement / approach to incentive
   - B) Anxiety / behavioural inhibition system
   - C) Fight-flight system: Panic / pain, emergency, or attack
4. Temporal Processing
5. Non executive memory processes

Attention and Arousal

Attention is the ability to routinely filter the vast amounts of information that surround all of us all of the time. It can be further subdivided into the relatively reflex processes of the posterior attention system i.e. reflexive spatial orientating (where do I look) and perceptual selection (what do I look at) and the arousal and vigilance processes. There are, of course, also additional more active, strategic attentional processes, however, these will be covered in the section on executive functioning.

Posterior attention system

At least 14 studies have investigated the integrity of reflexive visual orientating in AD-HKD using the spatial orientating task. A meta-analysis of these studies concluded that there is no evidence for a deficit in AD-HKD (Huang-Pollock & Nigg 2003). Early studies of visual early perceptual selection reported no differences between AD-HKD and healthy children. Unfortunately these studies failed to control for "perceptual load" (i.e. the levels of distraction surrounding the child in the testing session). However, when Huang-Pollock conducted a series of experiments where perceptual load was carefully controlled, these confirmed the earlier reports that there is no obvious deficit in reflexive visual orientating in subjects with AD-HKD (Huang-Pollock, Nigg, & Carr 2005). Although not well studied, these findings seem to hold up in inattentive as well as combined type AD-HKD (Huang-Pollock, Nigg, & Carr 2005).

The findings with respect to early auditory perceptual selection are less clear. There is some evidence that children with AD-HKD perform poorly in dichotic listening tasks where they need to concentrate on information fed into one ear whilst ignoring the information fed into the other (e.g. Manassis, Tannock, & Barbosa 2000; Satterfield, Schell, & Nicholas 1994). There are, however, many methodological issues relating to these studies.

Vigilance system

It is often assumed that sustained attention is the core deficit in AD-HKD. Sustained attention refers to the ability to maintain an attentive state during prolonged mental activity. The most commonly used measure of sustained attention is the continuous performance task CPT. In the CPT the subject is expected to continue to respond to a rare target over extended periods of time (e.g. around 15 minutes). If there is a deficit in sustained attention then accuracy should fall off over time. Interestingly, when children with AD-HKD complete this task their performance does not fall off any faster than that of control children suggesting that, under normal circumstances, there is no deficit in sustained attention (Sergeant, Oosterlaan, & Van der Meere 1999). A deficit can, however, be demonstrated in these children when very slow event rates are used (e.g. 8 seconds per trial rather than 1 -2 seconds) (Van der Meere 2002). Children with AD-HKD do have difficulties with the continuous performance task compared with control however these are evident from the beginning of the task and do not get worse as the trial proceeds (Sergeant & van der 1990). It has been suggested that this pattern of effects is more likely to be due to an alerting dysfunction than one of selective attention. There are other lines of evidence that support alerting and arousal difficulties. Subjects with AD-HKDS also have slow and variable responses from the start of fast reaction time tasks (Huang-Pollock & Nigg 2003; Oosterlaan, Logan, & Sergeant 1998), and slow responses on a series of unwanted abrupt-onset events in a fast reaction time experiments (Nigg, Swanson, & Hinshaw 1997). Taken together, these findings can be interpreted as a deficit in either alerting or phasic arousal (Nigg 2006).

Executive Functioning

The “executive functions” have been defined in many different ways. Willcutt et al (2005) suggest that they “represent “top-down” cognitive inputs, which facilitate decision making, by maintaining information about possible choices in working memory and integrating this

knowledge with information about the current context to identify the optimal action for the situation." They comprise a series of inter related constructs, including high level control of attention and attentional set-shifting, response inhibition, working memory, planning / organisation and state regulation.

Executive Control of Attention

Children with AD-HKD are often described as distractible and appear to have difficulties filtering out irrelevant information in order to focus and concentrate on a task. In attention research these abilities are termed "late selection" or "interference control" and are measured by tasks such as the Stroop, the Flanker and directed forgetting tasks. Of these, the Stroop task has received the most attention in AD-HKD research. Both van Mourik et al. (2005) and Homack and Riccio (2004) conducted meta-analyses of the Stroop in AD-HKD and concluded that the Stroop task did not discriminate AD-HKD groups from other clinical groups consistently across studies, and that the available evidence does not provide strong evidence for a deficit in interference control in AD-HKD.

Attentional set-shifting refers to the ability to shift attention from one aspect of a task to another. It is measured by a range of tasks including the Trail Making Test, the Wisconsin Card Sort Test, the Switching task and the Intradimensional/Extradimensional Shift task. Willcutt et al. (2005) included data from several studies, using the Trail Making Test and the Wisconsin Card Sort Test in their meta-analysis. They concluded that Wisconsin Card Sorting Test perseverative errors were more weakly related to AD-HKD than many of the other executive function (EF) tasks and noted that only a minority of studies (11/24, 46%) detected a significant group difference. The mean effect size for these tasks was among the lowest of all the tasks (d = .46). The results for the Trails B test were only slightly more positive (8/14 positive, 57%; d = .55). Thus it would appear that whilst there is an

association between set-shifting and AD-HKD this appears to be weaker than for other executive functions.

Control of motor response and behaviour

Response suppression or response inhibition is the ability to quickly interrupt an ongoing behaviour and is recognised as crucial to effective self regulation. Frequently used tasks include the Go/NoGo task, the Stop task and the Antisaccade task. Of these, the Stop task has received the most attention in recent studies as it allows the researcher to model the ability to inhibit a prepotent response and estimate the time required to withhold a response. Willcutt et al. (2005) found that of all tasks studied, the stop task was the one on which group differences between AD-HKD and controls were most consistently reported (82% of 27 studies; d = 0.61). The evidence for an inhibition deficit from Go/NoGo tasks and antisaccade tasks is less clear with variable findings between studies (Nigg 2006).

Barkley (1997a) proposed that deficits in response inhibition constitute the "core" deficit in AD-HKD and that all other executive deficits are a consequence of this primary deficit. Several lines of investigation, including the present study, have suggested that, whilst children with AD-HKD do seem to have deficits in response inhibition, this does not appear to be the primary deficit and that it is certainly not an essential component in the causal chain for AD-HKD (Rhodes, Coghill, & Matthews 2005).

Working memory

The term working memory has been used in different ways by different authors. Whilst some authors consider working memory simply as the process of actively maintaining relevant information in mind for brief periods of time (Gleitman, Fridlund, & Reisberg 1999), a more comprehensive and influential view emphasises the importance of computational processing and states that working memory is best considered as the capacity to simultaneously store and manipulate information (Baddeley 1986; Baddeley

2003). Indeed, Baddeley (1996) endorses Daneman and Carpenter's definition of a working memory task as "one that simultaneously requires the storage and manipulation of information" (Daneman & Carpenter 1980), thus differentiating such tasks from those that require storage but no manipulation. Whilst there have been fewer studies of working memory than of the other executive domains, Willcutt et al. (2005) analysed data from eight studies using one of two such "true" visual working memory tasks (the Self Ordered Pointing task and the CANTAB Spatial Working Memory Task) and reported that 75% of these studies reported group differences with a pooled effect size d of 0.63. Significant group differences were also reported by 55% of the 11 studies (*d* = 0.55) that included one of the verbal working memory tasks (Working Memory Sentence Span and Digits Backward), and three of the non-significant results were moderate effects (*d* = 0.49 –0.53) that were probably not significant due to small sample size. A separate meta-analysis, focused on working memory, that examined a somewhat different subset of studies including measures of simple storage, detected stronger effects (d = 0.85–1.14) for spatial working memory manipulation tasks when they were distinguished from simple storage (Martinussen et al. 2005). They suggest that manipulation of spatial working memory may offer the strongest evidence in AD-HKD, but direct comparison studies have not yet been conducted.

Planning / organisation

Several tasks have been used in AD-HKD samples to measure planning / organisation. These include the Tower of Hanoi / London / Stockings of Cambridge, the Porteus Mazes and the Ray-Osterreith Complex Figure. These tasks (excepting the Stockings of Cambridge for which there was insufficient data at the time) were included in the Willcutt et al (2005) meta-analysis. The majority of studies reported significant group differences on the measures of planning (59% of 27 studies). The results were stronger and more consistent on the Tower of Hanoi (4/7, 57%; *d* = 0.69) and Porteus Mazes (4/5, 80%; *d* = 0.58) than the

Tower of London (3/6, 50%; *d* = 0.51) and Rey–Osterreith Complex Figure Test (5/9, 56%; *d* = 0.43).

State regulation/ activation

Activation is the ability to maintain a level of readiness to respond. Two types of task have been used to measure activation; the "time-on-task" design (does the child respond as quickly towards the end of the task as they did at the beginning?), and the "event rate" design (does a child show better levels of activation with faster trial presentation than a slower one?). Evidence supporting an activation deficit has come mainly from the event rate design. Children with AD-HKD perform best at a medium event rate (e.g. presentation rate of 1 target every 4 seconds) with poor performance at either a slow event rate (e.g. every 10 seconds) or a fast event rate (e.g. every second), on both the continuous performance task (Van der Meere et al. 1995) and on Go/NoGo tasks (Borger & van der 2000; Van der Meere & Stemerdink 1999). These researchers interpret this data as indicating that AD-HKD is associated with under-activation and that it is this under-activation that explains the other performance deficits in AD-HKD (Sergeant, Oosterlaan, & Van der Meere 1999; Van der Meere 2002). Other supportive data for this position comes from studies in which children are found to respond slowly when asked to respond quickly on a motor task (Carte, Nigg, & Hinshaw 1996). It is also in line with some of the EEG and ERP data presented earlier (Van der Meere 2002). Studies looking at cardiac response to the stop task (Jennings et al. 1997), the Go/NoGo task (Borger & van der 2000)and to warning stimuli (Dykman, Ackerman, & Oglesby 1992) have also supported an under-arousal hypothesis. There are, however, also some contradictory findings particularly from continuous performance task data, where the predicted deficits on the beta parameter, which is an index of risky vs. conservative response bias, have not been confirmed (Losier, McGrath, & Klein 1996).

Executive functioning and AD-HKD Subtypes

Relatively few studies have investigated the relationship between executive function and DSM-IV ADHD subtypes. In their meta-analysis Willcutt et al. (2005) report that both the combined and inattentive subtypes differ significantly from healthy comparison groups on Stop Signal Reaction Time (inattentive type *d* = 0.68, combined type *d* = 0.86) and on most other neuropsychological measures (*d* across measures = 0.58 for the inattentive type and 0.57 for the combined type). There were, by comparison, few differences between the inattentive and combined types on any measure. Only three studies included the hyperactive/impulsive subtype (Bedard et al. 2003; Chhabildas, Pennington, & Willcutt 2001; Schmitz et al. 2002). When taken together these studies suggest that the hyperactive / impulsive type is associated with only minimal executive functioning impairment (mean *d* = 0.14) Whilst these results need to be interpreted with caution until data from larger samples are collected, they do provide some initial support for the hypothesis that executive dysfunction is associated with the inattentive rather than hyperactive / impulsive symptoms of AD-HKD. This is in keeping with a study that included both symptom dimensions in a regression model predicting executive dysfunction (Chhabildas, Pennington, & Willcutt 2001) and found that inattention, but not hyperactivity /impulsivity, was independently associated with executive impairments.

Several studies have reported that, although the AD-HKD main effects were weakened, group differences on Stop Signal Reaction Time, Continuous Performance Task omission errors, planning tasks, and spatial and verbal working memory tasks remained significant after the effects of intelligence, reading achievement and symptoms of comorbid disorders were controlled for (Barkley et al. 2001; Nigg et al. 1998; Nigg 2001; Nigg et al. 2002; Rucklidge & Tannock 2002; Willcutt et al. 2001; Willcutt et al. 2005). These results suggest that whilst other factors may contribute to the executive dysfunction in AD-HKD subjects, they do not completely explain this association.

Motivation

Motivation can refer to several differing levels of representation. In common usage it often refers to questions like “Are they trying” and “How can we motivate them to do better?”, both of which are frequently asked about children with AD-HKD. Motivation can also refer to long term goals and values and it is possible that children with AD-HKD have problems in this respect. However, as this has not been rigorously studied, I will restrict my discussion to the motivation encountered in more immediate situations defined by Nigg as “the child’s interest in and response to immediate incentives (reminders of or cues to impending reward or punishment)” (Nigg 2006).

In this sense motivation is seen as being perhaps most relevant to the hyperactive – impulsive symptoms of AD-HKD. It has been linked with the approach / withdrawal aspects of temperament and children with AD-HKD have been described as having difficulties with approach rather than withdrawal (Nigg 2006).

Approach and reward response

Approach in this context is typically operationalised as responding to potential rewards. Approach and reward response difficulties have been suspected in AD-HKD for many years (Douglas 1972) and have received renewed interest recently (Sagvolden, Johansen, Aase, & Russell 2005). The theoretical underpinnings of this work are largely based on the theories of Gray (1971; 1982; 1991) who proposed a “behavioural activation system” that activates motor response to signals for reward (“conditioned appetitive stimuli”) and active avoidance behaviours in response to cues of non-reward or punishment. Neural mediation was proposed to occur via the ascending dopaminergic pathways, which pass from the substantia nigra and ventral tegmental area to the basal ganglia, limbic system, lateral hypothalamus and prefrontal cortices. Current theorists continue to accept the broad outline of Gray’s proposals (Sagvolden, Johansen, Aase, & Russell 2005).

Lumen et al. (2005) recently reviewed the literature on reward responding in AD-HKD. They reported mixed findings with no consistent support for any one position. They were however able to make several observations; AD-HKD is associated with increased weighting of immediate over delayed reward; children with AD-HKD may respond better to high-intensity reinforcement; and the limited physiological literature suggests under response to reward. Douglas has proposed that children with AD-HKD are over responsive to immediate reward and under responsive to delayed reward (Douglas 1988), a proposal, which is supported by evidence from Tripp and Alsop (Tripp & Alsop 1999), and which, deserves further attention. Johansen et al. (2002) have proposed that AD-HKD is characterised by an abnormally steep "delay-reward" gradient i.e. the effectiveness of a reward drops off more quickly than expected as it becomes more distant in time from the cue. This hypothesis is supported by animal studies and some data on learning and extinction in children with AD-HKD (reviewed in Sagvolden 2001). However difficulties in finding an appropriate measure of delay-reward gradient in human subjects have somewhat hindered progress (Coghill 2005).

Another aspect of motivational behaviour, which has become prominent in the study of AD-HKD is the concept of "delay aversion" (Sonuga-Barke, Taylor, Sembi, & Smith 1992; Sonuga-Barke, Taylor, & Heptinstall 1992). Here children are proposed to have difficulty in tolerating delay such that they will consistently choose immediate small rewards over delayed larger ones and that this occurs, not because they can't wait, but rather that they find doing so intolerable (Sonuga-Barke et al. 2002). This is one of the few tasks to have been tested "head to head" with an executive functioning task. In this study delay aversion was found to have an equivalent, but independent, effect as the Stop Signal Task (Solanto et al. 2001).

Withdrawal response

Hypotheses regarding withdrawal response and AD-HKD suggest that children with AD-HKD will have difficulties in benefiting from warnings of possible punishments. As a consequence they will fail to learn from mistakes and fail to develop appropriate systems of self control. As adolescents, they would be expected to display impulsive, poorly socialised behaviours typical of much younger children. With respect to AD-HKD such theories would be expected to be associated with hyperactive / impulsive symptoms rather than inattention (Quay 1997). In Gray's model (Gray 1982) a behavioural inhibition system was proposed which was postulated to be mediated via the noradrenergic and serotonergic neurotransmitter systems. Quay (1988) suggested that AD-HKD may be a consequence of a failure in avoidance learning due to a breakdown in this behavioural inhibition system. It has, however, been difficult to test this proposal as it has, again, been difficult to find an appropriate probe of this withdrawal system in children. Those studies, which have attempted to investigate this system, using tasks such as a motivated Go/NoGo task, the Card Playing Task and physiological measures of changes in skin conductance following removal of reward, have not reported consistent evidence for a weak behavioural inhibition system in AD-HKD (Nigg 2006, pages 151 - 155). Further study is, however, warranted to investigate alternative paradigms. Such studies could also focus their attention on groups, which may be at particularly high risk for such difficulties, such as those with low anxiety scores (high anxiety is inconsistent with weak behavioural inhibition).

Response Modulation

In a modification of Gray's model Newman and colleagues (MacCoon, Wallace, & Newman 2004; Newman & Wallace 1993) have proposed "response modulation" as a relatively automatic process by which new information is regularly sampled from the environment in order to inform ongoing behaviours. Deficient response modulation will result in the failure to modify an ongoing behaviour as a consequence of new information. They suggest that disinhibition can result from a failure in cross regulation between the behavioural inhibition and activation systems (Newman & Wallace 1993). This hypothesis has only had limited evaluation to date. Studies using the Card Playing / Door Opening Tasks report mixed results and do not yet provide strong support for this theory (Daugherty, Quay, & Ramos 1993; Matthys et al. 1998; Milich et al. 1994). Further study is required.

"Hot" and "Cold" Executive Functions

Castellanos et al. (2006) have drawn attention to the contrast between what Zelazo and Muller (2002) describe as "hot" and "cool" executive functions. Cool executive functions comprise those processes, which are more purely cognitive in nature and are usually associated with the dorsolateral prefrontal cortex, whilst "hot" aspects of executive functioning have a greater affective component, often have a motivational component and tend to be associated with the orbitofrontal and medial prefrontal cortices. The tasks previously reviewed in the section on executive functions are examples of the cool executive functioning and, in view of their importance in AD-HKD Zelazo and Muller (2002) concluded that AD-HKD, is a disorder of cool executive functioning. Castellanos et al. (2006) suggest that this may be a rather premature conclusion as few investigators have studied the hot aspects of executive functioning in AD-HKD. They include the evidence supporting the role of delay aversion and preliminary evidence demonstrating that deficits on the Iowa Gambling task are associated with hyperactivity/impulsivity symptoms, but not with either symptoms of inattention, or the 'cool' EF measures such as working memory or IQ (Toplak,

Jain, & Tannock 2005). They therefore suggest that increased attention should be focused on the development of new paradigms to evaluate these motivational aspects of functioning in children with AD-HKD.

Temporal Processing

Castellanos and Tannock (2002) point out that some of the most striking clinical characteristics of children with AD-HKD are their transient but frequent lapses of intention and attention, their moment-to-moment variability and inconsistency in performance. AD-HKD symptoms are expressed variably over time and indeed response variability is possibly the one ubiquitous finding in AD-HKD research across a variety of tasks, researchers and cultures (Douglas 1999; Kuntsi, Oosterlaan, & Stevenson 2001; Kuntsi & Stevenson 2001). This response variability reflects a high frequency of both slow and fast/anticipatory responses. Although they may merely represent a non-specific association with sub-optimal neural functioning, they may be rather more specific. Abnormalities in the reproduction of temporal durations have been documented in children, adults and adolescents with AD-HKD (Barkley et al. 1997; Barkley, Edwards, Laneri, Fletcher, & Metevia 2001; Barkley, Murphy, & Bush 2001), albeit at relatively long time intervals (i.e. 2–60 sec.), which are thought to require cortical mediation and rehearsal in working memory. Performance for intervals of less than 1 sec. is dependent on subcortical circuits (the basal ganglia and cerebellum)(Ivry 1997). A study using intermediate durations (1.0 and 1.3 sec.) also detected an isolated time perception deficit in subjects with AD-HKD (Smith et al. 2002). Toplak et al. (2003) investigated time estimation and time reproduction with intervals as brief as 400 ms in children and adolescents with AD-HKD. AD-HKD groups were impaired in duration discrimination, reproduction and showed high variability in their performance on the reproduction task even at these relatively brief intervals. Castellanos and Tannock have therefore proposed that temporal processing deficits should be considered further as a

potential candidate endophenotype for AD-HKD (Castellanos & Tannock 2002), and have further suggested that these temporal difficulties may be linked to cerebellar dysfunction.

Non executive memory processes

Whilst there has been much interest in the potential role of working memory deficits in AD-HKD, few studies or commentators have considered the potential role that non-executive memory processes could play in the causality of AD-HKD. Indeed, in his otherwise comprehensive review of the causes of AD-HKD, Nigg dismisses basic memory functions in a sentence (2006, page 65). In part this may be due to the often imprecise use of the term "working memory" by many authors whereby it is assumed that any short term memory task is a "working memory" task and therefore a measure of executive functioning. As a consequence memory deficits on these more basic tasks have not been differentiated from "true" working memory tasks with a high executive demand. Further to this, and even more generally applicable, to many if not all of the deficits reported on "executive" tasks, is the failure to use non-executive control tasks, which allow the researcher to ensure that the deficits seen on the executive tasks are indeed executive in nature and are not confounded by more 'primitive' cognitive or physiologic processes (Castellanos et al. 2005). Two recent studies highlight the seriousness of this issue by demonstrating that when non-executive abilities are accounted for by using appropriate control tasks, little evidence of executive dysfunction remains (Marks et al. 2005; Rhodes, Coghill, & Matthews 2005). The findings of the Rhodes, Coghill and Matthews study will be described in detail in subsequent Chapters. Their findings are not, however, unique and several other published studies have reported deficits in memory tasks with low executive demands (e.g. Chelonis et al. 2002; Wilson et al. 2006).

Limitations of Neuropsychological Approaches

Whilst neuropsychological testing can play an important role in developing our understanding of the cognitive mediators that bridge the gap between the structural and functional neurological consequences of genetic and environmental causal agents and the symptoms of AD-HKD, it is important to bear in mind the various limitations associated with these tasks, their administration and the interpretation of their results.

Perhaps the most important limitation concerns the measurement error associated with these tasks, and the failure of researchers to take this measurement error into account. Whilst measurement error is an inevitable component of all types of measure it is a particular issue for neuropsychological tasks. All tasks are associated with measurement error and whilst some have demonstrated better reliability than others few, if any, perform well under all circumstances. Executive functioning tasks, which are somewhat dependent on novelty, have been demonstrated to have particular problems with test retest reliability (Rabbitt 1997). In addition to the error associated with the task itself additional error arises from the interaction between the task, the subject and the tester. Aspects of the subject that may increase the error include the presence of; hearing and visual difficulties, motor problems, attentional difficulties and distractibility, problems with working memory and retrieval, frustration, fatigue and motivational problems and mood and anxiety symptoms. Variability between, and within, test administrators can introduce error by using non-standard and inconsistent administration protocols and by failing to standardise their interactions with the subjects and the testing conditions. Brain dysfunction in general and ADHD specifically, is associated with performance inconsistency and it is therefore possible that neuropsychological deficits seen on one testing session would not be seen at another session. Whilst modern tasks such as those included in the Cambridge Neuropsychological Test Automated Battery (CANTAB, Fray & Robbins 1996) that was used in this study have attempted to reduce error by utilizing automated computerised tasks with simple scripted

instructions and imbedded control tasks that can help to identify many of the in-subject problems described above, it is not possible to account for all factors and a degree of error remains likely.

A further limitation inherent to neuropsychological tasks relates to validity and, in particular, their relationship with real world functioning. Many of the tasks used in early studies were originally developed as clinical tools whose purpose was to differentiate between those who had and had not suffered brain damage either as a result of trauma or disease. Validity was dependent on their ability to differentiate between these two groups rather than their ability to measure a particular aspect of functioning. In general those studies that have reported on the ability of these tasks to predict everyday and vocational functioning have found it to be moderate at best (Sbordone & Guilmette 1999). More recently a new generation of tasks, such as those used in the CANTAB battery, which were grounded in neuroscience rather than clinical practice, have been developed. These tasks were developed to be “purer” than the clinically driven tasks and to index specific neuropsychological functions and their links to particular aspects of brain functioning. Whilst these tasks have advanced the field considerably is remains necessary to acknowledge their limitations. Whilst their neuroanatomical specificity may be more precise than that of the clinically driven tasks they continue to rely on large and divergent neural networks and performance may index not only an absolute or relative deficit but also the use of compensatory neural networks. Also the relationships between task performance and real life functioning has not been well studied making it difficult to draw clinical conclusions from task performance.

For these reason caution must be exercised when drawing conclusions from neuropsychological tasks data to ensure that the data is not over interpreted.

Neuropsychology Summary

Even taking these limitations into account these findings demonstrate the broad range of neuropsychological deficits associated with AD-HKD. There is no consistent evidence to support the notion that one aspect of functioning or deficit has primacy over any others. Indeed, when one looks at the available data on effect sizes they all tend to be in the range *d* = 0.4 – 0.6 with only a few tasks showing consistently stronger effects and none reaching anywhere near the effect sizes reported for AD-HKD symptoms in case - control studies (e.g. d = 2.5 - 4.0 in the studies which were included in the meta analysis of Willcutt et al. 2005)). The correlations between AD-HKD symptoms and neuropsychological measures, whilst usually significant and similar to those for the AD-HKD structural imaging studies, are relatively small (r = 0.15 - 0.35; Nigg, Hinshaw, Carte, & Treuting 1998; Willcutt, Pennington, Boada, Ogline, Tunick, Chhabildas, & Olson 2001). Effect sizes of this magnitude suggest a substantial overlap between AD-HKD and non-AD-HKD samples on these measures and that a significant proportion of children with AD-HKD are performing in the normal range. Efforts to evaluate the predictive power of executive function measures in relation to a diagnosis of AD-HKD suggest that whilst sensitivity is reasonable, specificity is poor (Barkley, Grodzinsky, & DuPaul 1992; Doyle et al. 2000; Hinshaw et al. 2002). In other words, those with poor performance are likely to have AD-HKD but very few of those with AD-HKD will perform poorly on any particular task and that the absence of a specific neurocognitive deficit does not rule out the presence of AD-HKD (Grodzinsky & Barkley 1999). It has also been suggested that whilst family and twin studies suggest that these small to medium associations between executive functioning deficits and AD-HKD symptoms are mainly due to genetic factors, the majority of the genetic and environmental influences on AD-HKD symptoms are independent from the influences that lead to weaknesses in executive control (Doyle et al. 2005).

In summary, it is currently the case that none of the neuropsychological deficits that separate cases from controls can be considered either necessary or sufficient on their own to cause AD-HKD. As a consequence neuropsychological (as well as genetic, environmental, neuroanatomical, pathophysiological and clinical) heterogeneity is to be expected and will need to be accounted for within causal models of AD-HKD.

Summary and Conclusions

In this Chapter I have summarised the literature pertaining to the causes of AD-HKD. From this review it is clear that in addition to the clinical heterogeneity described in Chapter 1, there is considerable heterogeneity with respect to the potential genetic and environmental causal factors, which have been associated with AD-HKD. The evidence here supports the notion that AD-HKD is a highly heritable but complex polygenic disorder, which is also likely to be influenced by a wide range of environmental factors. It is not yet clear whether these environmental factors exert their influence independently of the genetic factors or through complex gene x environment interactions and/or correlations, but it seems likely that there is at least some degree of interaction between the two and that this explains some degree of the observed heritability.

There also appears to be considerable heterogeneity with respect to the various pathophysiological and neuropsychological mediators that bridge the gap between the genetic and environmental causal factors and clinical symptoms. Taken together, this evidence strongly suggests the presence of complex multiple causal pathways. Although there has been some attempt to integrate these findings, most studies published to date have been conducted at a single level of analysis and have tended to focus on single causes. Such studies are not able to fully address the complexity that is AD-HKD, nor are they able to develop and test the multiple pathway models that are required to make sense of existing data.

In Chapter 3, I will consider the implications of these findings on current causal models, investigate some of the limitations of current knowledge and suggest some ways that understanding can be moved forward.

Chapter 3

Causal Modelling in AD-HKD

In Chapter 2, I summarised contemporary knowledge, and limitations, regarding our understanding of the causes of AD-HKD. From this discussion it is clear that the simple statement made in 2000 by the National Institute for Mental Health (Kupfer et al. 2000), and which is frequently quoted by those who continue to question the validity of AD-HKD, that; "*after years of clinical research and experience with ADHD, our knowledge about the cause or causes of ADHD remain largely speculative*" (page 3) is unhelpfully simplistic. There are clearly many genetic, neuroimaging, neurophysiological and neuropsychological studies, which not only support the validity of the disorder, but also provide evidence for it having a biological basis. However, whilst it is true that the field has reached a point at which relatively sophisticated causal theories are proposed, (Barkley 1998; Sonuga-Barke 2002), we still remain some distance from demonstrating a full causal model of AD-HKD, or its component symptom dimensions, in a way, which incorporates multiple levels of analysis (Coghill, Nigg, Rothenberger, Sonuga-Barke, & Tannock 2005). That this is the case should come as no surprise. The brain is the most complex of biochemical 'machines' and this, linked with the complex polygenic genetic underpinnings of AD-HKD (Stevenson et al. 2005) , means that a full causal model will need to be able to *"predict a ballet choreographed interactively over time among genotype, environment, and epigenetic factors, which gives rise to a particular phenotype"* (Gottesman & Gould 2003).

This Chapter summarises current thinking about the use of causal modelling in developmental psychopathology and its relationship with heterogeneity then, focussing on AD-HKD, explores some of the important considerations which must be addressed if we are to shift from positing causal theories to demonstrating formal causal effects. Several

sections of this Chapter draw heavily on a previous paper "**Whither Causal Models in the Neuroscience of ADHD"** (Coghill, Nigg, Rothenberger, Sonuga-Barke, & Tannock 2005, reprint included as appendix 1)[3].

Current thinking about the use of causal models in developmental psychopathology.

The Shift towards cognitive neuroscience

Whilst we still lack an agreed, satisfactory and comprehensive theoretical framework, which can fully integrate information from across the various levels of analysis into a complete account of the development of psychopathology, considerable progress has been made over recent years.

Initial theories related to Freud's psychoanalytic theories of development and remained dominant, from their beginnings in the early 20th century, for at least 50 years and in some regions, for much longer. However, from the 1950s onwards there started to be a divergence of thinking with psychology replacing psychoanalytic theories, first with learning theory and later through cognitive-behavioural theory, whilst within psychiatry the school of biological psychiatry assumed prominence. Whilst both of these approaches clearly had their own distinct advantages and disadvantages, neither was able to offer a complete understanding of the causes and development of the psychopathology. One frequently utilised solution was to lay each approach alongside the other without any attempt at integration. Another was to discuss the importance of a "biopsychosocial" model of understanding but as Pennington (Pennington 2002, page 2) eloquently describes, this

[3] DC & E S-B conceived the paper, DC wrote the first draft, JN, AR, E S-B & RT commented on this draft, DC wrote the final manuscript.

approach is frequently “an ecumenical umbrella for covering disparate approaches rather than an integration”.

More recently the field of cognitive neuroscience has developed as an explicit attempt to integrate these approaches in order that, through study of the neural substrates of mental processes and their behavioural manifestations, the biological mechanisms underpinning cognitive processes can be better understood. As a general field, cognitive neuroscience aims to describe these processes as they occur within the healthy adult, however, it has been possible to adopt and adapt the methods of cognitive neuroscience to enable us to move closer to the goal of developing integrated, comprehensive and developmental sensitive causal models for developmental psychopathologies. This has required the introduction of experimental techniques and designs, which can address individual differences, the impact of environmental factors and an explicit developmental approach.

The causal modelling approach

Perhaps the most influential approach to utilise these theoretical advances has been the developmental causal modelling framework initially proposed by Morton and Frith (1995). In this paper they set out a series of ground rules for guiding the construction and use of causal models;

1. ***Start with biology.*** The causal chain should start with the biological origins or a clear statement that there are no such factors.

2. ***Build causal chains.*** The causal chain should be specified, or at least sketched, from the origin to the behaviour.

3. ***Give full account.*** The causal model should account for, or at least mention, all signs and symptoms of the disorder.

4. ***Specific over general.*** A distinction between specific and general conditions must be made. Features, which can be accounted for as part of a general condition, need not be mentioned within the causal model of a specific condition.

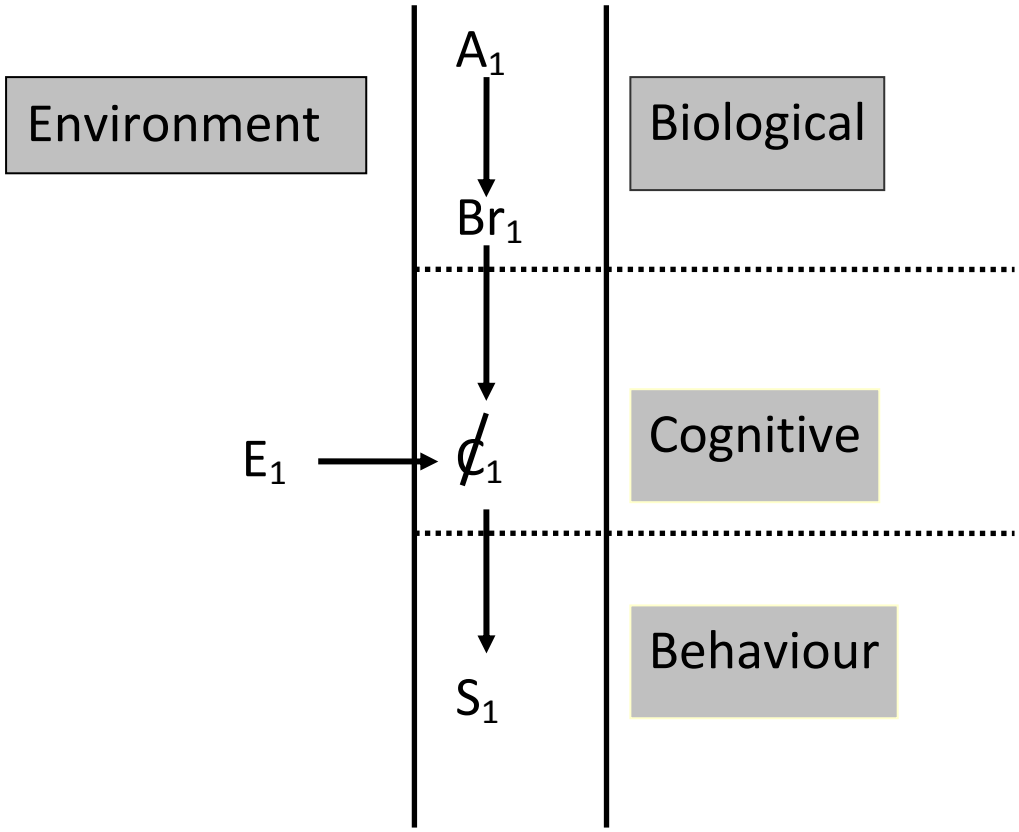
5. ***Correlation is not causation.*** Do not confuse correlation with cause.

Another key tenet of this approach is the recognition that, in order to fully describe psychopathological conditions, it is necessary to integrate information across several levels of analysis. Morton and Frith describe three basic within person levels of analysis, namely biological, cognitive and behavioural, with a separate domain for environmental influences, which can interact at any of the three levels. Causal models are built by linking elements within the same or different levels into causal chains (Figure 3.1).

As demonstrated in Figure 3.1, when originating causes (genetic or environmental) are separated from mediating processes (brain mechanisms or cognitive/neuropsychological) and the behavioural phenotype, there are five key levels of analysis that require to be integrated into a causal model – genetic and environmental causal factors, brain mechanisms, neuropsychological and behavioural. It should be noted that this notation is not unique to Morton and Frith; Pennington (1991; Pennington 2002) has proposed a very similar organisational structure. These models can embrace the concept of change over time and encourage integration across multiple levels of analysis, providing the structure for a more complete explanation of the disorder than is otherwise possible.

In line with the basic aims of cognitive neuroscience, the theoretical neutrality of these frameworks also allows for the comparison and integration of very different theoretical approaches.

Figure 3.1: A hypothetical simplified causal model. A_1 refers to genetic originating causes, E_1 refers to environmental originating causes, Br_1 to the abnormal brain conditions, the struck out C_1 to a cognitive process/neuropsychological process which is altered by virtue of the brain condition and S_1 to the signs and symptoms. (Coghill et al. 2005)



Endophenotypes and causal modelling.

A further advantage of the causal modelling framework is that it provides a helpful notation to visualise potential endophenotypes within a causal model. Endophenotypes are those mediating factors, the unseen components, which sit between the observed manifestations of a disease or disorder and its originating causes. With respect to neuropsychiatric conditions they may be neuroanatomical, biochemical, neurophysiological or neuropsychological in nature (e.g. Gottesman & Gould 2003). They are particularly useful in helping us to develop our understanding of conditions in which complex genetic and environmental factors must be linked to a behavioural phenotype, which is itself difficult to define precisely and consistently. The endophenotype concept fits comfortably within the causal modelling framework, with endophenotypes representing aspects of abnormal functioning at either the biological or cognitive levels. Accurate characterisation of candidate endophenotypes for developmental psychopathological disorders will suggest simpler clues to the originating causes of this disorder than does the behavioural phenotype itself. Properly characterised endophenotypes have the potential to further aid genetic research by acting as measurable markers of genetic risk. Inherent to this argument is the suggestion that by deconstructing a developmental disorder into its underlying component processes, we will not only simplify genetic analysis but also provide alternative ways of describing and classifying those with the disorder and hopefully reduce the heterogeneity associated with the current behavioural phenotypes.

Various criteria, which should be met by a valid endophenotype have been described (e.g. Almasy & Blangero 2001; Castellanos & Tannock 2002). The endophenotype should:

1.) Be associated with illness in the population

2.) Predict the disorder probalistically

3.) Be closer to the site of the primary causative agent (whether genetic or environmental) than the diagnostic categories are

4.) Be rooted in biology and be biologically plausible

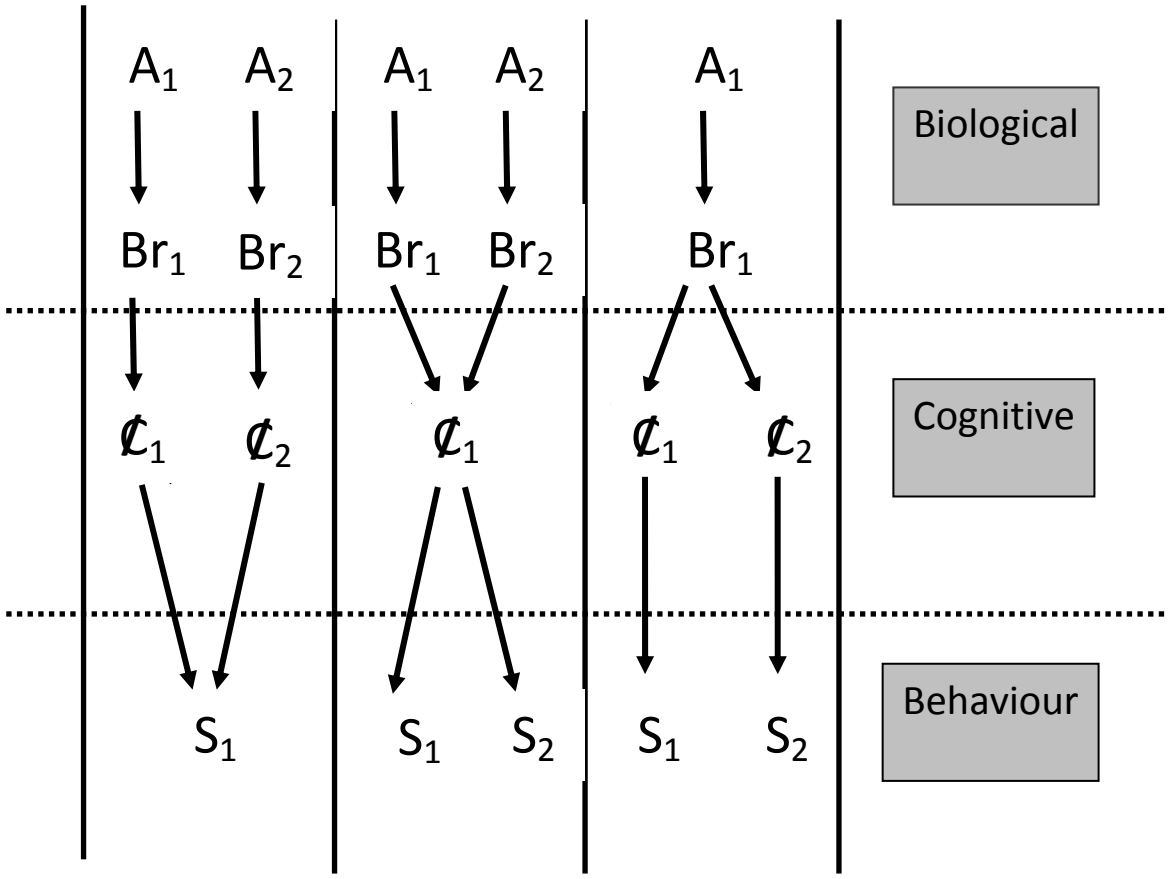
5.) Be continuously quantifiable

6.) Be state independent i.e. manifest in an individual whether or not illness is active.

Although a requirement in the models proposed by several other authors, Castellanos and Tannock (2002), suggest that an endophenotype should not be excluded solely on the basis that existing data suggests that the phenomena in question are not heritable/familial (i.e., 'genetic'). Nevertheless, it is clearly of considerable importance to know whether or not a particular endophenotype relates to genetic causes of a disorder. Where this is so, three further criteria apply(Gottesman & Gould 2003);

1. The endophenotype should itself be heritable
2. The endophenotype should co-segregate with illness within families and
3. The endophenotypes found in affected family members should also be found in non-affected family members at a higher rate than in the general population.

Figure 3.2: Examples of simple "V", "X" and "A" multi-pathway causal models drawn using the notation of Morton & Frith (1995). A_{1-2} refers to genetic originating causes, Br_{1-2} to the abnormal brain conditions, the struck out C_{1-2} to cognitive process/neuropsychological processes which are altered by virtue of the brain conditions and S_{1-2} to the signs and symptoms of the disorder.



Causal Modelling and Heterogeneity

The causal modelling framework is also able to accommodate heterogeneity occurring at any level of analysis. Clearly the very simplistic model presented in Figure 3.1 would not account for the phenotypic heterogeneity found in AD-HKD and described in Chapter 1, which could itself be the result of several different patterns of pathways. Neither would it appropriately describe the situation described in Chapter 2 whereby multiple causal and mediating factors appear to result in an identical behavioural outcome (phenocopies). Clearly there are near infinite possibilities and it is unlikely that any of the slightly more complex, but essentially still very simplistic models, described in Figure 3.2 will be of sufficient complexity to adequately describe either AD-HKD or any of the developmental psychiatric disorders. Such models are, however, useful starting points that enable us to begin to describe the possible variations and can assist when designing studies to investigate these possibilities or to interpreting existing datasets.

Causal modelling approaches have been used successfully with several developmental disorders including autism (Frith, Morton, & Leslie 1991), dyslexia (Morton & Frith 1993) and conduct disorder (Krol, Morton, & De Bruyn 2004).

Several authors have utilised a causal modelling framework to structure discussions on the pathophysiology of AD-HKD (Sonuga-Barke 2005), to propose possible endophenotypes for AD-HKD (Castellanos & Tannock 2002), to describe the likelihood of multiple developmental pathways (Coghill, Nigg, Rothenberger, Sonuga-Barke, & Tannock 2005; Sonuga-Barke 2005) and to investigate the limitations of current evidence regarding cause (Coghill, Nigg, Rothenberger, Sonuga-Barke, & Tannock 2005).

The use of the causal modelling approach in AD/HKD

This causal modelling framework suggests a number of considerations that, if met, could guide theoretical work on AD-HKD and help move towards the demonstration or evaluation of causal claims.

The need to work across multiple levels of analysis

A complete causal model for AD-HKD or its symptom dimensions will require integration of genetic, neural, cognitive and behavioural mechanisms to describe complete causal chains occurring in development. The complexity inherent within each of these levels requires a wide range of specialist knowledge and skills and implies input from researchers with differing scientific backgrounds. Unfortunately most research groups have, to date, had access to only a limited range of such skills and have therefore only been able to work at one level. As a consequence disparate evidence has been generated, which supports the following causal pathway: genetic variations → functional abnormalities in both dopaminergic and noradrenergic neurotransmission within fronto-striatal pathways → deficits in executive and reward related functioning → the behavioural manifestations of AD-HKD (Castellanos & Tannock 2002). Yet few studies have accepted the challenge of working across these levels of analysis in order to define their inter-relationships empirically within the same sample. Exceptions are beginning to emerge. For example, functional neuroimaging (e.g. Durston, Tottenham, Thomas, Davidson, Eigsti, Yang, Ulug, & Casey 2003; Rubia et al. 1999) and electrophysiological studies (e.g. Brandeis et al. 2002; Jonkman et al. 2004; Rothenberger et al. 2000) have started to describe the links between brain and cognitive function. Pharmacogenomic (Roman, Rohde, & Hutz 2004; Seeger, Schloss, & Schmidt 2001) and family and genetic studies of neuropsychological functioning (e.g. Durston et al. 2004; Nigg et al. 2004; Swanson et al. 2000) are also starting to appear and strive to make links between the genetic, neural and cognitive levels of analysis.

Some relevant studies have emphasised the importance of taking comorbidities into account; for example, studies from the UK and Republic of Ireland showed evidence of association with the DRD4 7 repeat allele in a sample of children with both AD-HKD and antisocial behaviour, which was not present in those with AD-HKD alone (Holmes et al. 2002; Kirley et al. 2004). As is often the case, there are also contradictory findings; for example, some studies suggest a greater neurocognitive impairment in children with AD-HKD who also carry the DRD4 7 repeat allele (Langley et al. 2004; Manor et al. 2002), whilst others failed to find such deficits in 7 repeat carriers (Bellgrove et al. 2005; Swanson, Oosterlaan, Murias, Schuck, Flodman, Spence, Wasdell, Ding, Chi, Smith, Mann, Carlson, Kennedy, Sergeant, Leung, Zhang, Sadeh, Chen, Whalen, Babb, Moyzis, & Posner 2000). Much more emphasis now needs to be placed on these types of bridging studies in order that the causal chains linking the genetic and environmental causes of AD-HKD or its component symptom dimensions, through the subsequent biological and cognitive levels, to the behavioural phenotype, can be understood.

It would, for example, be informative to integrate neuroimaging / electrophysiological, psychopharmacological and /or neuropsychological protocols within the large scale molecular and behavioural genetic studies into AD-HKD (Asherson & the IMAGE consortium 2004). The analysis of the data from the neuropsychological arm of this study will assist in the building of causal chains by exploring the associations between candidate genes and neuropsychological endophenotypes and the mediating/moderating effects of these endophenotypes, on genetic effects in AD-HKD. Another useful strategy might be to incorporate cognitive, neuroimaging, and molecular genetics methods into existing prospective epidemiological studies of the impact of perinatal factors on developmental outcomes. For example, maternal smoking during pregnancy independently impacts on the expression of attention problems, other externalizing problems and academic problems (Batstra, Hadders-Algra, & Neeleman 2003). The inclusion of neuroimaging and genetics

strategies would permit an assessment of causal chains between maternal psychopathology, genetic susceptibility for smoking, the prenatal and perinatal environment, and AD-HKD or attention problems in the offspring. Similar arguments could be made for a broad range of other important domains.

The need to recognise the existence of, and then effectively model for, heterogeneity within AD-HKD samples

The need to embrace and to address vertical integration across the different levels of analysis discussed in the previous section is mirrored by the need to recognise the heterogeneity inherent within AD-HKD samples. Clearly such heterogeneity will require there to be multiple pathways within a complete causal model of AD-HKD. It is also very likely that in addition to a need for horizontal integration between these pathways at each level of analysis, they will probably also relate to each other diagonally across the levels.

Until recently simple single cause models dominated the AD-HKD literature. Such models carried with them an implicit suggestion that the behavioural symptoms of AD-HKD are a consequence of a single underlying factor such as deficient inhibitory control (Barkley 1998), state regulation deficits (Sergeant 2000) or abnormalities in the relationship between reinforcement and response and/or motivational deficits (Sagvolden, Johansen, Aase, & Russell 2005). Whereas these theoretical approaches have resulted in several important findings (and indeed, have identified various processes, which may be involved in the development of AD-HKD), they have also tended to lead to a continuation of empirical designs that implicitly assume all children diagnosed with a given type of AD-HKD have the same causal aetiology. Such an assumption is unlikely to stand up to scrutiny, yet failure to model for multiple pathways, when designing studies and analysing data, may

ensure that studies utilizing between group designs (AD-HKD versus control) will continue to find relatively small, mixed effects.

In short, single cause models have difficulty accounting for the heterogeneity, which is being increasingly recognised as a key factor in the understanding of the causes of AD-HKD (Nigg et al. 2005; Sonuga-Barke 2002).

Whilst within-sample heterogeneity is likely to be found across all levels of analysis, the rest of this report will primarily focus on the neuropsychological level of analysis and for this reason cognitive heterogeneity will be used as an example in the present discussion. Data from several datasets suggests considerable neuropsychological heterogeneity within samples of DSM-IV diagnosed ADHD subjects (Nigg, Willcutt, Doyle, & Sonuga-Barke 2005; Solanto, Abikoff, Sonuga-Barke, Schachar, Logan, Wigal, Hechtman, Hinshaw, & Turkel 2001).

Such heterogeneity may be manifest in several ways. First, cognitive dysfunctions may be differentially associated with the inattention and hyperactivity/impulsivity dimensions. A growing corpus of research suggests that inattention, but not hyperactivity/impulsivity, may be associated with deficits in executive functioning and working memory, and poor academic achievement, even in non-clinical community samples (Chhabildas, Pennington, & Willcutt 2001; Martinussen et al. 2004; Martinussen & Tannock 2006; Rabiner & Coie 2000). By contrast, hyperactivity/impulsivity appears to be more closely related to dysfunctions of reward mechanisms (Solanto, Abikoff, Sonuga-Barke, Schachar, Logan, Wigal, Hechtman, Hinshaw, & Turkel 2001; Sonuga-Barke, Dalen, & Remington 2003; Toplak, Jain, & Tannock 2005). Second, there is emerging evidence that not all individuals with AD-HKD manifest cognitive deficits, suggesting heterogeneity in underlying neural mechanisms and/or marked heterogeneity in risk and protective factors (e.g. Nigg, Willcutt, Doyle, & Sonuga-Barke 2005). Third, various cognitive deficits within individuals with AD-

HKD may not be correlated, suggesting that AD-HKD may be the developmental outcome of a variety of anomalies in separable neural networks (Solanto, Abikoff, Sonuga-Barke, Schachar, Logan, Wigal, Hechtman, Hinshaw, & Turkel 2001; Toplak, Jain, & Tannock 2005).

Thus causal models of AD-HKD will need to account not only for both those with and without cognitive deficits, but also for the heterogeneity found within the cognitively affected group. Such data require us to consider the single cause models not as separate entities but as potentially complementary approaches, which when viewed together, can provide a fuller appreciation of a complex multidimensional scenario. Needed are more studies in which researchers investigate these contrasting theoretical models within the same samples to further the development of multi pathway models (Sonuga-Barke 2003), and identify specific causal claims more formally in AD-HKD.

It is crucial to recognise that multiple pathways may not simply represent alternative routes into AD-HKD. Rather it may be the norm for most children to have contributions from several, but not necessarily all, pathways, in varying degrees. At least three general patterns of multi-pathway models could be generated.

- First, we could posit that AD-HKD is the common final behavioural consequence of any of several relatively independent pathways, such as "cognitive deficit pathways" (e.g., a working memory pathway; (Kempton et al. 1999) and/or a non-working memory pathway (Rhodes, Coghill, & Matthews 2004)) and one or more non-cognitive pathways (for example a motivational pathway:(Sonuga-Barke 2003) and/or a adaptation to stress pathway (Johnston & Mash 2001a), with each of these pathways being sufficient on its own to result in the AD-HKD behavioural phenotype.

- Second, we could posit that AD-HKD is caused by a similar array of dysfunctions in each of these domains, with at least some dysfunction in all domains required before the phenotype is expressed. The extensive overlap in function demonstrated between AD-HKD and non-AD-HKD samples would require that AD-HKD arises due to the small but additive and interactive effects of each pathophysiological process with the phenotype only being expressed once a threshold has been reached.
- Third, it may be that the correct model is a combination of the two described above. Thus, whilst AD-HKD could arise as a consequence of one of several independent pathways, it might be more common for there to be an interaction between several pathways, with the detail of the interactions dictating the precise presentation severity, and possibly response to treatment.

The situation for AD-HKD with comorbidity will, of course, be even more complex.

This analysis highlights the importance of looking beyond the frequently emphasized fronto-striatal /executive networks in the brain to account fully for AD-HKD even at the cognitive level of analysis. Thus, as described in Chapter 2 structural and functional neuroimaging studies and electrophysiological studies, including transcranial magnetic stimulation, have shown various brain abnormalities in AD-HKD patients (e.g. Brandeis, Banaschewski, Baving, Georgiewa, Blanz, Warnke, Steinhausen, Rothenberger, & Scheuerpflug 2002; Castellanos et al. 2002c; Moll et al. 2001; Rubia, Overmeyer, Taylor, Brammer, Williams, Simmons, & Bullmore 1999; Yordanova et al. 2001). These studies have mostly demonstrated the now well-recognised abnormalities in frontal cortical regions and basal ganglia. Yet, less often addressed are the morphological and functional differences, which have been revealed in the motor cortex, temporal and parietal lobes, cerebellum, and corpus callosum (Castellanos et al. 2002b; Roessner et al. 2004). Further, the alteration

of the REM-sleep seen in AD-HKD (Kirov et al. 2004) cannot be explained by the neuropsychological models described above.

Along similar lines, recent neuropsychological studies have utilised batteries of neuropsychological tasks measuring a range of abilities dependant on a broader range of neuronal substrates. Toplak et al (2003; 2005) reported deficits in AD-HKD children on several short duration timing tasks dependent upon the cerebellum for accurate performance (Mangels, Ivry, & Shimizu 1998). These studies suggest that a conceptualisation of AD-HKD largely restricted to frontal-striatal circuits may require broadening within a multi-pathway framework. However, further study is required to confirm the inter-relationships between these and other cognitive deficits, to evaluate relative effect sizes, and to examine their relationships with genetic and environmental causal factors and associated neural mediating mechanisms.

The experimental section of this thesis will present new data regarding the neuropsychological heterogeneity in children with severe and pervasive AD-HKD, and address several of the methodological problems associated with current studies (e.g. small sample size, previous stimulant treatment, and lack of control for comorbidity).

The need to properly characterise endophenotypes

Several potential neuropsychological endophenotypes for AD-HKD have been proposed including;

- A specific abnormality in reward-related circuitry that leads to shortened delay gradients and delay aversion (Sonuga-Barke 2002)
- Deficits in temporal processing that result in high intra-subject inter-trial variability (Smith, Taylor, Rogers, Newman, & Rubia 2002; Toplak et al. 2003)
- Deficits in working memory (Bedard et al. 2004; Rhodes, Coghill, & Matthews 2004)

- Deficits in non-working visual memory (Rhodes, Coghill, & Matthews 2004)
- Impaired stop-signal inhibition (Schachar et al. 2000)
- Attentional set-shifting (Nigg, Blaskey, Stawicki, & Sachek 2004).

Whilst each of these meets several of the expected criteria for endophenotypes listed above, none meet them all. For example, the heritability and co-segregation within families remains unexplored for most endophenotypes and only attentional set-shifting and stop signal inhibition have been demonstrated to be familial and to occur more frequently in non-affected family members than in the general population (Nigg, Blaskey, Stawicki, & Sachek 2004) .

Proposed neuroimaging and electrophysiological endophenotypes include;

- The volumetric differences found in the prefrontal cortex, basal ganglia and cerebellum (Seidman, Valera, & Makris 2005)
- Increased slow wave (delta and theta) activity and reduced alpha and beta waves (Barry, Clarke, & Johnstone 2003)
- Various event related potentials findings, including the reduced amplitude of the posterior P3 wave in children below the age of 12 years after presentation of a stimulus, and in response to an auditory oddball task that taps aspects of attention and working memory. Reduced P3 amplitude is also seen in the visual attention mode, and a reduced N2 peak has been found following stimuli, which evoke inhibitory processes(Barry, Johnstone, & Clarke 2003).

Similar to the neuropsychological findings, there is some preliminary data to suggest a genetic contribution to these proposed endophenotypes but much work needs to be done to fully describe and validate them.

Whilst several of these endophenotypes have been demonstrated to be relatively sensitive markers for AD-HKD, their specificity to AD-HKD is less clear (Banaschewski et al. 2005). As previously suggested, it is unlikely that all endophenotypes will be present in all cases. It is therefore not surprising that cohort level analyses on such heterogeneous samples suggest high sensitivity but low specificity. This is one of the reasons for neuropsychological tests being relatively ineffective tools in the diagnosis of AD-HKD. Also several of the proposed endophenotypes appear to be common to several neurodevelopmental disorders. For example, working memory has also been proposed as an endophenotype for schizophrenia (Gottesman & Gould 2003), and stop signal inhibition has been implicated in schizophrenia, language disorders, conduct disorder and autism. Indeed, the neuropsychological and neurophysiological similarities and dissimilarities between AD-HKD and other commonly comorbid conditions such as conduct disorder (Banaschewski et al. 2004; Oosterlaan & Sergeant 1998a; Schachar & Tannock 1995) and specific learning difficulties (Tannock, Martinussen, & Frijters 2000), remain contentious and unresolved. This does not, however, imply that we should abandon our search for, and description of endophenotypes. Rather it may suggest that we should be looking for neuropsychologically rather than behaviourally defined subtypes of ADHD (see Nigg, Willcutt, Doyle, & Sonuga-Barke 2005). The neuropsychological assessment of those with AD-HKD could then be used to more fully describe an individual's condition and to aid clinicians in target the most appropriate pharmacological, psychological and educational treatment strategies towards the right groups of patients. A more adventurous but potentially far more profitable strategy would be to concentrate on mapping out the causal pathways both to and from cognitive deficits

in delay sensitivity, behavioural inhibition, working and non-working memory and timing, rather than those for AD-HKD per se.

The need to take developmental aspects seriously

Despite widespread recognition of AD-HKD as a developmental neuropsychiatric condition, very few causal explanations have seriously considered the potential for two-way interactions between pre-existing abnormal functioning and biological, cognitive, emotional, motor and social developmental processes, and their contribution to the expression of the behavioural phenotype (Nigg, Goldsmith, & Sachek 2004; Olson et al. 2002). Nigg et al. (2004) provide an outline of various temperament-based early precursors to AD-HKD that warrant consideration. Sonuga-Barke (2005) has discussed this issue with respect to the development of delay aversion and associated deficits in self-organisational skills, suggesting that at least three related developmental phenomenon are implicated. The first is characterised by *child x environment correlation,* whereby the developmentally antecedent impulsive response of the child shapes their social and family environment by eliciting a punitive or negative response from parents and siblings to a failure to engage effectively with the delay-rich environment. Second is *person x environment interactions,* whereby the punitive social environment, partially created by the behaviour of the child, moderates the links between underlying and early appearing impulsiveness and the emergence of a more generalised delay aversion. The final developmental process is characterised by *individual accommodation* to the child's underlying predisposition toward impulsiveness and the constraints this imposes on experience. It is likely that similar processes play a role in other causal pathways to AD-HKD.

Causal models must also take into account the ways by which a failure of development in one cognitive ability can impact on the development of successive cognitive abilities. The

potential importance of this concept to causal modelling for AD-HKD can be illustrated by considering the role played by working memory deficits in the development of AD-HKD. Working memory deficits, although relatively understudied, have been considered by many to be core cognitive risk factors for AD-HKD requiring accommodation within a causal model of AD-HKD (Castellanos & Tannock 2002). Deficits in timing (Toplak, Rucklidge, Hetherington, John, & Tannock 2003) and non-working visual memory (Rhodes, Coghill, & Matthews 2004), which whilst not dependent on working memory performance, may themselves impact on the development of working memory, have been recently identified. Thus if the usual development of accurate spatial working memory performance is contingent upon the development of cerebellar timing functioning and/or spatial recognition memory, then impaired development of either of these abilities may impact on the development of spatial working memory functioning. Whilst such hypotheses are still speculative they warrant further investigation and illustrate the potential importance of such considerations. Further, the possibility that very basic sensory and perceptual processes may be impaired in AD-HKD, which over the course of development may manifest subsequently as impaired performance on various tasks and be interpreted as "impairments in executive function", remains relatively unexplored (e.g. Jonkman, Kenemans, Kemner, Verbaten, & van Engeland 2004).

Finally, with regard to development, a causal model of AD-HKD must also account for changes in phenotypic expression over time. Future studies will need to differentiate between "true" and "apparent" changes in symptoms across the lifespan. For example, is the reduction in hyperactivity symptoms frequently noted in adolescence (Hart et al. 1995) a true shift towards normality, or simply an apparent change resulting as a consequence of normative development? That is, does that shift represent a change over time, mirroring normative development, from a more visible motoric hyperactivity to an inner restlessness and fidgetiness, which whilst less noticeable and impacting on others, is still both impairing

to the individual and remains as far removed from the normal distribution of experience as were the symptoms in earlier life (Barkley, 1998)? In each case, a causal modelling paradigm would make different, testable, predictions. If the shift is towards normalisation then this should be reflected by a similar shift in the underlying pathophysiology (e.g. Rothenberger, Woerner, & Blanz 1987), which would not be the case in the converse scenario. The accurate developmental description of each of these levels within causal chains would both aid the clarity of the resultant causal models and provide a more objective basis from which descriptions of AD-HKD across the lifespan, particularly in adolescence and adulthood, can be developed.

Summary and Conclusions

In this Chapter I initially summarised current thinking about the use of causal modelling in developmental psychopathology and its relationship with heterogeneity. I then discussed several of the important considerations, which require to be addressed in order that we can move from proposing causal theories to demonstrating formal causal effects. Taking this discussion, together with the findings presented in Chapters 1 and 2, it is apparent that the neuroscience of AD-HKD stands at a watershed. New brain study and genetic technologies have provided us with the tools to examine the neurobiology of AD-HKD in an increasingly sophisticated and powerful way. However, if this is power is to be harnessed effectively then research must be guided by equally sophisticated and powerful models of causes and causal processes. In this Chapter I have made a number of recommendations to overcome existing barriers to the development of empirically-based causal models and so facilitate model-guided research programmes in the neuroscience of AD-HKD. In the subsequent Chapters I will develop some of these ideas further with reference to the results of a study that explored the baseline neuropsychological performance of a sample

of stimulant naïve boys with well defined HKD, and their subsequent clinical and neuropsychological response to acute and chronic challenges with MPH. After first describing the methods and general statistical procedures (Chapter 4) and previously published results (Chapter 5), I will present new data relating to neuropsychological heterogeneity in drug naïve boys with HKD (Chapter 6), review data on the potential contributions of development and comorbidity to this heterogeneity (Chapters 7 and 8 respectively), and then investigate the heterogeneity of clinical and neuropsychological response to MPH (Chapter 9).

Chapter 4

Methods and general statistical procedures

The aim of this Chapter is to provide a detailed account of the methods and procedures used in this thesis. Specifically, information is provided concerning recruitment of the two subject groups involved in the study, the neuropsychological tests used, the study design and conduct and the statistical methods employed.

Subjects

Hyperkinetic disorder Group

All boys aged between 7 and 16 years, referred for a first time, to the Tayside Child and Adolescent Mental Health outpatient services between October 1998 and December 2000, whose parents/carer had sought treatment for them because of concerns regarding severe hyperactivity and/or problems with inattention, were considered for inclusion into the study. A two stage screening and assessment process was used. Eligible and consenting subjects scoring >1.5 standard deviations from the mean on both the Revised Conners' Parent Rating Scale short version (CPRS-26, Conners et al. 1998b; appendix 2a)and Revised Conners' Teacher Rating Scale short version (CTRS-28, Conners et al. 1998a; appendix 2b), were assessed and screened by an experienced child and adolescent psychiatrist (Specialist Registrar or Consultant grade) using the Kiddie-SADS Present and Lifetime (K-SADS-PL) Version 1.0 (Kaufman et al. 1996) semi-structured interview. This diagnostic interview is designed to assess current and past episodes of psychopathology in children and adolescents. (For the Attention Deficit Hyperactivity Disorder supplement, which forms one part of this interview, see appendix 3).

Recruitment, screening, and selection procedures aimed to collect a rigorously defined sample of children and adolescents with 'Hyperkinetic Disorder' (HKD) as described in the International Classification of Diseases version 10 (ICD-10, World Health Organisation 1993) and discussed in detail in Chapter 1. The cardinal features of HKD are outlined in the International Classification of Diseases (1CD-10) as impaired inattention and overactivity/ impulsivity. Both are necessary for the diagnosis and must be evident in more than one situation (e.g. home, classroom, or clinic).

ICD-10 further specifies that deficits in attention should be diagnosed only if they are considered excessive for the child's age and IQ. The standard of judgement for overactivity should be that the activity is excessive in the context of what is expected in the situation and by comparison with other children of the same age and IQ. Learning disorders and motor clumsiness occur with undue frequency: they are not, however, part of the actual diagnosis of Hyperkinetic Disorder.

A diagnosis of HKD (ICD-10) also requires the following criteria:

(1) The symptoms must be persistent over time with a long duration (at least 6 months or longer);

(2) Symptoms that cause impairment must have arisen early in development (no later than age 7);

(3) Symptoms must be impairing across two or more situations (e.g. school and home).

Exclusion criteria included a history of neurological impairment, previously determined learning disability (IQ < 80), chronic physical illness, sensory or motor impairment, current or previous exposure to stimulant medication, and abuse of any illegal drugs. Despite the fact that the presence of a range of commonly occurring comorbid conditions, including

Oppositional Defiant Disorder, Conduct Disorder, and Anxiety Disorder, is actively discouraged within the ICD-10 HKD construct, presence of these disorders did not result in exclusion from the study as long as the child and adolescent psychiatrist making the assessment was certain that the HKD symptoms were independent of, and not secondary to, this other disorder. These criteria were designed to ensure that the sample recruited was representative of those children with HKD (severe pervasive and impairing ADHD) seen in typical clinical practice within the National Health Service in the U.K. Thus the inclusion criteria were; male, aged between 7 and 16 years of age, Conners' scores CPRS-26 and CTRS-28 > 1.5 S.D. from mean, meeting criteria for ICD 10 hyperkinetic disorder (with the exception of the comorbidity requirements) and failure to meet exclusion criteria.

One hundred and ninety five boys were screened for inclusion in the study. One hundred and twenty boys either failed to meet inclusion criteria (n = 87), met exclusion criteria (n = 12) or refused to participate (n = 21) and so were not entered into the study (see Figure 4. 1.) Seventy five subjects met study criteria and agreed to randomisation. Informed written consent to participate in the study was obtained from both children and parent(s) in accordance with the guidelines from the Tayside Committee on Medical Research Ethics.

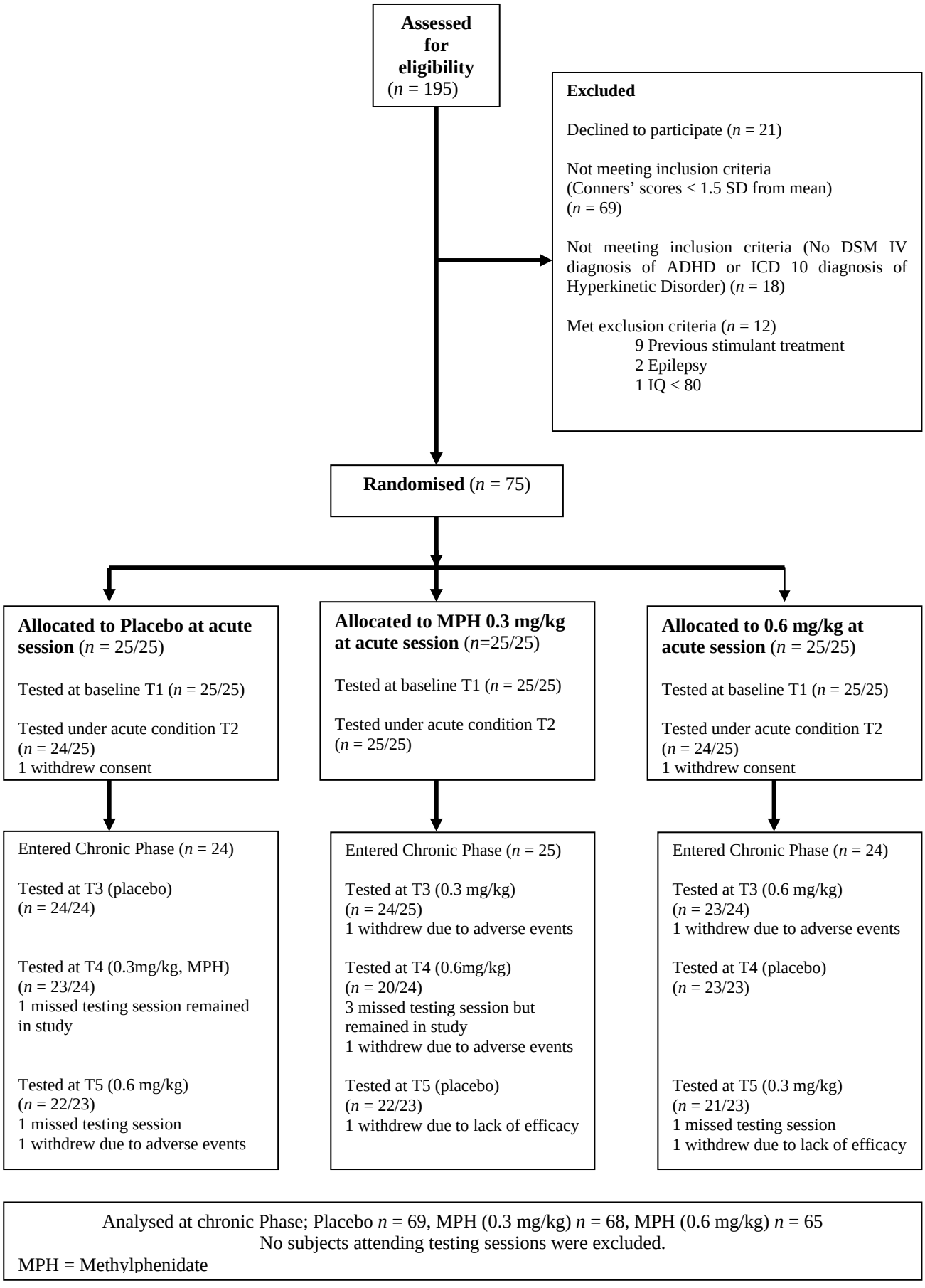


Figure 4.1: Flow of HD subjects through the study

Control Group

The Control group consisted of 70 healthy normally developing boys aged between 7 and 16 years of age who were attending Dundee City Council Education Department (state sector) primary and secondary schools. Informed written consent to participate in the study was obtained from child and parent(s). Five hundred and twenty five information leaflets detailing the procedures involved in the study were distributed among classes Primary 2-7 and Secondary 1-4 to children whose names appeared first on the school registers (alphabetical order) of randomly selected primary and secondary schools in Dundee. Ninety six parents consented (53/152 from primary schools; 43/373 from secondary schools) to their child's participation in the study. Of these, 85 returned fully completed screening questionnaires. Twenty seven parents returned letters refusing to grant permission for their children to take part in the study.

All Control subjects were screened initially for mental health problems using the Child Behaviour Checklist (CBCL, Achenbach 1991, appendix 4) and the CPRS-26 and the CTRS-28 rating scales (Conners, Sitarenios, Parker, & Epstein 1998a; Conners, Sitarenios, Parker, & Epstein 1998b) that were used for the HKD group. Of the 85 who returned screening questionnaires, 10 failed to meet inclusion criteria due to failing to meet the cut-off criteria on at least one of the screening questionnaires (<1 standard deviation from the mean on all subscales of the CPRS-26, the CTRS-28 and the CBCL). One subject consented to take part and met inclusion criteria but was subsequently unable to take part in the study because of a family bereavement. Children rated as symptom-free (N = 74) on these screening questionnaires were subsequently interviewed with the K-SADS-PL semi-structured interview (Kaufman, Birmaher, Brent, Rao, & Ryan 1996). Exclusion criteria for Control subjects were identical to those for the HKD group with the additional criterion that children were also excluded if they had a current or past history of psychiatric illness

identified on the K-SADS-PL. Seventy boys meeting inclusion criteria and who matched HKD subjects for age (within 6-month) were asked to participate in the study. All agreed.

Tests used in the study

Intelligence testing (verbal IQ)

The British Picture Vocabulary Scale (BPVS 2nd Edition, Dunn et al. 1997) was used to estimate general intellectual ability for both the HKD and Control subjects. The BPVS assesses verbal intelligence and was chosen for its ease of administration and ability to be used with children aged between 3 and 15 (Dunn, Dunn, Whetton, & Burley 1997). It is an individually administered, norm-referenced, test of receptive vocabulary for Standard English. It contains four training plates, followed by 14 sets of 12 test items. The items are arranged such that each successive set is more difficult than the preceding one. Each item has four simple black and white illustrations on a plate arranged in a two-by-two array. The subject's task is to select the picture considered to best illustrate the meaning of a stimulus word that is presented orally by the examiner. The second edition, used in the present study, has a wide range feature of 168 items, thus reducing the probability of floor or ceiling effects. Vocabulary has been found to be the best single predictor of school success (Dale & Reichart 1957) and vocabulary subtests have proved to be among the most important contributors to comprehensive tests of intelligence (Elliott 1983; Elliott 1990). The measure used in this study is the Percentile Rank score, which indicates on which percentile of the UK child population of that particular age a subject scores.

Neuropsychological tasks

Subjects performed a computer-based Go/NoGo task (Murphy et al. 1999; Rubinsztein et al. 2001) at the beginning of each testing session. The remaining cognitive tasks were selected from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Morris et al. 1987). This battery consists of a series of computerised tests presented on a high-resolution colour monitor with a touch sensitive screen. Eleven tests taken from the three batteries: (1) working memory and planning; (2) visual memory; (3) attention, were used in this study. At the beginning of the testing session, subjects were shown a line marked on the table to which they were instructed to keep their 'pointing' finger on at the beginning of each test and between trials. This line was measured as 12 inches from the centre of the screen. The instructions given for each task originated from manuals provided by CENES (now Cambridge Cognition), the company responsible for commercial development and marketing of the CANTAB tests.

Go/NoGo Task

This task is a measure of the ability to detect and respond to a target stimulus and to inhibit responding to distracter stimuli, when all stimuli are presented in a pseudo-randomly changing order. Subjects were instructed to keep their 'pointing finger' over the spacebar of a PC keyboard and to watch the centre of the computer screen. A random sequence of eighteen letters and numbers (nine of each) were rapidly presented in the centre of the screen, one by one. Stimuli were presented on screen for 300ms, with an inter-stimulus interval of 900ms. A 500ms/450Hz tone sounded following a response error, providing immediate feedback. Omission errors (failure to respond to target stimuli) were not signalled. The first two trial sequences were for practice purposes only to familiarise subjects with the test. Subjects were instructed to respond to target stimuli by pressing the space bar as quickly as possible but not to respond to distractors. Eight test trials followed – alternating between numbers and letters as targets after two sets of each stimulus. Trials

were divided into two blocks for analysis: Block 1 represents the 'switch' block where the task has changed from letters to numbers or vice-versa. Block 2 represents the 'non-switch' block, which involves a second trial of a target stimulus. The principal dependent measures for this task are the mean number of errors for distractors (false positive responses) and reaction time to target stimuli across the eight trials.

CANTAB Tests

Motor Screening

At the beginning of each of the three batteries, subjects performed a motor screening task. This simple reaction time test measures psychomotor speed and accuracy and is designed to screen for psychomotor impairments, which would interfere with later task performance. On each of ten trials, a large 'X' appeared at a random location on the computer screen. Subjects had to touch the centre of the 'X' as quickly but as accurately as possible. Accuracy of touch and response latency was recorded.

Spatial Span

The Spatial Span task is a test of spatial short-term memory capacity based on the Corsi block-tapping task (Milner 1971). This task assesses a subject's ability to remember the spatial locations of a sequence of squares on a computer screen and is believed to preferentially activate neural circuitry that includes the right ventrolateral prefrontal cortex, and the parietal cortex (Owen et al. 1996a; Robbins et al. 1994). On each individual trial, an array of 9 white boxes is displayed on the screen. Subjects watch while each white box changes colour before being asked to reproduce this sequence. The length of the sequence presented begins with two boxes and increases steadily up to a maximum of nine. A subject's spatial span is defined as the longest sequence that they can reproduce correctly within three attempts.

Spatial Working Memory (SWM)

This is a self-ordered searching task (Petrides & Milner 1982) that assesses working memory for spatial stimuli and requires a subject to use mnemonic information to work towards a goal. Positron Emission Tomography (PET) imaging studies have indicated that this task preferentially activates neural circuitry, which includes the dorsal and ventral prefrontal regions (Mehta et al. 2000; Owen, Doyon, Petrides, & Evans 1996a; Robbins et al. 1998). Subjects are required to 'search through' a spatial array of coloured boxes presented on the screen by touching each one such that it 'opens up', revealing what is inside (see Figure 4.2. The object of the task is to collect 'blue tokens' hidden inside the boxes and, once found, to use them to fill an empty column on the right corner of the screen. Each coloured box could only contain one token in the course of each trial. The key instruction for subjects is that once a blue token has been found within a particular box (within any individual trial), then that box would not be used again to hide a token within that trial. Consequently, two types of search error are possible. Returning to a box where a token has already been found constitutes a 'between-search' error (BSE). Returning to a box already opened and shown to be empty earlier in the same search sequence constitutes a 'within search' error (WSE). A 'strategy score' can also be derived from this task. Previous studies have shown that, in Control subjects, performance on this task can be facilitated by the adoption of a repetitive search strategy. This strategy involves beginning each search with a particular box and then returning to start each new sequence with that same box as soon as a token has been found. The optimal strategy is then to repeat the previously employed order of choices until a reinforced location is encountered when it is necessary to sample a novel location. Such strategies, when applied to self-ordered search tasks of this type, may serve to reduce the load on active working memory and would, presumably, enhance performance at all levels of task difficulty. The strategy score is calculated by counting the number of different

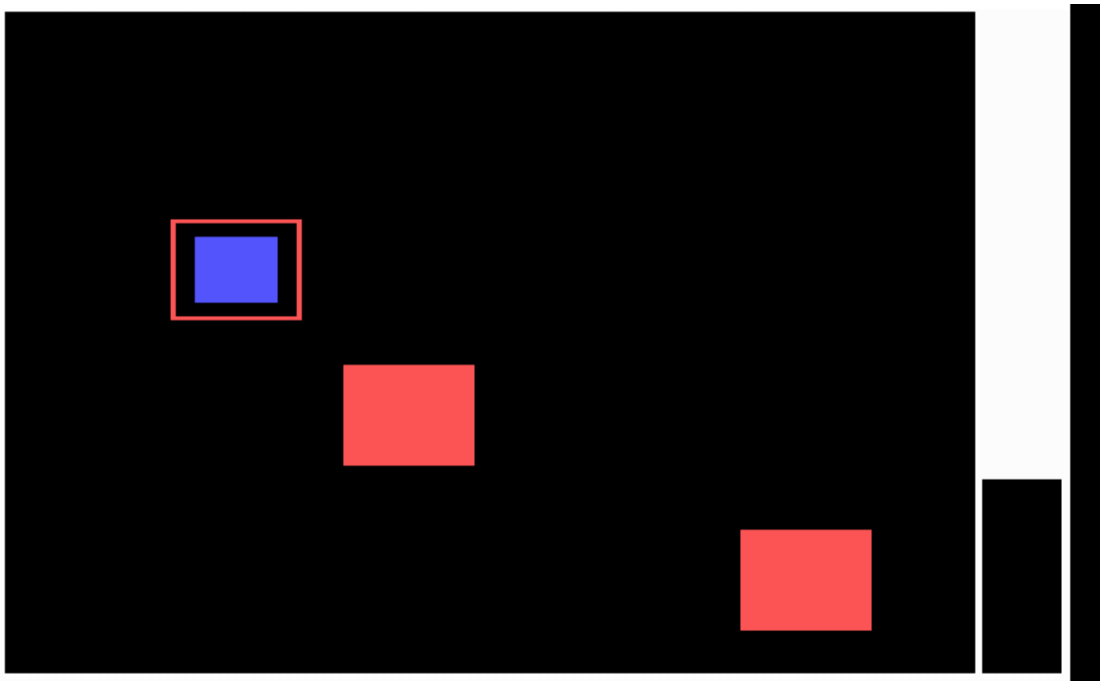


Figure 4.2: The CANTAB Spatial Working Memory task

boxes initially opened at each trial, hence, the lower the score, the greater the use of strategy.

Stockings of Cambridge (SOC, Tower of London)

This task was derived from the 'Tower of Hanoi' task and measures spatial planning, working memory, and behavioural inhibition (Shallice 1982). Based on several PET studies, it has been concluded that this task preferentially activates neural circuitry, which includes the parietal lobes bilaterally, as well as the left dorsolateral prefrontal cortex and left caudate nucleus in the dorsal striatum (Baker et al. 1996; Morris et al. 1993; Owen, Doyon, Petrides, & Evans 1996a). In this task, two sets of three coloured balls are presented, each arranged in three hanging pockets (see Figure 4.3).

Subjects are asked to move the balls in the arrangement in the lower half of the screen according to specified rules, to match the upper or 'goal' arrangement. Problems can be solved in a certain minimum number of moves (two, three, four or five moves) and subjects are instructed to work out the solution prior to moving any balls. The maximum moves allowed correspond to twice the minimum number possible plus one, or plus two in the case of 'five move' problems. If the maximum number of moves is exceeded the computer indicates 'too many moves' before beginning the next trial. Initial and subsequent 'thinking' latencies during trials are recorded to provide estimates of cognitive speed during the preparatory and execution phases of task performance. For each trial, a yoked control condition is also executed. During these 'following' trials, subjects were instructed to execute a sequence of single moves as quickly as possible. The 'following trials' are exact reproductions of the subject's earlier planning moves. Initial and subsequent movement latencies in these 'following' trials provide estimates of motor speed. These 'movement times' are subtracted from the test condition times, which included both 'thinking times'

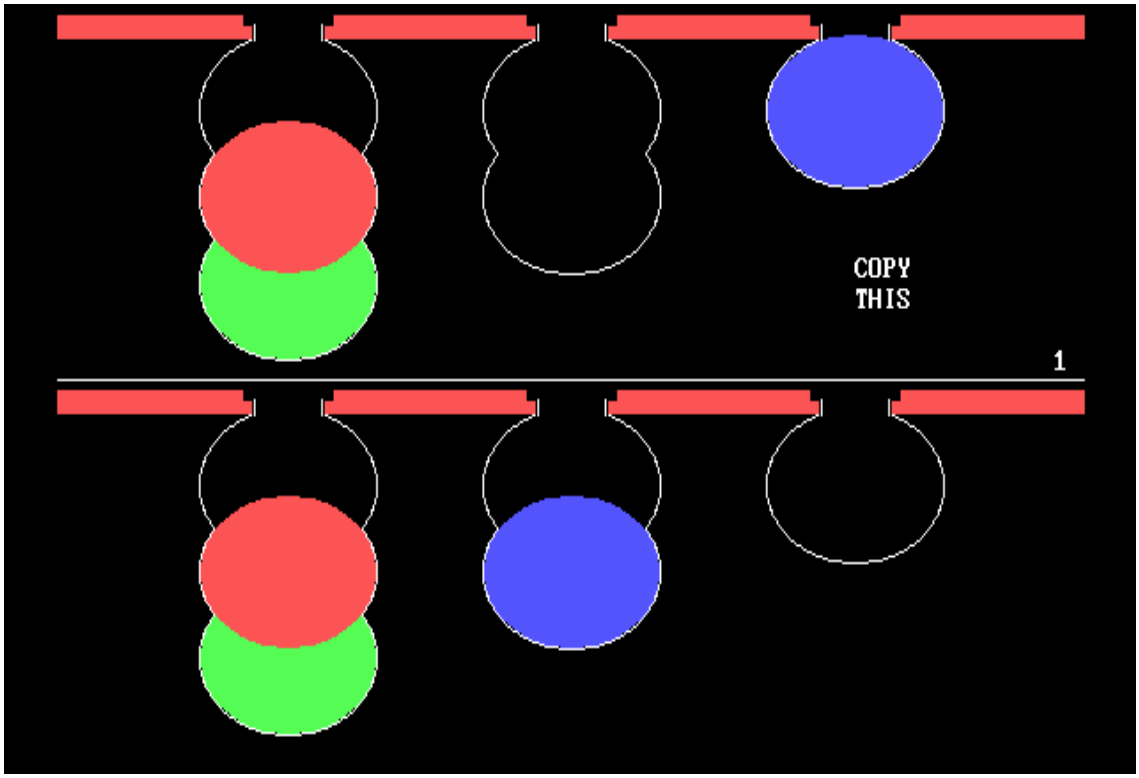


Figure 4.3: The CANTAB Stockings of Cambridge task

and ‘movement times’ in order to provide an estimate of cognitive deliberation /planning times in the test conditions.

Spatial Recognition

This task assesses the subject’s ability to recognise the spatial locations of target stimuli. A study using PET scanning has shown that this task activates the dorsolateral prefrontal cortex (Goldberg et al. 1996), and lesion studies suggest that it is sensitive to frontal but not temporal or amygdale-hippocampal lesions (Owen et al. 1995). The task is presented in two stages: a presentation and a recognition phase. In the presentation phase, subjects are shown a series of five (one-inch) white squares, appearing one at a time, at different locations on the screen. Each square is presented for three seconds before the screen is cleared and the next square appears. Subjects are instructed to remember the location of the five boxes presented. In the recognition phase, two squares appear simultaneously on the screen and the subject was required to select which of the two locations had been shown earlier. The target squares are presented in reverse order and paired with distracter squares that appear in novel locations that had not been used as target locations. Again, each response was accompanied by an auditory tone and visual feedback in the form of green ticks for correct responses and red crosses for incorrect responses. This task involves four sets with five squares presented in each set. The primary measure in this task is the number of correct locations chosen across the four trials.

Pattern Recognition

This task measures a subject’s ability to recognise a previously presented abstract pattern from two adjacent stimuli. Lesion studies suggest that this task is sensitive to either temporal lobe or amygdale-hippocampal, but not frontal lobe excision (Owen, Sahakian, Semple, Polkey, & Robbins 1995). The task is presented in two phases; a presentation and a recognition phase. Initially, subjects are shown a series of 12 simple, but abstract, coloured

visual patterns appearing one at a time inside a white box located in the centre of the screen (presentation phase). Each of the 'target' patterns is presented for 3 seconds, the screen is then cleared and the next pattern appears. Subjects are instructed to try and remember each of these patterns. In the recognition phase, each target pattern is presented in reverse order and is paired with an adjacent novel distracter pattern that differs in form but not in colour from the target pattern. The subject is required to respond to the pair by touching the stimulus previously seen during the presentation stage. Each response elicits an auditory tone and visual feedback is automatically provided in the form of green ticks for correct responses and red crosses for incorrect responses. This task involves two sets of 12 patterns in each set. The primary measure in this task is the number of correct patterns chosen across the two trials.

Simultaneous and Delayed Matching– Delayed Matching to Sample task (DMtS)

This task assesses a subject's ability to remember the visual features of a complex, abstract, target stimulus. Lesion studies suggest that this task is sensitive to both temporal lobe or amygdale-hippocampal damage, whereby there is a pattern of delay-dependent deficit whilst subjects with frontal lobe excision were indistinguishable from controls (Owen, Sahakian, Semple, Polkey, & Robbins 1995). At the beginning of each trial, a pattern consisting of four quadrants, each differing in colour and form appears in the centre of the screen in a white box for a presentation period of 4.5 seconds. Subjects are asked to remember the pattern as they would later be required to identify it from among three 'distracter' patterns. In the 'simultaneous condition', four choice patterns then appear in red boxes located under the target pattern. The subject is then required to respond by touching the choice pattern that corresponds exactly (in both colour and form) to the target pattern above. Only one of the choice patterns is identical to the target. One of the other choice patterns is a novel distracter, differing in both colour and form from the

sample. The remaining two choice patterns are 'partial distracters' in that one has the colours of the target but the form of the novel distracter, whilst the other has the form of the target but the colours of the novel distracter. In addition, each of the four choice patterns has one (random) quadrant in common to discourage mnemonic strategies based on remembering the colour and form of a single quadrant (see Figure 4.4). The subject's response elicits an auditory tone and visual feedback in the form of green ticks and red crosses. If the subject made an incorrect response they were required to continue to choose until the target stimulus was chosen.

The delay task is identical to the simultaneous task with the exception that after the initial 4.5 seconds presentation period, the target pattern disappears from the screen. The four choice patterns are then presented following one of three delays; 0 seconds (i.e. immediately), 4 seconds, and 12 seconds.

Following three practice trials (simultaneous, 0 sec delay, and 12 sec delay), a total of twenty test trials are presented with each of the four conditions presented in a pseudorandom order. [n.b. For this study, the task was shortened from 40 trials to 20 as it was considered too lengthy (and thus aversive) during pilot testing for children to perform 40 trials]. The primary measure in this task is the number of correct targets chosen at each of the simultaneous and delay conditions.

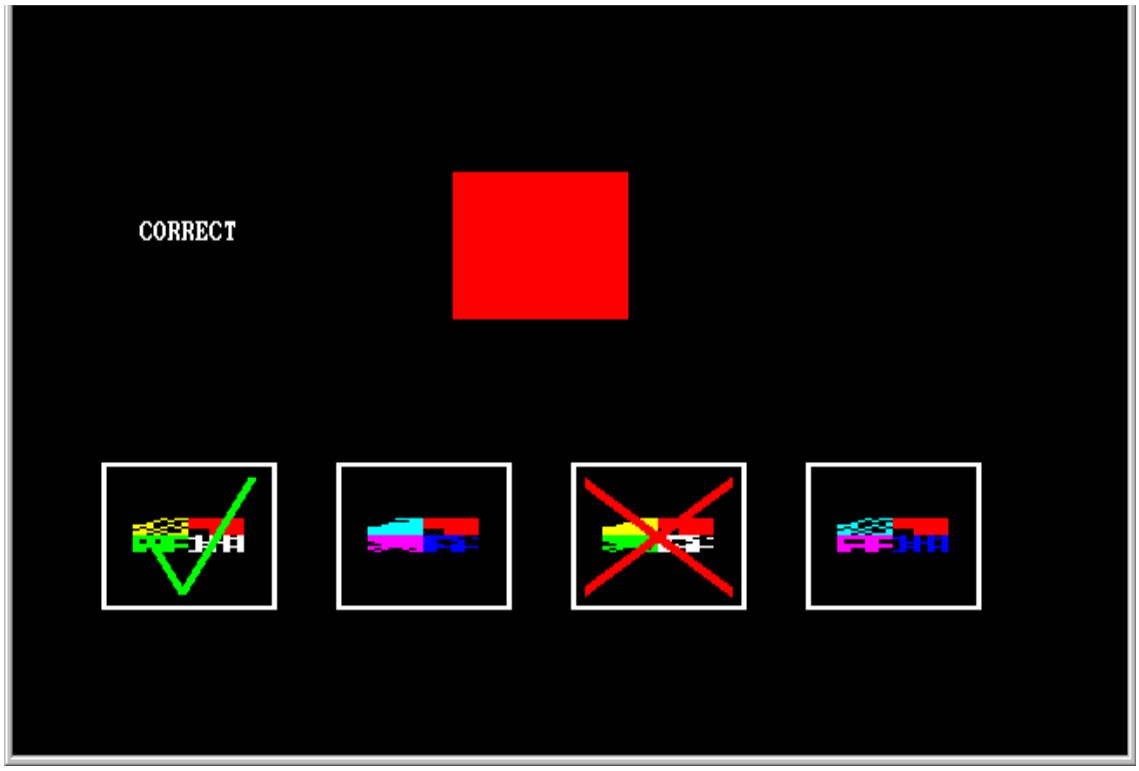


Figure 4.4: The CANTAB Delayed Matching to Sample task

Paired Associate Learning Task (PAL) – a 'spatial delayed response task'

In this task, subjects are required to learn the locations of a progressively increasing number of abstract stimuli. Subjects with frontal and temporal lobe and amygdale-hippocampal excisions all demonstrated deficits on this task compared with controls but were indistinguishable from each other (Owen, Sahakian, Semple, Polkey, & Robbins 1995). Initially subjects are presented with six boxes arranged in an ellipse formation on the screen, each of which opens up to show a pattern inside. The subject's task is to look at the coloured patterns in the boxes and to remember which pattern appeared in which box. Each of the boxes opens for 3 seconds and then closes again in a pseudo-random sequence. Immediately after the final box in the sequence closes, a pattern is presented in the centre of the screen and the subject is required to respond by touching the box in which the pattern appeared earlier. Feedback is not provided after each individual response, but if all choices are correct the words "all correct" appear on the screen and the computer progresses to the next sequence. If the choice is incorrect, the boxes reopen for a further 2 seconds each, and the subject is given further attempts (up to a maximum of 10 trials in total, at which point the program terminates) until he/she chooses all correct locations. The task involves two trials each of one, two and three patterns followed by one trial of six patterns. In a final phase, two further boxes are added to the display and the subjects have to remember in which boxes each of eight patterns appeared. The main measures in this task are the number of trials taken to complete the task and the total number of errors across all trials.

Big/Little Circle

The purpose of this simple discrimination task is to ensure subjects can reliably choose between two stimuli according to a simple rule before progressing to a more complex task (the ID/ED Attentional Set-Shifting Task). Subjects are presented with two filled, yellow circles displayed in boxes. One circle is small (described during the task as 'little') in size and

one big in size. In the first twenty trials, subjects are instructed to touch the 'little' circle each time, and in a second set the 'big' circle each time. All subjects were deemed to understand this task. Hence, data from this task were not analysed in any detail and are not discussed further.

ID/ED (Intra Dimensional/Extra Dimensional) Attentional Set-Shifting Task

This task assesses a subject's ability to first focus attention on specific attributes of compound stimuli (intra-dimensional stages) and then to shift attention, when required, to a previously irrelevant stimulus dimension (extra-dimensional stages). Here "dimension" refers to the attributes of an object. Clearly an object can have several "dimensions" – shape, colour etc. Although subjects are not told as much it is the shape – filled shape or line – that is relevant here. The subject is required to learn a series of rules about various discriminations in which responding to one of two stimuli is correct and the other wrong. The subject is not told what the current rule is or when it has changed, however the computer provides automatic and immediate feedback. The task involves nine stages with subjects proceeding to the next stage when they attain a criterion of six consecutive correct responses. Failure to achieve this criterion within 50 trials results in the premature discontinuation of the test. In the first two stages, subjects are tested on simple discrimination and reversal for two stimuli varying in just one dimension (irregular purple filled shapes). A second alternative dimension is then introduced (two different white line configurations) resulting in a compound figure (purple shapes and white lines) and compound discrimination and reversal were tested (see Figure 4.5). To succeed, at this stage subjects must continue to respond to the previously relevant dimension (purple shapes) while ignoring the presence of the new irrelevant dimension (white lines). At the Intra-dimensional Shift stage, novel exemplars of each of the two dimensions (shapes and lines) are introduced and subjects must continue to respond to one of the two exemplars from the previously relevant dimension (purple shapes) and complete a reversal stage

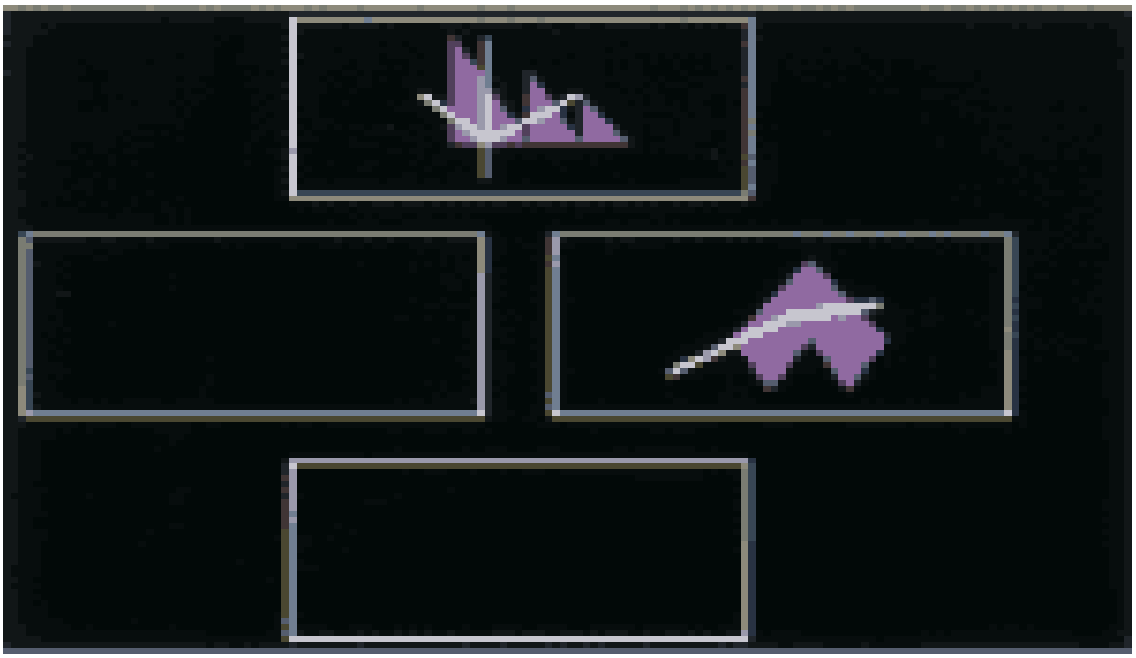


Figure 4.5: The CANTAB ID/ED Attentional Set-Shifting Task

where they followed the other relevant exemplar (second purple shape). The final two stages, the Extra-dimensional Shift and Reversal stages commence with the introduction of novel exemplars of each stimulus dimension. In order to succeed at this stage, the subject has to shift 'response set' to the previously irrelevant stimulus dimension (white lines) while ignoring the previously relevant dimension (purple shapes). Neuroimaging, using PET scanning, has shown that the neural correlates of the critical ED Shift stage are in specific regions within the anterior frontal lobe (Rogers et al. 2000), and frontal lobe patients show impairment at this specific set-shifting stage (Owen et al. 1991). The main measure of performance on this task is the furthest stage successfully attained. Errors at each stage are also measured.

Reaction Time

In this task, subjects are assessed on their reaction and movement times in response to a stimulus. Subjects are first required to perform three practice trials before commencement of two test trials. In the first test condition (simple reaction time), subjects are presented with one circle on the screen. This task requires the subject to hold down the pad and then release it as soon as they see the yellow dot appear and to then press inside the circle using the same hand they were holding the pad down with. In the second test condition (5 choice reaction time), subjects are presented with five circles on the screen. This task again requires the subject to hold down the pad and to release it as soon as they see the yellow dot and to then press inside the circle in which they see the yellow dot appear (again using one hand only). The main measures of performance in this task are reaction time and movement time. Reaction time is recorded as the time (in milliseconds) from the appearance of the yellow dot to the release of the pad. Movement time is recorded as the time (in milliseconds) from releasing the pad to pressing inside the circle (All latencies are calculated automatically within the task).

Table 4.1: Summary of Neuropsychological Tasks used in the Study and their key Outcome Measures

Test	Measure
Go/NoGo	Errors for Distractors Blocks 1 +2 Reaction Time for Targets Blocks 1+2
Motor Screening	Mean Error (Arithmetic Mean [AM]) Mean Latency (AM)
Spatial Span	Span Score Total Errors Total Usage Errors
Spatial Working Memory	Between-search Errors Within Search Errors Strategy Score
Tower of London	Number completed in minimum number of moves Average Moves at Each Stage (2, 3, 4, & 5 move problems) Initial Thinking at Each Stage Subsequent Thinking at Each Stage
Pattern Recognition	Percentage Pattern Correct Latency for Correct and Incorrect Responses
Spatial Recognition	Percentage Spatial Correct Latency for Correct and Incorrect Responses
Delayed Matching to Sample	Percentage Correct Simultaneous Percentage Correct Delay (D) (0, 4, & 12) Latency for Correct Responses (S) Latency for Correct Responses (D)
Paired Associates Learning	Number of Trials Number of Errors
ID/ED	Stage Reached Score Total Number of Trials Proportion Reaching ED-Shift and Reversal Stages Errors at Each Stage
Reaction Time	Reaction Time Simple (one-choice) Reaction Time 5-Choice Movement Time Simple (one-choice) Movement Time 5-Choice

Parallel Batteries

The description of the CANTAB tests presented in this thesis refers to the tests selected from the three batteries used at baseline testing (i.e. the clinical version). Parallel versions of the tests in the visual memory and attention batteries are available for repeated testing. These parallel versions were employed for all testing sessions following baseline testing. The parallel versions differ in three key aspects. First, the parallel batteries present the subject with different patterns and locations to be remembered. Specifically, the tasks involving patterns (Pattern Recognition, Delayed Matching to Sample, Paired Associate Learning) present different patterns in each battery. The Spatial Recognition task varies the locations of the boxes to be remembered. Second, two tests - the Paired Associate Learning and Reaction Time - are shorter in duration due to a reduction in practice trials. Third, the Big/Little circle task is not presented within the parallel batteries. Subjects performed this task at baseline testing only.

Procedure

General Study Design

This study was a randomised, double blind, placebo –controlled, crossover trial. There were three phases: baseline, acute drug challenge, and chronic drug challenge. HKD boys were tested on five occasions: once at baseline, once at the acute drug challenge, and on three occasions 4 weeks apart during the chronic MPH challenge. The study design is detailed in Figure 4.6. Control boys were tested once only at baseline.

Figure 4.6: Flowchart of study procedures

Testing Session	1 **Baseline**		2 **Acute**	3 *4 weeks*	4 **Chronic** *4 weeks*	5 *4 weeks*
Group						
Hyperkinetic Disorder	Baseline	➔	placebo	placebo	0.3 mg/kg	0.6 mg/kg
		➔	0.3 mg/kg	0.3 mg/kg	0.6 mg/kg	placebo
		➔	0.6 mg/kg	0.6 mg/kg	placebo	0.3 mg/kg
Control	Baseline		No further follow up after baseline			

In the first phase of the study, the baseline testing session, drug-naïve boys with HKD and age-matched healthy Control boys performed the neuropsychological tasks (summarised in Table 4.1). For boys with HKD, this session was conducted approximately two weeks prior to commencement of medication.

Boys with HKD were subsequently randomised into one of three treatment groups (placebo, 0.3 mg/kg MPH or 0.6 mg/kg MPH). This group allocation dictated the treatment given at the acute drug challenge and also the order in which medications were given during the third - chronic MPH - phase of the study.

At the second testing session (the acute challenge) boys with HKD performed the neuropsychological tests 90 minutes after receiving a first-ever dose of either placebo, 0.3mg/kg methylphenidate (MPH), or 0.6mg/kg MPH under double-blind conditions.

Then in a randomised, double blind, placebo-controlled, crossover, Latin Square design, boys with HKD were tested on three further occasions, after approximately 28 days in each of these three drug conditions, so that all subjects were tested in all three chronic drug conditions (placebo, 0.3 mg/kg/dose MPH and 0.6 mg/kg/dose MPH).

Baseline session

Neuropsychological testing was first carried out approximately two weeks (ranging from 1 week 5 days to 2 weeks 3 days) prior to commencement of medication. At this first testing session, each boy in both the Control and HKD groups completed all the neuropsychological tasks and the verbal IQ test (British Picture Vocabulary Scale, BPVS). The Control group exited the study at this point.

Acute Challenge

This phase of the study was conducted using a randomised, placebo-controlled, double-blind parallel group, design. Boys in the HKD group were assigned randomly to one of three

groups. At the acute challenge all groups received a single dose of medication. Group 1 received placebo, group 2 received 0.3mg/kg MPH, and group 3 received 0.6mg/kg MPH (See Figure 4.6). Randomisation was conducted independently by a clinical trials pharmacist based at Ninewells Hospital and Medical School, who also dispensed all medication but was not involved in any other aspect of the study. Randomisation was stratified in blocks of 15. Statistical analyses were conducted to confirm that boys with HKD were distributed equally between the three groups following randomisation, with respect to a range of subject variables.

An appointment was made with each parent to pick up the first batch of medication 1 day prior to commencement of acute dose. This timescale was chosen in order to reduce the possibility of children taking medication prior to the acute dose. Each boy received an acute dose at 8am the following morning and was tested ninety minutes after taking the first dose. This timing was chosen because the pharmacodynamic effects of MPH on behaviour reach a peak within 1 to 3 hours (e.g. Sonuga-Barke, Swanson, Coghill, DeCory, Hatch, Sonuga-Barke, Swanson, Coghill, DeCory, & Hatch 2004).

Chronic Challenge

This phase of the study was conducted using a randomised, placebo-controlled, double-blind, crossover, Latin Square design. HKD boys in each of the three groups initially continued to take medication at the dose given at the acute challenge. Each HKD boy was then tested on a third occasion after 28 days on this dose (range 25-31 if sickness/holidays). Each boy the switched to a second medication condition and was tested again at the end of 28 days on this dose. They then switched to the 3rd and final medication condition, which was again taken for 28 days at the end of which they were tested for a fifth and final time. All medication was given in identical gelatine capsules. Each medication

batch was taken twice daily at 8am and 12pm. The order in which the three groups received medication is described below and in Figure 4.6:

- Those who had received placebo at the acute challenge continued to receive placebo for the next four weeks, they were then switched to 0.3 mg/kg/dose MPH for four weeks and finally to 0.6 mg/kg/dose MPH for a further four weeks

- Those who had received 0.3 mg/kg/dose MPH at the acute challenge continued to receive 0.3 mg/kg/dose MPH for the next four weeks, they were then switched to 0.6 mg/kg MPH for four weeks and finally to placebo for a further four weeks

- Those who had received 0.6 mg/kg/dose MPH at the acute challenge continued to receive 0.6 mg/kg MPH for the next four weeks, they were then switched to placebo for four weeks and finally to 0.3 mg/kg/dose MPH for a further four weeks

Clinical status was assessed at baseline and at the end of each 28 day treatment period by an experienced and blinded senior child and adolescent psychiatrist who completed a structured interview and made ratings using the Clinical Global Impressions – Improvement scale (CGI-I) (CGI-I, NIMH 1985), and gathered parent and teacher ratings using the Parent and Teacher-rated 10-item Conners' Global Index rating scales (CGI-P and CGI-T, appendices 5a & b, Conners 1997). Treatment adherence was assessed by pill count and clinical enquiry. Individual treatment assignment was revealed to parents and children approximately 1 week following the boy's final testing session.

Attrition

The flow of subjects through the study is detailed in Figure 4.1. All 75 HKD subjects and all 70 Controls were tested at baseline. Two subjects withdrew consent at the acute challenge phase and were not tested for a second time. In the chronic phase there were a total of 12 missed testing sessions. Six subjects missed one data point for reasons unrelated to trial

participation when holidays and sickness made it impossible to reschedule their appointment within a three-day period. Four subjects withdrew due to medication related adverse events (2 at session 3, one at session 4 and 1 at session 5) and two withdrew at session 5 due to perceived lack of treatment efficacy. Nine subjects missed one session only. Five subjects missed more than one testing session.

General Statistical Considerations and Methods

All data analysed were either continuously distributed measurements or dichotomised responses. All analyses were conducted using SPSS for Windows V.14 (SPSS Inc. Chicago Ill.). Initial descriptive analyses were conducted to determine whether data met with normality, homogeneity of variance, homogeneity of regression slopes and sphericity assumptions.

Although the assumption of normality of distribution is made in the derivation of many significance tests, its importance in the analysis of a data set remains controversial (Tabachnich & Fidell 1996). For example, sample size affects the degree to which non-normality may affect robustness – the larger the sample size the smaller the effect non-normality is likely to have on both power and significance level (Pearson 1929). The relatively large sample size in the present study is likely to have reduced the effects of non-normality on robustness. The majority of theorists in this field argue that violation of the normality assumption should be of little concern for most parametric tests (Pearson 1931; Rider 1929; Tabachnich & Fidell 1996). Games and Lucas (1966) reported that the effect of non-normality on power of ANOVA was only significant when the non-normal populations were extremely skewed or leptokurtic. Moderate departures from normality had minimal impact on the power or sensitivity of tests. However, the literature on robustness of significance testing and the degree to which assumptions can be violated is far from conclusive. For some non-normal distributions a transformation can be found, which brings

the data more closely in line with the normal distribution. Tabachnick and Fidell (1996) recommend transforming non-normally distributed data unless “there is some compelling reason not to” (p70). Where necessary, to stabilise variance and to diminish skewness and kurtosis, data were subjected to either square root (SQRT) or logarithmic transformation (log10), depending on the relationship between the variances and the group means (Tukey 1977). The robustness of ANOVA to violation of homogeneity of variance has been intensively studied. Recent guidelines (Glass, Peckham, & Sanders 1972) have become more stringent than the earlier, more cavalier ones (Box 1953). The effects of violating both normality and homogeneity of variance assumptions are regarded as compounding the impact on power and significance of the F-test. Where transformation was either not possible or failed to normalise the data, and data failed to meet the homogeneity of variance assumption, analyses were conducted using non-parametric statistics such as the Kruskal Wallis one-way analysis of variance or the Mann-Whitney U test. The homogeneity of variance across groups in repeated-measures design ANOVAs was assessed by the Mauchly Sphericity test (Mauchly 1940). Where data sets significantly violated this requirement for a repeated-measures design ANOVA, the Greenhouse Geisser Epsilon correction parameter for degrees of freedom (Greenhouse & Geisser 1959; Winer, Brown, & Michels 1991) was used to calculate a more conservative *p* value for each F ratio.

Where suitable, Analysis of Covariance (ANCOVA) was used as it provides a method of managing sources of variation that are out with the control of the experimenter. ANCOVA is considered extremely robust with respect to non-normality of the dependent variable when the covariate approximates normality. When the concomitant variable is a random variable and is not normally distributed, the result is to increase the sensitivity of the F-test to non-normality in the dependent variable (Atiquallah 1964). ANCOVA carries the additional underlying assumption of homogeneity of regression (HOR) slopes, whereby the

relationship between the dependent variable and the covariate are assumed to be similar for all groups of subjects. Data not meeting this assumption were analysed using ANOVA.

Effect sizes were calculated when appropriate. An effect size is a measure of the strength of a relationship between two variables. The calculation of effect sizes standardises the magnitude of the difference between groups such that a 1-point difference indicates that the groups differ by 1 standard deviation on a particular outcome measure. This allows a direct comparison of treatment effectiveness across studies. There are several different techniques for calculating effect sizes. Here I have used the method of Cohen (Cohen 1992), which calculates the statistic *d* which is defined as the difference between two means divided by the pooled standard deviation for those means.

Cohen's *d* is calculated using the formula;

$$d = \frac{(mean1 - mean2)}{\sqrt{(SD1^2 + SD2^2)/2}}$$

Where SD is the standard deviation.

Cohen has suggested that an effect size (*d*) of ≤ 0.2 should be considered small, 0.5 – 0.79 medium and > 0.8 large (Cohen 1992).

Analysis of specific tests

The Delayed Matching to Sample task comprises a simultaneous condition and three delay (0, 4, & 12 second) conditions. Unlike the simultaneous condition, where the target stimulus remains on the screen, the delay conditions tap the subject's ability to recognise the target pattern from memory. Hence, analyses on percentage correct and latency data were conducted separately for simultaneous and delay conditions. This method of analyses

has been used in other studies using this task (Kempton, Vance, Maruff, Luk, Costin, & Pantelis 1999; Owen, Sahakian, Semple, Polkey, & Robbins 1995).

For analysis of performance on the Go/NoGo task, trials were divided into two blocks: Block 1 represented the 'switch' blocks where the task has changed from letters to numbers (or vice-versa) and Block 2 the 'non-switch' block. Blocks were entered into a repeated-measures ANOVA for analysis.

The ID/ED attentional set-shifting task has a number of important measures and has been analysed in studies using the CANTAB tests in a variety of ways. Measures analysed in this thesis were stage reached, reflecting the highest stage successfully attained; proportion of subjects reaching the ED Shift and ED Reversal stages (stages 8 and 9); errors at each stage and total number of trials. The proportion of subjects reaching stages 6 and 7 (ID Shift and Reversal) were not analysed, as boys showed similar performance regardless of group and treatment at these stages. Analysis was conducted in accordance with other studies using this task in healthy children (Luciana & Nelson 1998), and children with ADHD (Kempton, Vance, Maruff, Luk, Costin, & Pantelis 1999) to aid comparison of results.

Specific statistical considerations

Specific statistical considerations relevant to the analyses presented in each Chapter are detailed at the beginning of each Chapter.

Chapter 5

A Comparison of the Neuropsychological Functioning of Drug Naïve Boys with Hyperkinetic Disorder and Healthy Controls, and an Investigation into the Effects of Acute and Chronic Methylphenidate(MPH) on Neuropsychological Functioning in Boys with Hyperkinetic Disorder.

In this Chapter I, describe the key findings from the primary analyses of the study data in order to orientate the reader and to put the subsequent analyses, described in Chapters 6 to 9, into perspective. Sample characteristics and the main data from baseline, acute and chronic challenges with methylphenidate (MPH) are described. Preliminary findings of this dataset were reported in the PhD Thesis of Dr Sinead Rhodes (Rhodes, 2002) and most of the data included here have now been published in peer reviewed journal articles (Coghill, Rhodes, & Matthews 2007; Rhodes, Coghill, & Matthews 2004; Rhodes, Coghill, & Matthews 2005; Rhodes, Coghill, & Matthews 2006, included as appendices 5 - 8).

Statistical considerations

The basic statistical considerations have been described in Chapter 4. Here I will describe specific considerations relevant to the analysis of the baseline neuropsychological data and the impact of the acute and chronic MPH challenges on neuropsychological functioning.

Baseline

The purpose of these analyses was to test for differences in neuropsychological functioning between the hyperkinetic disorder (HKD) and Control groups. As HKD boys scored significantly lower than Controls on the BPVS, the BPVS percentile rank scores were used as a covariate in all analyses. Data meeting assumptions of normality and homogeneity of

variance were analysed using ANCOVA and, thereafter, by determination of simple effects or interactions (Winer, Brown, & Michels 1991). In several other situations, ANCOVA was unsuitable because of the need to use a repeated-measures analysis to analyse data from those tasks with differing levels of difficulty. In cases where the tasks included incremental levels of difficulty within the testing session it was not possible to use simple ANCOVA due to the need to include a second within-subject variable DIFFICULTY level, e.g. Spatial Working Memory (Between-search Errors), Stockings of Cambridge (average moves) and Delayed Matching to Sample (percent correct across 0, 4 and 12 sec. delays). In these situations, a repeated-measures ANCOVA was conducted, with the BPVS percentile rank scores as covariate, and an additional within-subject variable added (DIFFICULTY). When interpreting difficulty levels for Spatial Working Memory Between-search Errors, Stockings of Cambridge Average Moves, and Delayed Matching to Sample Percentage Correct and Latency under delay conditions, the most difficult level (final level e.g. 12 seconds delay Delayed Matching to Sample) was compared with all other levels. All other data were compared using appropriate non-parametric tests (e.g. Mann-Whitney test).

Acute drug challenge

Data meeting the assumption of homogeneity of regression (HOR) slopes were analysed using ANCOVA, with one between-subject factor, TREATMENT group, reflecting treatment group (placebo, 0.3 mg/kg MPH, 0.6 mg/kg MPH), with baseline performance data as a covariate. In practice, however, only stage reached in the ID/ED attention set-shifting test and total errors and usage errors in the Spatial Span task were analysed using ANCOVA. Where data failed to meet the HOR assumption, a mixed design ANOVA with one between-subjects factor, TREATMENT, and with repeated-measures on one within-subject factor, SESSION, was used. In several other situations, ANCOVA was unsuitable because of the need to again use a repeated-measures analysis to analyse data from those tasks with differing levels of difficulty. In these situations, a repeated-measures ANOVA with the

within-subject factor, SESSION and, a second within-subject variable DIFFICULTY was used, which precluded the use of SESSION 1 as a covariate. These data were analysed using a mixed design ANOVA with one between-subject factor, TREATMENT, in addition to the two within-subject factors. Where normality and homogeneity of variance assumptions were not met, data were analysed using the Wilcoxon Sign test for repeated-measures.

Chronic drug challenge

For the chronic challenge, the neuropsychological performance of boys with HKD under chronic treatment with either placebo, 0.3mg/kg or 0.6mg/kg MPH is described. Data for subjects were pooled for each of the three treatments across the chronic sessions (n=69 in placebo, 68 in 0.3mg/kg MPH, 65 in 0.6mg/kg MPH). Results were analysed using a mixed design ANOVA with repeated-measures on one within-subject factor, DRUG (placebo, 0.3mg/kg MPH, or 0.6mg/kg MPH), and with one between-subject factor, ORDER, representing the first drug dose taken (at the acute session and during the first chronic period). The decision to examine order effects through analysis of first drug dose taken was based on findings reported by Elliot and colleagues (1997), who found that subjects who took placebo at a first testing session demonstrated impaired performance (or at least a reduced 'enhancement') on the Spatial Span and Stockings of Cambridge tasks following MPH administration at a subsequent testing session. Where there was a significant interaction between ORDER and DRUG, data were reanalysed comparing baseline performance with chronic session 1 (as conducted for acute analysis). Where measures within tasks incorporated increasing difficulty levels, data were analysed using a mixed design ANOVA with repeated-measures on two within subject factors, DRUG taken and DIFFICULTY level, and one between-subject factor, ORDER, representing the drug taken at the first chronic session. Because of the within-subject crossover design, it was considered unnecessary to control for pre-existing baseline differences. Following ANOVA/ANCOVA, further exploration of the data was conducted by determination of simple effects or

interactions (Winer, Brown, & Michels 1991). Where appropriate, post hoc comparisons between individual data points were made using planned contrasts. When using planned contrasts to interpret drug effects, the 0.3mg/kg and 0.6mg/kg MPH dose conditions were compared with the placebo condition.

Results

Sample Characteristics

Full details of the recruitment and assessment process are described in Chapter 4.

Hyperkinetic disorder (HKD) boys

Seventy five drug naïve boys aged between 7 and 15 years of age with ICD-10 HKD were recruited into the study and completed at least one neuropsychological testing session. All of the boys in the HKD group also met the diagnostic criteria for DSM-IV ADHD combined type (American Psychiatric Association 2000). As described in Chapter 4, to ensure that recruitment into the study was representative of the clinical populations seen in routine practice within the UK National Health Service, the only exception to the ICD-10 HKD criteria implemented was a relaxation on the co-morbidity criteria whereby subjects with oppositional defiant disorder, conduct disorder, depressive disorder, tic disorders and anxiety disorders were allowed to enter the study. The pattern of comorbidity within the sample is described in table 5.1. Five children met criteria for multiple co-morbid diagnoses: 4 met criteria for two comorbid conditions: 1 met criteria for Depressive Episode and Conduct Disorder; 2 met criteria for separation anxiety disorder and Conduct Disorder, and 1 met criteria for Tic Disorder and Oppositional Defiant Disorder. One boy met criteria for three comorbid conditions: Generalised Anxiety Disorder, Tic Disorder, and Oppositional Defiant Disorder.

The demographic and clinical characteristics of the HKD group are detailed in table 5.2

Table 5.1: Comorbid diagnoses in HKD group

	n	*% of sample*
Pure HKD (no comorbidity)	18	24
Comorbid diagnoses		
Oppositional defiant disorder (no CD)	31	41.3
Conduct disorder (CD)	21	28
Depressive disorder	3	4
Generalized anxiety disorder	2	2.7
Separation anxiety disorder	3	4
Tic disorder	2	2.7
Social phobia	1	1.3

Control Group

The Control group comprised 70 healthy developing boys recruited from local schools with no current or past psychiatric disorder, aged between 7 and 15 years of age and matched for age with the HKD sample. The clinical and demographic characteristics of the Control group are detailed in table 5.2.

As expected, there were no significant differences between the HKD and Control groups with respect to age and the HKD group were rated by both parents and teachers as having more problems on the CPRS and CTRS scales. The mean British Picture Vocabulary Scale (BPVS) (Dunn, Dunn, Whetton, & Burley 1997) (2nd Edition) percentile rank scores (population mean = 50) for the Control group (58.94) were significantly higher than those for the HKD group (35.43), indicating that the boys in the Control group were of average intelligence and that they had higher levels of verbal intelligence than the HKD group. As a consequence BPVS percentile rank score was, where statistically appropriate, included as a covariate when comparing the performance of these two groups.

Table 5.2: Age, BPVS and clinical characteristics of the HKD and Control samples

	HKD Boys	Control Boys		
n	75	70		
	Mean (s.d.)	*Mean (s.d.)*	*p*	*Effect size (d)*
Age	10.85 (2.46)	10.74 (2.47)	>.05	
BPVS Percentile Rank	35.43 (27.93)	58.94 (26.25)	<0.001*	0.86
Conners':				
Parents (T scores)				
Oppositionality	75.57 (11.38)	45.25 (6.42)	<0.001*	3.3
Cognitive	72.94 (7.07)	44.16 (3.47)	<0.001*	5.2
Hyperactive	83.08 (8.88)	46.12 (3.43)	<0.001*	5.5
ADHD Index	77.01 (6.09)	43.96 (3.37)	*<0.001**	6.7
Conners':				
Teachers (T scores)				
Oppositionality	65.05 (19.52)	49.15 (9.49)	<0.001*	1.0
Cognitive	62.77 (12.78)	47.66 (7.95)	<0.001*	1.4
Hyperactive	71.00 (14.34)	47.36 (7.42)	<0.001*	2.1
ADHD Index	72.23 (14.93)	47.79 (8.12)	<0.001*	2.0

* = statistically significant difference HKD vs. Controls

Baseline Neuropsychological Assessment

Each subject in the HKD and Control groups performed all tasks in the order in which they are described in Chapter 4, starting with the Go/NoGo task, followed by the CANTAB tasks from the Working Memory and Planning, Visual Memory and Attention batteries in that order .

All subjects completed all of the tests. Mean performance (raw scores and those adjusted for covariate), statistical comparisons and effect sizes (d) for each task, for both groups, are summarized in Table 5.3.

Table 5.3: Summary of baseline neuropsychological findings (HKD vs. Controls)

	HKD N = 75		Controls N = 70				
Measure	Raw Mean (s.d.)	Adjusted Mean (s.d.)	Raw Mean (s.d.)	Adjusted Mean (s.d.)	Sig.	ES raw	ES Adjusted
Go/NoGo							
Errors for Distractors (Block1)	2.3 (1.5)	2.4 (1.4)	2.2 (1.4)	2.13 (1.6)	NS		
Errors for Distractors (Block1)	2.2 (1.7)	2.3 (1.6)	1.9 (1.5)	1.9 (1.7)	NS		
Reaction Time to Targets B1 (log10)	2.7 (0.1)	2.7 (.1)	2.6 (.1)	2.6 (.1)	NS		
Reaction Time to Targets B2 (log10)	2.7 (0.1)	2.7 (.08)	2.6 (0.1)	2.6 (0.1)	NS		
Spatial Span							
Span Score	5.1 (1.5)	5.1 (1.3)	5.9 (1.5)	5.9 (1.5)	**	0.57	0.6
Spatial Working Memory							
Total Between-search Errors	50.7 (19.5)	50.8 (21.0)	35.1 (20.7)	35.0 (21.8)	***	0.77	0.75
Strategy Score	36.3 (4.5)	36.3 (5.1)	32.7 (5.2)	32.7 (5.3)	***	0.73	0.70
Stockings of Cambridge							
No. Solved in Min. Moves	7.1 (2.0)	7.2 (2.1)	8.07 (2.0)	8.0 (2.2)	*	0.46	0.38
Pattern Recognition							
% correct	80.8 (11.1)	81.3 (11.7)	91.0 (8.4)	90.4 (12.1)	***	0.92	0.89
Spatial Recognition							
% correct	67.3 (13.6)	68.2 (13.9)	77.6 (13.7)	78.2 (13.8)	***	0.89	0.72
Delayed Matching to Sample							
Simultaneous	90.9 (15.5)	90.8 (12.4)	97.1 (7.03)	97.3 (1.5)	**	0.53	0.52
Delay (0, 4 +12)	59.4 (18.8)	59.5 (17.8)	75.8 (17.7)	75.7 (17.9)	***	0.91	0.90
Paired Associates Learning							
Stage Reached	7.9 (0.3)	7.9 (0.3)	7.9 (0.3)	7.9 (0.3)	N.S.		
Total Errors	11.6 (11.5)	11.1 (9.7)	6.7 (7.1)	7.2 (10.4)	**	0.51	0.47
Total Trials	12.8 (4.09)	12.6 (4.1)	10.7 (2.9)	10.9 (3.9)	***	0.57	0.58
ID/ED							
Stage Reached	7.6 (1.1)	7.5 (1.0)	7.9 (1.0)	8.0 (1.1)	*	0.38	0.46
Reaction Time							
Reaction Time Latency (5 Choice) $\log_{10}$	2.61 (0.13)	2.62 (0.09)	2.58 (0.11)	2.57 (0.17)	*	0.24	0.71
Movement Time Latency (5 Choice) $\log_{10}$	2.61 (0.14)	2.63 (0.26)	2.55 (0.34)	2.53 (0.25)	*	0.23	0.39

"Adjusted" data is controlled for BPVS group differences; ID/ED, Intradimensional-Extradimensional set-shifting; * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$.

Go/NoGo: HKD boys showed no impairments on the Go/No-Go task. There was no difference between groups for errors to distractors at either the shift or non-shift block ($F(1, 142)<1$), or in reaction times to targets ($F(1, 142)=3.1$, $p>0.05$).

Spatial Span: There was a significant group difference in performance on the Spatial Span task with HKD boys obtaining a lower Spatial Span score than Control boys ($F(1, 142)=9.89$, $p<0.002$, $d=0.6$).

Spatial Working Memory: HKD boys made more between-search errors on the spatial working memory task ($F(1, 142)=18.8$, $p<0.001$, $d=0.75$). There was a significant interaction between group and difficulty level and post hoc tests revealed that HKD boys made more errors at the 8-box stage relative to the 3-, 4- or 6-box stages. HKD boys also had higher (impaired) strategy scores ($F(2, 142)=16.52$, $p<0.001$, $d=0.70$) on the spatial working memory task but there were no differences in within-search errors ($F(1, 142)=1.5$, $p>0.05$).

Stockings of Cambridge: HKD boys solved fewer problems in the minimum number of moves on the Stockings of Cambridge task ($F(1, 142)=4.7$, $p<0.03$, $d=0.38$) but there was no significant difference in the average moves made ($F(1, 141)=3.5$, $p>0.05$) and no significant interaction between group and difficulty level in average moves ($F(2.3, 321)=1.6$, $p>0.05$). There was no significant overall difference between the two groups with respect to either initial ($F(1, 141)=1.1$, $p>0.05$) or subsequent ($F(1, 141)<1$) thinking times, but there was a significant interaction between group and difficulty level ($F(2.5, 349)=3.8$,$p<0.02$) for subsequent but not for initial ($F(1.7, 236)<1$) thinking times. Planned contrasts revealed that Controls had longer subsequent thinking times for 5-move problems relative to 3-move problems ($p<0.01$).

Pattern Recognition: HKD boys made fewer correct responses on the Pattern Recognition task ($z=x5.267$, $p<0.001$, $d=0.89$) but latencies for correct responses did not differ. HKD

boys had shorter response latencies for incorrect choices. However, regression analysis revealed that the latencies for incorrect responses did not predict overall accuracy of responding for the HKD boys ($F(1, 72)<1$).

Spatial Recognition: HKD boys obtained a lower percentage of correct responses on the Spatial Recognition task ($F(2, 142)=17.4$, $p<0.001$, $d=0.72$). There was no significant difference in latencies for correct responses ($F(1, 142)=1.07$, $p>0.05$), but HKD boys had shorter latencies to respond when making incorrect choices ($F(1, 141)=13.9$,$p<0.001$). Again, however, regression analysis revealed that latencies for incorrect responses did not predict overall accuracy of responding for the HKD boys ($F(1, 72)<1$).

Delayed Matching to Sample: HKD boys demonstrated deficits at both the simultaneous and delay conditions of the Delayed Matching to Sample task. There was a significant interaction between performance accuracy and duration of task delay ($F(2, 284)=4.7$, $p<0.01$) and HKD boys made fewer correct responses with increasing delay, whilst Control boys performed equally across all delays. This performance deficit was not explained by differences in response latency on the task ($F(1, 72)<1$).

Paired Associates Learning: Groups did not differ as to the Stage Reached on the Paired Associates Learning task ($F(1, 142)<1$). HKD boys, however, made more errors ($z=x2.9$, $p<0.003$, $d=0.47$) and required more trials ($z=x3.7$, $p<0.001$, $d=0.58$).

Intradimensional- Extradimensional Set-Shifting (ID-ED): HKD boys achieved lower stage-reached scores on the ID-ED attentional set-shifting task ($F(1, 142)=7.0$, $p<0.009$, $d=0.46$). They made more errors prior to the ED shift stage ($F(1, 142)=10.17$, $p<0.002$). Fewer HKD boys completed the ED shift stage ($F(1, 142)=6.7$, $p<0.01$), and examination of errors made by boys who did reach the ED Reversal stage (HKD boys, n=26; Control boys, n=40), revealed that HKD boys made more errors at this stage ($F(1, 63)=5.4$, $p<0.02$).

Reaction Time: Groups differed significantly at the most complex (5-choice) condition of the Reaction Time task. HKD boys were slower to respond than Controls both in terms of reaction times ($F(1, 133)=5.5$, $p<0.02$, $d=0.71$) and movement times ($F(1, 133)=3.94$, $p<0.05$, $d=0.39$). Groups did not differ in reaction or movement times at the simple condition (both $F<1$).

In view of the group differences in BPVS scores a further analysis was conducted on a subset of the sample comprising 47 HKD boys and 47 Controls matched for age and BPVS. This broadly confirmed findings for the total group analyses above. Some differences narrowly failed to reach statistical significance; Stockings of Cambridge number of problems solved in minimum moves ($F=3.66$, $p=0.059$); total errors on the Paired Associates Learning task ($F=3.33$, $p=0.07$); and stage reached on the ID-ED task ($F=2.87$, $p=0.09$); and movement time latency on the 5-choice condition of the Reaction Time task ($F=3.81$, $p=0.054$). It is likely that these findings simply reflect reduced statistical power due to smaller sample size.

The neuropsychological effects of an acute challenge with MPH.

The Control boys exited the study after the baseline testing session. The boys in the HKD group were randomly assigned to one of three treatment groups based on the dose of medication given at the acute testing session. Group 1 received placebo, Group 2 received 0.3mg/kg MPH, and Group 3 received 0.6mg/kg MPH (See Figure. 4.6). Each child received their first dose of stimulant at 8am on the morning of the second testing session and testing started ninety minutes later in order that testing took place during the period of peak drug availability.

Statistical analyses were conducted to confirm that boys with HKD were distributed equally between the three groups following randomisation with respect to a range of subject variables (Table 5.4). There were no significant differences between the three treatment groups with respect to age ($F(2,72) < 1$), BPVS Percentile Rank ($F(2,72) < 1$), parent-rated ADHD composite score (Conners) ($F(2,69) < 1$), and teacher-rated ADHD composite score (Conners) ($F(2,63) < 1$). There were also no significant differences with respect to a range of comorbid conditions; Conduct Disorder ($F(2,70) < 1$), Oppositional Defiant Disorder ($F(2,70) < 1$), Social Phobia ($F2,70) < 1$), Generalised Anxiety Disorder ($F(2,70) = 2.1$, $p = .13$), and Tic Disorder ($F(2,70) < 1$). However, there was a significant difference in the distribution of boys with Separation Anxiety Disorder between the three groups ($F(2,70) = 3.4$, $p < .04$). All three boys diagnosed with this comorbid condition were in Group 1. The low number of children with this condition is unlikely to account for significant findings. Separation Anxiety is not thought to be associated with neuropsychological deficits.

Table 5.4: Baseline characteristics of HKD subjects in each of the three treatment groups at the acute challenge (placebo, MPH 0.3mg/kg and MPH 0.6 mg/kg)

	Placebo N = 24	MPH 0.3 mg/kg N = 25	MPH 0.6 mg/kg N = 24
Age (mean, s.d.)	11.1 (2.5)	10.4 (2.4)	10.9 (2.6)
BPVS percentile rank (mean, s.d.)	37 (30.4)	32.4 (25.2)	38.63 (29.0)
Social Deprivation (DepCat score)	4.2 (1.9)	4.0 (1.4)	3.8 (1.9)
Conners': Parents (T scores)			
Oppositionality	74.4 (9.8)	74.6 (13.7)	78.4 (9.0)
Cognitive	73.7 (5.6)	72.0 (8.3)	72.9 (7.4)
Hyperactive	81.5 (9.0)	82.2 (9.2)	85.2 (8.5)
ADHD Index	77.1 (5.4)	76.0 (7.1)	77.5 (5.7)
Conners': Teachers (T scores)			
Oppositionality	63.0 (20.1)	61.5 (21.4)	71.1 (16.4)
Cognitive	63.5 (11.3)	61.2 (16.3)	63.7 (9.9)
Hyperactive	76.0 (9.8)	66.1 (17.8)	71.1 (12.2)
ADHD Index	72.0 (18.8)	71.1 (16.6)	73.8 (8.3)
Comorbid Conditions (n)			
Oppositional defiant disorder (No CD)	11	12	8
Conduct disorder (CD)	7	6	7
Depressive disorder	1	1	1
Generalised anxiety disorder	2	0	1
Separation anxiety disorder	3	0	0
Tic disorder	1	1	1
Social phobia	0	1	1

The results of the acute MPH challenge on neuropsychological performance are summarised in table 5.5. F and p values reported in Table 5.5 represent SESSION · TREATMENT interactions. Main effects of TREATMENT group, task DIFFICULTY and SESSION are reported only when significant. Seventy three subjects were tested at this session. Two subjects withdrew from the study prior to the acute challenge (one from the placebo group and one from the 0.6mg/kg group). There were no obvious baseline differences between these subjects and those remaining in the study.

Table 5.5: Summary of Acute MPH Challenge Findings for each Treatment Condition (placebo vs. 0.3 mg/kg/dose vs. 0.6 mg/kg/dose)

		Acute Challenge				
Measure	**Total HKD sample (Baseline)**	**Placebo Mean (s.d.) N = 24**	**MPH 0.3mg/kg Mean (s.d.) N = 25**	**MPH 0.6mg/kg Mean (s.d.) N = 24**	*F*	p
Go/NoGo						
Errors for Distractors Block 1	2.4 (1.5)	1.9 (1.6)	1.8 (1.5)	1.8 (1.9)	*F*<1	NS
Errors for Distractors Block 2	2.3 (1.7)	1.4 (1.6)	1.8 (1.7)	2.0 (2)	*F*<1	NS
Reaction Time to targets Block 1 (log_{10})	2.66 (.09)	2.69 (.06)	2.66 (.10)	2.66 (.08)	*F*=2.7	NS
Reaction Time to targets Block 2 (log_{10})	2.67 (.09)	2.69 (.07)	2.65 (.13)	2.67 (.09)	*F*=1.3	NS
Spatial Span						
Span Score	5.1 (1.5) †	4.8 (1.4)	5.5 (1.3)	5.5 (1.3)	F = 2.6	NS
Spatial Working Memory						
Total Between-search Errors	50.8 (21.0) †	47.1 (22.9)	40.8 (19.9)	38.8 (19.9)	F<1	NS
Strategy Score	36.3 (5.1) †	35.7 (5.3)	35.6 (4.2)	35.5 (4.3)	F<1	NS
Stockings of Cambridge						
No. Solved in Minimum Moves	7.2 (2.1)	8.0 (1.5)	8.0 (2.0)	8.5 (1.8)	F<1	NS
Average Moves (5 move problems)	7.6 (1.5)	6.9 (1.3)	7.0 (1.6)	6.8 (1.6)	F<1	N.S.
Initial Thinking Times (5 move problems) (log_{10})	3.59 (.34)	3.47 (0.31)	3.69 (0.37)	3.73 (0.3)	*F*<1	NS
Pattern Recognition						
% Correct	80.8 (13.1) †	84.4 (11.1)	86.3(10.9)	91.1 (7.4)	F=1.4	NS
Latency Correct (log_{10})	3.31 (0.10)	3.34 (0.13)	3.33 (0.10)	3.29 (0.12)	F<1	NS
Latency Incorrect (log_{10})	3.37 (0.16)	3.51 (0.30)	3.44 (0.19)	3.43 (0.23)	F<1	NS
Spatial Recognition						
% Correct	68.2 (13.9) †	57.7 (13.3)	61.4 (16.7)	65.2 (16.8)	*F*<1	NS
Latency Correct (log_{10})	3.32 (.15)	3.26 (.13)	3.32 (.12)	3.44 (.24)	*F* = 3.4	*
Latency Incorrect (log_{10})	3.27 (.14) †	3.3 (.16)	3.39 (.15)	3.55 (.32)	*F* = 7.3	**
Delayed Matching to Sample						
Simultaneous (% Correct)	90.93 (15.5) †	90 (15.6)	91.2 (19.2)	98.26 (5.8)	F=1.4	NS
0 s delay (% Correct)	70.0 (25.6) †	59.2 (20.8)	62.4 (24.7)	78.3 (18.0)	F=7.1	**
4s delay (% Correct)	56.5 (24.0) †	55.0 (21.5)	62.4 (23.3)	83.5 (16.7)	F=11.84	***
12 s delay (% Correct)	50.9 (27.2)†	51.7 (22.0)	60.0 (27.7)	74.8 (20.2)	F=5.75	**
Paired Associates Learning						
Stage Reached	7.96 (0.3)	8 (0.0)	8 (0.0)	8 (0.0)	*F*<1	NS
Total Errors	11.6(11.5) †	11.7 (7.9)	13.0 (12.4)	6.5 (5.0)	*F*=2.8	NS
Total Trials	12.8 (4.1) †	9.3 (2.7)	8.8 (2.1)	7.2 (2.4)	*F*=1.5	NS
ID/ED						
Stage Reached Score	7.5 (1.0) †	7.8 (1.0)	8.2 (1.0)	8.0 (1.0)	*F*=1.1	NS
Total Errors	9.3 (6.2)	8.2 (3.5)	7.0 (3.8)	7.6 (3.3)	F<1	NS
Total Trials	21. 4 (9.74)	18.8 (10.0)	15.8(11.05)	16.2(10.68)	F<1	NS
Reaction Time (all log_{10})						
Reaction Time Latency: Simple	2.60 (0.10)	3.10 (0.17)	3.06 (0.6)	2.57 (0.11)	F=1.2	NS
Movement Time Latency: Simple	2.60 (0.16)	2.73 (0.47)	2.71 (0.36)	2.61 (0.15)	F<1	NS
Reaction Time Latency: 5 choice	2.62 (0.09)	2.89 (0.12)	2.62 (0.09)	2.60 (0.10)	F=3.3	*
Movement Time Latency: 5 Choice	2.63 (0.26)	2.68 (0.37)	2.61 (0.11)	2.62 (0.14)	F<1	NS

† indicates tasks on which HKD boys demonstrated baseline performance deficits compared with healthy boys
NS indicates non-significant, * = p < 0.05, ** = p < 0.01, *** = p < 0.001.

Go/NoGo: Whilst subjects showed a significant reduction in Errors for Distractors from baseline to acute challenge, this improved performance was not attributable to MPH, which had no effect on either performance accuracy or reaction times, at either dose, for either of the blocks.

Spatial Span: Acute MPH had no effect on spatial span score at either dose.

Spatial Working Memory: Acute MPH did not affect performance on any of the key measures from the Spatial Working Memory task. There was no significant effect of treatment group on between-search errors. A significant effect of SESSION ($F_{1,70}=19.0$, $P<0.001$) revealed that, overall, boys showed a reduction in between-search errors at the acute challenge session. There was no significant SESSION x TREATMENT group interaction ($F_{2,70}<1$); however, showing that reduction of errors at the acute challenge session cannot be attributed to MPH. There were no other significant interactions between task DIFFICULTY, TREATMENT group and SESSION.

Stockings of Cambridge: Acute MPH did not influence performance on the Stockings of Cambridge Task either in terms of the number of Problems Solved in Minimum Number of Moves, Average Moves, or on Initial and Subsequent Thinking times. There were significant effects of SESSION on each of these measures. Overall, subjects showed improved performance during the second test session. However, as there were no significant SESSION · TREATMENT interactions, these improvements cannot be attributed to MPH. There was a significant effect of task DIFFICULTY on Average Moves ($F(3,207) = 944.6$, $p < .001$), Initial ($F(3,207) = 68.8$, $p < .001$),and Subsequent Thinking ($F(3,207) = 79.7$, $p < .001$) times. There were no significant task DIFFCULTY · TREATMENT group interactions.

Pattern Recognition: Acute MPH did not affect performance or latencies on the Pattern Recognition task. There was no significant effect of TREATMENT group on percentage of

correct responses (F2,70=1.1, P=0.34). Whilst subjects demonstrated improved responding at the acute challenge session (F1,70=18.9, P<0.001), there was no significant TREATMENT group x SESSION interaction.

Spatial Recognition: Acute MPH had no effect on accuracy but did increase the time to respond on the Spatial Recognition task. Whilst accuracy was significantly improved at the acute challenge session compared with baseline (F(1,69) = 12.0, p<.001), there was no significant SESSION x TREATMENT group interaction. MPH (0.6 mg/kg), slowed responding for both correct and incorrect choices on the spatial recognition task. Although there was no significant effect of SESSION on latency to make correct responses, there was a significant SESSION x TREATMENT group interaction (F(2,69) = 3.36, p<.04). Planned contrasts showed that the MPH 0.6mg/kg group showed longer latencies when making correct responses at the acute challenge session than did those taking placebo (t(45) = -2.07, p<.04). There was also a significant effect of TREATMENT group (F(2,68) = 4.91, p<.01) on latencies to make incorrect responses, a significant effect of SESSION (F(1,68) = 25.8, p<.001) and a significant TREATMENT group by SESSION interaction (F(2,68) = 7.27, p<.001). Planned contrasts revealed that the MPH 0.6mg/kg group showed longer latencies when making incorrect responses at the acute challenge session (t(45) = -2.43, p<.003) compared with placebo**.**

Delayed matching to sample: Acute MPH had no effect, at either dose, on performance accuracy under simultaneous test conditions. MPH at a dose of 0.6 mg/kg, restored performance accuracy in HKD boys, across each of the delay conditions, to the levels previously observed in Controls (F1,88=1.2, P>0.05). However, the HKD group continued to show impaired functioning across each of the delay conditions under both placebo (F1,91=29.9, P<0.001) and 0.3 mg/kg MPH (F1,90=10.8, P<0.001). Enhanced performance

under MPH 0.6 mg/kg was not accompanied by significant changes in latencies to make correct responses.

Paired Associates Learning: Acute MPH had no effect on performance of the Paired Associates Learning task. For stage reached and mean error scores there was no effect of TREATMENT group or SESSION, nor an interaction between the two. There was a significant effect of TREATMENT group ($F(2,70) = 3.5$, $p<.04$) and of SESSION ($F(1,70) = 170.8$, $p<.001$) on total number of trials, but no interaction indicating an absence of effect of MPH. The significant effect of TREATMENT group seems likely to reflect a non-statistically significant trend towards a smaller number of trials taken by the 0.6mg/kg MPH treatment group at baseline in comparison to the placebo group.

Intradimensional- Extradimensional Set-Shifting (ID/ED): Acute MPH did not affect performance on the ID/ED attentional set-shifting task. There was no effect of TREATMENT group on Stage Reached, errors up to and including ID reversal, errors at the ED shift or at the ED reversal stages. There was a significant effect of SESSION ($F(1,70) = 12.05$, $p<.001$) on the proportion successfully completing the Extra-Dimensional Reversal stage (stage 9) but no significant effects of TREATMENT group ($F(2,70) <1$) or significant TREATMENT group by SESSION interaction.

Reaction Time: There were no significant effects of acute MPH on reaction time or movement time in the simple reaction test condition. However, MPH 0.6 mg/kg shortened latencies to respond during the 5-Choice condition. While there was no significant effect of TREATMENT group, or SESSION on Reaction Time latencies, there was a significant TREATMENT group by SESSION interaction ($F(2,68) = 3.30$, $p<.05$). Planned contrasts revealed that the MPH 0.6mg/kg group had shorter latencies during the acute challenge session ($t(46) = 2.13$, $p<.03$). MPH did not improve movement time latencies in the 5-choice condition.

The neuropsychological effects of a chronic challenge with MPH.

Boys in each group continued to take the dose taken at acute challenge twice daily for the next 28 days. Each child was tested on a third occasion at the end of this period and on two further occasions at the end of 28 days of the 2nd and 3rd batches of medication. Clinical examinations and questionnaires (CGI-P and CGI-T) and neuropsychological testing were performed at the end of each of the three chronic phases of medication. Clinicians, neuropsychological testers, children, parents and teachers all remained blinded throughout this period. The results for the neuropsychological testing are reported here. The clinical results and the associations between the clinical and neuropsychological data are reported in Chapter 9.

The results of the chronic MPH challenge on neuropsychological performance are summarised in table 5.6.

Table 5.6: Summary of Chronic MPH Challenge Findings for each Treatment Condition (placebo vs. 0.3 mg/kg/dose vs. 0.6 mg/kg/dose)

Measure	Baseline	Chronic Challenge (collapsed across order)			P		Effect size (d)		Effect size (d)
		placebo Mean (s.d.)	0.3mg/kg Mean (s.d.)	0.6mg/kg Mean (s.d.)	Pla vs. 0.3 mg/kg	Pla vs. 0.6 mg/kg	Pla vs. 0.3 mg/kg	Pla vs. 0.6 mg/kg	Baseline vs. Placebo
Go/NoGo									
Errors for Distractors b1	2.4 (1.5)	1.6 (1.5)	1.4 (1.4)	1.2 (1.4)	NS	0.01		0.27	0.54
Errors for Distractors b2	2.3 (1.7)	1.6 (1.6)	1.3 (1.4)	1.1 (1.3)	0.03	0.004		0.33	0.4
Reaction Time to targets b1 ($\log_{10}$)	2.66 (0.09)	2.70 (0.07)	2.68 (0.09)	2.67 (0.09)	NS	0.005		0.37	0.5
Reaction Time to targets b2 ($\log_{10}$)	2.67 (0.09)	2.69 (0.07)	2.68 (0.09)	2.69 (0.08)	0.02	NS	0.12		0.25
Spatial Span									
Span Score*	5.1 (1.5)	5.5 (1.7)	5.7 (1.6)	5.7 (1.5)	NS	NS			0.26
Spatial Working Memory									
Total Between-search Errors*	50.8 (21.0)	39.9 (20.6)	38.7 (23.0)	35.9 (19.8)	NS	NS			0.53
Strategy Score*	36.3 (5.1)	35.2 (4.0)	34.4 (5.0)	34.4 (5.2)	NS	NS			0.26
Stockings of Cambridge									
No. Solved in Minimum Moves	7.2 (2.1)	8.3 (1.9)	8.8 (2.2)	8.8 (2.1)	NS	NS			0.57
Initial Thinking 5 move ($\log_{10}$)	3.59 (0.34)	3.54 (0.40)	3.63 (0.38)	3.64 (0.35)	NS	NS			0.14
Subsequent Thinking 5 move ($\log_{10}$)	2.83 (0.58)	1.88 (1.16)	2.08 (1.06)	2.28 (0.97)	NS	NS			1.04
Pattern Recognition									
% Correct*	80.8 (13.1)	81.8 (13.3)	86.0(12.9)	87.8 (12.5)	<0.001	<0.001	0.32	0.47	0.07
Latency Correct ($\log_{10}$)	3.32 (0.15)	3.30 (0.11)	3.30 (0.11)	3.32 (0.09)	NS	NS			
Latency Incorrect ($\log_{10}$)*	3.27 (0.14) †	3.38 (0.17)	3.39 (0.17)	3.42 (0.16)	NS	NS			
Spatial Recognition									
% Correct*	68.2 (13.9)	57.8 (14.0)	67.2 (14.4)	68.9 (13.4)	<0.001	<0.001	0.66	0.81	-0.75
Latency Correct (log 10)	3.32 (0.15)	3.27 (0.16)	3.3 (0.15)	3.37 (0.15)	NS	<0.001		0.64	0.32
Latency Incorrect (log 10)*	3.27 (0.14)	3.32 (0.17)	3.34 (0.2)	3.40 (0.15)	NS	0.01		0.50	0.32
Delayed Matching to Sample									
Simultaneous(% Correct)*	90.9 (15.5)	85.2 (18.0)	91.3 (13.6)	95.4 (9.2)	<0.001	<0.001	0.38	0.71	0.34
Delay (0, 4 & 12 sec combined) (% correct)*	59.5 (17.8)	56.0 (19.2)	65.8(21.2)	68.8 (16.3)	<0.001	<0.001	0.48	0.72	0.19
Paired Associates Learning									
Stage Reached	7.96 (0.3)	8 (0)	8 (0)	8 (0)	NS	NS		Ceiling effect	
Total Errors*	11.6(11.5)	6.7 (6.6)	5.7 (5.7)	5.5 (5.6)	NS	NS			0.53
Total Trials*	12.8 (4.1)	7.7 (2.2)	7.3 (2.03)	7.2 (1.9)	NS	NS			1.61
ID/ED									
Stage Reached Score*	7.5 (1)	8.0 (.99)	8.2 (.95)	8.0 (.97)	NS	NS			0.45
Reaction Time									
Reaction Time Latency: 5 choice (log 10)	2.62 (0.09)	2.86 (0.11)	2.62 (0.11)	2.62 (0.11)	NS	NS			0.24
Movement Time Latency: 5Choice (log10)	2.63 (0.26)	2.67 (0.35)	2.63 (0.12)	2.66 (0.12)	NS	NS			0.13

* indicates measures on which HKD boys demonstrated baseline performance deficits compared with healthy boys.

Go/NoGo: Chronic MPH improved performance on the Go/NoGo task. MPH reduced mean errors for distractors (ERD) during both Block 1 (the 'shift' block) ($F(2,116) = 4.1$, $p < .02$) and Block 2 ($F(2,116) = 5.9$, $p < .005$). MPH 0.3mg/kg ($p < .03$) reduced errors during Block 2 and MPH 0.6mg/kg during both Blocks ($p < .01$ and $p < .004$). There was also a significant overall effect of MPH to shorten response latencies during Blocks 1 ($F(2,116) = 4.1$, $p < .02$) and 2 ($F(2,116) = 3.1$, $p < .049$). This was accounted for by 0.6mg/kg MPH shortening response latencies relative to placebo ($p < .005$).

Spatial Span: There was no effect of chronic MPH on spatial span score ($F(2,116) < 1$)

Spatial Working Memory: Chronic MPH did not affect performance on the Spatial Working Memory task, although effects on between-search error scores narrowly failed to reach significance ($F(2,116) = 2.85$, $P=0.067$).

Stockings of Cambridge: There was no effect of chronic MPH on the number of minimum move solutions ($F(2,116) = 1.9$, $p = .16$), but there was a significant effect of ORDER ($F(2,58) = 5.38$, $p < .007$) and a significant interaction between TREATMENT group and ORDER ($F(4,116) = 3.3$, $p < .02$). Re-analysis with SESSION as a within-subjects and TREATMENT group as a between-subjects factor ($n = 24$ per group) revealed no significant effect of TREATMENT group ($F(2,68) = 2.1$, $p = .13$), although performance improved overall from baseline to chronic challenge ($F(1,68) = 17.6$, $p < .001$). There was a significant interaction between SESSION and TREATMENT group ($F(2,68) = 3.3$, $p < .04$), but planned contrasts revealed no significant differences between the groups (all $p > .05$). There were no significant effects of MPH on initial (ITT) ($F(2,116) < 1$) or subsequent (STT)($F(2,116) = 1.6$, $p = .21$) thinking times. There was a MPH and ORDER interaction for STT ($F(4,116) = 3.1$, $p < .02$); planned contrasts revealed that boys taking placebo at the first chronic test session had longer STT than when taking 0.3mg/kg ($p < .049$) or 0.6mg/kg ($p < .043$).

Pattern recognition: Chronic administration of MPH improved accuracy of responding on the pattern-recognition task (F(2,116)=6.02, P<0.001) at both the 0.3-mg/kg (P<0.02) and 0.6-mg/kg (P<0.003) doses relative to placebo. There were no significant effects of MPH on latencies for correct or incorrect responding on the pattern recognition task.

Spatial Recognition Memory: Chronic MPH improved accuracy on the spatial recognition task ($F(2,116) = 16.3$, $p < .001$). Planned contrasts revealed improved performance when taking both 0.3mg/kg ($p < .001$) and 0.6mg/kg ($p < .001$) MPH doses relative to the performance deterioration observed with placebo. There was a significant effect of MPH to slow responses when making correct ($F(2,116) = 10.08$, $p < .001$) and incorrect ($F(2,114) = 3.8$,$p < .03$) responses, attributable to the differences between 0.6mg/kg MPH and placebo (correct ($p < .001$), incorrect ($p < .01$). There were no correlations between response latencies and accuracy of responding.

Delayed matching to sample: Chronic administration of MPH at both doses enhanced accuracy of responding under both simultaneous (F2,114=9.8, P<0.001) and delay (F2,116=15.4, P<0.001) conditions. This effect was smaller than that observed following acute challenge, with performance improved, but not normalised. The HKD group continued to display significant impairment in functioning under delay conditions compared with Controls. Chronic MPH treatment also slowed response latencies for correct choices at both 0.3 mg/kg (P<0.03) and 0.6 mg/kg (P<0.01). However, a positive correlation between response latencies and accuracy of responding was only observed for children taking the 0.3-mg/kg dose at the 4-s (r=0.344, P<0.004) and 12-s (r=0.347, P<0.005) delays. More detailed evaluation of this relationship using linear regression analysis revealed that the predictive association was modest (4 s, r 2=0.119; 12 s, r2=0.120).

Paired Associates Learning: All participants reached the final stage with chronic MPH treatment. There was no effect of MPH on total number of trials required to complete the task ($F(2,114) = 2.1$, $p <= .125$), nor on total errors made ($F(2,114) = 1.4$, $p = .2$).

Intradimensional- Extradimensional Set-Shifting (ID/ED): There was no significant effect of chronic MPH on stage reached on the ID/ED task ($F(2,116) = 1.78$, $p = .17$). There was no significant effect of MPH on errors made prior to ($F(1.7, 3.5) = 2.72$, $p > .05$), during ($F(2,116) = 2.1$, $p = .13$), or after ($F(2,116) = 1.1$, $p = .34$) the extradimensional shift stage.

Reaction Time: There was no effect of MPH on reaction time latencies during simple ($F(2,116) = 2.3$, $p = .13$) or 5-choice ($F(2,116) = 2.9$, $p = .09$) conditions.

Summary and discussion of findings

Baseline findings

Stimulant-naive boys with HKD showed significant deficits across several aspects of neuropsychological functioning. They displayed profound deficits in executive functioning in terms of visual working memory, strategy formation, planning, attentional set-shifting and were significantly slowed on a reaction time task. These data do not support earlier conceptualizations of HKD as a dysfunction in a single aspect of executive functioning, they do support the growing literature suggesting that AD-HKD is associated with impairment across a range of executive functions (Boonstra et al. 2005; Kempton, Vance, Maruff, Luk, Costin, & Pantelis 1999; Nigg, Blaskey, Huang-Pollock, & Rappley 2002; Pennington & Ozonoff 1996; Tripp, Ryan, & Peace 2002; Willcutt, Doyle, Nigg, Faraone, & Pennington 2005). Contrary to expectations, inhibitory performance on a Go/No-Go task was unimpaired.

In addition to these deficits in executive functioning, profound neuropsychological impairment was evident in several aspects of non-executive memory functioning. HKD boys

showed impairments in several tasks assessing the recognition and recall of patterns and spatial locations (Delayed Matching to Sample, Pattern and Spatial Recognition, Spatial Span and Paired Associates Learning).

With respect to the Delayed Matching to Sample task, these results are in line with previously reported findings. Using an identical task Kempton et al. (1999) also reported delay-independent performance deficits in un-medicated subjects with DSM-IV ADHD. Chelonis et al. (2002), using a different Delayed Matching to Sample task, reported delay-dependent deficits in DSM-IV ADHD subject withdrawn from stimulants for at least 18 h. These data support and extend these findings to drug naive subjects with ICD 10 defined HKD. The finding of no deficit at a 0-s delay suggests that these deficits are a consequence of difficulties in retention or recall rather than of encoding or attending. Previous studies have also identified deficits in spatial span, although they have usually included these within the "working memory" construct and failed to distinguish between the executive and non-executive aspects of memory (Kempton, Vance, Maruff, Luk, Costin, & Pantelis 1999). Whilst no previous studies have used the CANTAB Paired Associates Learning task in AD-HKD, several groups have used alternative versions of this task and have reported mixed results. For example, Shue and Douglas (1992) found no deficits whilst Chang et al. (1999) reported a robust deficit that was not related to either hyperactivity/impulsivity symptoms or oppositional defiant disorder, and Conte et al. (1986) reported differences between AD-HKD and Controls, but only at a slow presentation rate.

The deficits observed on the pattern-recognition task in the present study were not predicted. Previous studies have reported no group differences on this (Kempton, Vance, Maruff, Luk, Costin, & Pantelis 1999) and other similar recognition memory tasks (Douglas 1988). The differences between the present and previous studies may be related to differences in sample size, rigor of diagnostic assessment, diagnostic classificatory system

used and medication status of subjects. Importantly, as this was a drug naïve sample, these impairments in executive nor in non-executive functioning cannot be attributed to a previous exposure to stimulant medication. In addition, as BPVS was controlled for, these differences do not appear to be explained by verbal intelligence.

Whilst it is possible for a group of individuals to have a broad range of deficits across a range of neuropsychological tasks, such as is seen here, without there being with heterogeneity it is important to consider this possibility. Chapter 6 will therefore describe a detailed secondary analysis of the baseline neuropsychological performance data designed to identify and describe any neuropsychological heterogeneity within the HKD sample. Chapter 7 will investigate the impact of development, and Chapter 8 the impact of comorbid oppositional defiant disorder and conduct disorder, on neuropsychological heterogeneity.

Acute and chronic medication findings

Stimulant effects on tasks with relatively modest 'executive' demands have been relatively understudied. The finding that a single dose of MPH at a dose of 0.6 mg/kg restored the previously disrupted performance accuracy on the Delayed Matching to Sample delay conditions to the levels observed in Controls is striking. This observation support and extends the work of Chelonis et al. (2002) who also reported normalisation of Delayed Matching to Sample performance following administration of stimulant medication. Interestingly, my data suggest that whilst chronic MPH treatment still improves performance on this task, the effects are less pronounced than those seen with acute medication. I also found that chronic, but not acute, MPH treatment improved performance on the Pattern Recognition task and maintained subjects' performance on the Spatial Recognition task (compared with deterioration in performance under placebo conditions).

Notwithstanding these positive findings, these results are striking in that neither acute nor chronic MPH improved performance on several other tasks on which the boys with HKD had performed poorly at baseline. In this respect these findings contradict key aspects of the existing literature. Specifically, previously reported acute MPH performance improvements on the CANTAB Spatial Working Memory (Barnett et al. 2001; Bedard, Martinussen, Ickowicz, & Tannock 2004; Kempton, Vance, Maruff, Luk, Costin, & Pantelis 1999; Mehta, Goodyer, & Sahakian 2004), ID/ED (Kempton, Vance, Maruff, Luk, Costin, & Pantelis 1999; Mehta, Goodyer, & Sahakian 2004), and Stockings of Cambridge (Kempton, Vance, Maruff, Luk, Costin, & Pantelis 1999) tasks were not replicated.

These contradictory findings may relate to differences in study methods, statistical analyses and/or possible practice effects associated with the repeated testing in this study. Previous studies have made significant design compromises including the use of nonrandomized and uncontrolled protocols (Barnett, Maruff, Vance, Luk, Costin, Wood, & Pantelis 2001; Kempton, Vance, Maruff, Luk, Costin, & Pantelis 1999), small samples with nonstandard assessment procedures (Kempton, Vance, Maruff, Luk, Costin, & Pantelis 1999; Mehta, Goodyer, & Sahakian 2004), inclusion of previously medicated subjects with the potential for withdrawal and carryover effects of medication(Bedard, Martinussen, Ickowicz, & Tannock 2004; Mehta, Goodyer, & Sahakian 2004), and the use of only a single dose of MPH. It is also possible that differences in study inclusion criteria may be important. Previous studies' inclusion criteria were based on DSM-IV. We recruited participants meeting diagnostic criteria for ICD-10 HKD (who also met criteria for DSM-IV ADHD combined type).

These data also support the notion that the effects of MPH on neurocognitive functioning should not be considered as a simple restoration of baseline impairments (Rapport & Kelly 1991), particularly with respect to psychological processes with high 'executive' demands.

Indeed, in this data the only evidence of improved performance on an 'executive' task was that seen with the Go/NoGo task, which, it should be remembered, did not differentiate between HKD and Control subjects at baseline.

Taken together these data support the contention that MPH selectively enhances discrete aspects of neuropsychological functioning (Gao & Goldman-Rakic 2003). Importantly, MPH did not impair performance on any of the tasks studied.

These analyses and those reported in the literature fail to address several very important questions. What are the relationships between the neuropsychological functioning and clinical response to MPH? Most previous studies have relied on samples of medicated subjects (who presumably have responded to MPH), who are withdrawn from MPH for testing and/or on single dose MPH challenges and such studies have therefore been unable to investigate these associations. The clinical and neuropsychological data from the chronic challenge phase of this study are, however, ideally suited to address these questions. Chapter 9 of this thesis will focus on these relationships and address two specific questions. Does baseline neuropsychological performance predict response to MPH? And is there an association between clinical and neuropsychological response to MPH?

Chapter 6

Neuropsychological Heterogeneity in Drug Naïve Boys with Hyperkinetic Disorder

Chapter 5 described the baseline neuropsychological deficits in a group of 75 drug naïve boys with HKD and the acute and chronic effects of methylphenidate (MPH) on these deficits. Whilst this group of boys were found to have deficits, compared with Controls, on a wide range of tasks, it is not clear from these analyses whether the boys with HKD are homogeneous or heterogeneous with respect their neuropsychological functioning. That is; do all of the boys with HKD have deficits on all tasks or are there different patterns of deficits in different boys with some having deficits on one or more task but not on others? The purpose of this Chapter is to further explore the neuropsychological functioning in these boys in order to investigate whether there is evidence of neuropsychological heterogeneity.

Background

As described in Chapters 2 and 3 there is now considerable evidence to support the notion that AD-HKD is a heterogeneous disorder and that this heterogeneity is reflected across multiple levels of analysis. There are suggestions of genotypic and environmental causal heterogeneity as well as heterogeneity at the neuroanatomical, pathophysiological and neuropsychological levels, and in the behavioural phenotype itself. The data presented in Chapter 5 described the broad range of neuropsychological deficits, which are associated with HKD. Whilst confirming the traditional notion that HKD is associated with deficits in executive functioning, they also highlight broader deficits in non-executive tasks. They also support a multiple causal pathway model of HKD and challenge the historical notion of there being a single core deficit. The demonstration of multiple deficits across a range of

tasks does not prove that there are multiple causal pathways or that there is neuropsychological heterogeneity. It is plausible – if not likely – that this pattern of results could stem from a chain of neuropsychological deficits with an initial primary deficit and several further deficits with each of these subsequent deficits being dependent on the previous deficit. Such a single pathway model would allow multiple neuropsychological deficits without there being any heterogeneity of neuropsychological functioning. Further analyses are therefore required to investigate the relationships between different aspects of functioning and to look for evidence of neuropsychological heterogeneity within the sample.

Historically, single pathway explanations were predominant and there was an emphasis, within the neuropsychological investigation of AD-HKD, on the identification of *the* core deficit responsible for AD-HKD. Several "big" theories were proposed each of which, at least initially, attempted to provide a complete description of AD-HKD from a neuropsychological perspective. Each of these theories proposed a single primary deficit upon which other deficits were dependent.

Barkley (1997b) proposed a model, which linked inhibitory deficits with a range of other executive functioning deficits (working memory, self-regulation of affect-motivation-arousal, internalization of speech, and reconstitution). In this model the inhibitory deficit was seen as primary and each of the other executive functions being dependent on accurate inhibition for their effective execution.

Sergeant et al. (Sergeant, Oosterlaan, & Van der Meere 1999) described a state regulation model, whereby AD-HKD is seen to arise secondary to a state of low "activation" and cortical arousal.

Sagvolden et al. (Johansen et al. 2002; Sagvolden, Johansen, Aase, & Russell 2005) argued that AD-HKD is a consequence of altered reward and extinction processes, which lead on to problems with learning, conditioning and motivation.

In a somewhat related approach, based on carefully designed experimental studies, Sonuga-Barke et al. (Sonuga-Barke, Taylor, Sembi, & Smith 1992; Sonuga-Barke, Taylor, & Heptinstall 1992) observed that children with and without AD-HKD all tend to choose a large reward over a small reward when the waiting time was fixed. However, when it was possible for the children to Control the waiting time, children with AD-HKD tended to make choices that reduced the waiting time, even if this meant accepting a smaller reward, whilst healthy children generally preferred to wait for a larger reward rather than accept a smaller immediate reward. From these observations they proposed the delay-aversion hypothesis of AD-HKD, which suggests that rather than being unable to wait, children with AD-HKD find waiting more aversive than healthy children.

Each of these theories came with an assumption of causal homogeneity that now seems out of step with our understanding of AD-HKD. They were often theoretically rather than empirically based, or were based on the findings of studies designed to prove rather than disprove the validity of the theoretical approach rather than to pit one approach against another in a head to head design. In general, studies compared the performance of a group of children with AD-HKD with that of a group without, on either a single task or a small number of tasks designed to investigate a single aspect of neuropsychological functioning. Where significant differences in performance were demonstrated, it was assumed that a particular theoretical approach was either supported or not. Although influential, and frequently cited, Barkley's approach was never actually supported by experimental evidence. Whilst many of the other approaches are now supported by systematic review and meta analysis (e.g. van Mourik, Oosterlaan, & Sergeant 2005; Willcutt, Doyle, Nigg,

Faraone, & Pennington 2005; Willcutt, Sonuga-Barke, Nigg, & Sergeant 2008), it must be remembered that finding robust and reproducible group differences on a particular task, or even on a series of tasks measuring a single neuropsychological process, does not imply that this deficit is the sole cause of the disorder in question.

In the case of AD-HKD there are several reasons to question the appropriateness of a search for a single causal neuropsychological deficit.

There is evidence for impairment across a broad range of cognitive processes, which tap into very different aspects of functioning. The data presented in Chapter 5 confirms that this is as true for the more restrictive HKD phenotype as it is for the broader ADHD phenotype.

Each of these neuropsychological deficits is typically associated with an effect size that is only moderate in size ($d \approx 0.6 – 0.9$) compared with the typical effect sizes found for symptom scores ($d \approx 2.5 – 4.0$).

Effect sizes of this magnitude suggest that, although the groups are statistically distinct, there is considerable overlap between the AD-HKD and Control groups (i.e. many of the AD-HKD sample are likely to have task scores that fall within the normal range).

AD-HKD samples tend to have increased sample variance in their performance on neuropsychological tasks, which is usually at the “poor performance” end of the distribution, suggesting that the group effects are, at least in part, a consequence of poor performance by a small group of children rather than an overall shift in group performance (Nigg, Willcutt, Doyle, & Sonuga-Barke 2005).

Studies which have estimated the clinical predictive power of neuropsychological measures with respect to AD-HKD have tended to show reasonable sensitivity (those with poor

performance are likely to have AD-HKD) but poor specificity (many of those with AD-HKD have reasonable performance) (Barkley, Grodzinsky, & DuPaul 1992; Doyle, Biederman, Seidman, Weber, & Faraone 2000; Grodzinsky & Barkley 1999; Hinshaw, Carte, Sami, Treuting, & Zupan 2002). This means that the absence of a neuropsychological deficit cannot rule out AD-HKD (Grodzinsky & Barkley 1999).

Together, several findings suggest that heterogeneity at the neuropsychological level is likely in children with AD-HKD. Indeed Sonuga-Barke modified his original delay aversion hypothesis of AD-HKD into a dual pathway model (Sonuga-Barke 2003). Several groups have now used a range of experimental and statistical analytic approaches to investigate neuropsychological heterogeneity in AD-HKD samples.

Solanto et al. (2001) conducted a "head to head" investigation of inhibitory deficits (using the Stop Task) and delay aversion in a sample of children with DSM-IV ADHD combined type. Their results demonstrated that in this group both tasks made an independent contribution to the development of ADHD. Delay aversion was associated with a broad range of ADHD characteristics whereas inhibitory failure seemed to tap into a more discrete dimension of executive control.

Biederman et al. (2004) defined an executive function "deficit" as performing ≥ 1.5 standard deviations below the mean of the Control sample on two or more tasks. According to these criteria only 33% of subjects in their DSM-IV ADHD sample were classified as having an "executive functioning deficit" (compared with 12% of the Control sample). The ADHD children with an "executive functioning deficit" were at increased risk for academic failure compared with both the Control group and the ADHD group without an "executive functioning deficit".

Nigg et al. (Nigg, Willcutt, Doyle, & Sonuga-Barke 2005) focused on executive functioning and summarised the evidence for overlapping distributions and neuropsychological heterogeneity from 3 research sites in the US. Children in these studies, were, again diagnosed according to DSM-IV criteria. They defined an abnormality of neuropsychological functioning, more liberally than Biederman et al (2004), as performance within the bottom 10% of Control subjects on any task. They reported that:

- There was a significant overlap in the distributions of "impairment" between the ADHD and Control groups
- Whilst most ADHD subjects did have a "deficit" on at least one task a significant proportion (18 – 27%, mean 21%) had no observable "deficit".
- A significant proportion (42 – 56%, mean 47%) of Control subjects had at least one "deficit".
- The number of separate task "deficits" for each of the ADHD individuals was very variable (1 "deficit" = 26%, 2 "deficits" = 22%, 3 "deficits" = 13%, 4 "deficits" = 8% and 5 or more "deficits" = 10%

The results were fairly consistent across the different sites even though samples at each site had been recruited and diagnosed in very different ways (clinical vs. community) and different tasks were used at each site.

All of the above studies included subjects diagnosed with ADHD according to DSM-IV criteria and most included subjects that had been previously exposed to stimulant medication. There have, however, been no previous investigations of neuropsychological heterogeneity in drug naïve children with ICD-10 hyperkinetic disorder (HKD). As HKD represents a more refined diagnostic category it is possible that it identifies a more

homogeneous sub group of children suffering from the most pervasive and disabling AD-HKD. Similarly the inclusion of a group of drug naïve children may increase the homogeneity of presentation.

These previous studies also all focussed either on deficits in executive functioning or delay aversion. The data baseline neuropsychological data presented in Chapter 5 identified that, compared with Controls, the HKD boys also had deficits on several non-executive memory tasks. The relationship between performance on these non-executive tasks and the more traditional tasks of executive functioning has not been previously investigated in subjects with AD-HKD.

The aim of this Chapter, therefore, is it to describe the neuropsychological heterogeneity found within a sample of drug naïve boys with hyperkinetic disorder.

The research questions are;

- What is the distribution of neuropsychological “deficits” within the HKD sample?
- What are the associations between these “deficits”?
- Do these “deficits” independently discriminate between the HKD and Control groups and if so are they equally effective discriminators?

Specifically, I wished to test the hypotheses that;

- Drug naïve boys with hyperkinetic disorder will demonstrate less neuropsychological heterogeneity than that previously found with ADHD samples.

- HKD will be more strongly associated with “executive” rather than “non-executive” deficits in neuropsychological functioning and there will therefore be different patterns of between task association for HKD and Control boys.

- Both executive and non-executive tasks will independently discriminate between HKD and Controls but discrimination by executive tasks will be more effective than that by the non-executive tasks.

Statistical Considerations.

All analyses in this Chapter were conducted on the baseline (i.e. drug naïve) neuropsychological data from the HKD and Control samples described in Chapters 4 and 5.

In order to describe the performance of HKD subjects in comparison to the Control group, z – scores were calculated (standardised for age and BPVS percentile correct) for each HKD participant. Z-scores provide a standardised score (mean = 0, standardised distribution = 1), which allows performance on different tasks, measured in different units, to be compared directly. A z-score of greater than 1.28 identifies that a subject is in the top 10^{th} centile of performance. The z-scores were calculated for each individual in the HKD group by comparing their performance with that of the Control group subjects.

The definition of neuropsychological “deficit” as described by Nigg et al (2005) was adopted. Thus a subject was classified as having a “deficit” if they had a z-score for that measure of ≥ 1.28 or ≤ - 1.28 [depending on whether a poor score is high or low]), which means that their performance on a particular measure would place them in the bottom 10% of the Control group on that measure. Whilst it is acknowledged that this is a fairly liberal definition of “deficit”, using even this definition of “deficit” identified that a relatively large proportion of ADHD children (≈ 21%) did not exhibit any neuropsychological

"deficit" across a range of tasks in a previous analysis (Nigg, Willcutt, Doyle, & Sonuga-Barke 2005).

The associations between subjects' performance on different tasks were first investigated using bivariate correlations (Pearson). An exploratory analysis was then conducted using Principal Components Analysis as recommended by Field (2005) and Tinsley & Tinsley (1987). An acknowledged drawback of this technique is that the results of the analysis are restricted to the sample studied and can only be generalised if replicated in an independent sample. For the HKD subjects the z-scores for each measure were then used to calculate a z-score for each subject's performance on each of the components, taking into account the weightings of each measure on that component. Discriminant analysis was used to investigate the sensitivity and specificity of the neuropsychological measures as predictors of group membership (HKD or Control). Separate analyses were first conducted for each measure. The possibility that discrimination may be improved by using more than one measure simultaneously was then explored in two further analyses. First, the best predictors of group membership were entered together in a single step into the same discriminant function. They were then entered in a stepwise fashion into the same discriminant function.

Results

Patterns of neuropsychological "deficits"

The proportion of HKD subjects with a neuropsychological "deficit" on each of the neuropsychological tasks for which significant differences between the HKD and Control groups were reported at baseline are shown in table 6.1. Measures of effect size (*d*) and η^2_p (partial eta squared; a measure of proportion of variance explained by a component, (Cohen 1988) and the p value for the univariate analysis of variance comparing HKD with Controls are also included.

Table 6.1: Cohen's effect size (*d*), varience explained (partial eta squared, η^2_p) and significance (p) of the baseline neuropsychological deficits of drug naïve boys with HKD vs. healthy Controls, and the proportion of boys with HKD with a neuropsychological "deficit" at baseline relative to healthy Controls

Task	Effect Size			Proportion of HKD cases with "deficit" (%)[1]
	d	η^2_p	p	
Spatial Span				
Span Score	0.52	0.065	<.005	11
Spatial Working Memory				
Between-search Errors	0.73	0.117	<.001	24
Strategy Score	0.58	0.078	<.001	15
Stockings of Cambridge				
Solved in Minimum Moves	0.25	0.013	>0.05	13
Pattern Recognition				
Percent Correct	0.65	0.094	<.001	30
Spatial Recognition				
Percent Correct	0.61	0.085	<.001	28
Delayed Matching to Sample				
Percent Correct (all delays)	0.84	0.149	<.001	39
Paired Associates Learning				
Tot Trials	0.46	0.050	<.01	19
Tot Errors	0.33	0.050	<.05	21
Intradimensional-Extrdimensional Shift				
Total Trials	0.26	0.000	>.05	11
Reaction Time				
5 choice reaction Time	0.12	0.005	>0.5	8

[1] "Deficit" is defined as having an age and BPVS adjusted z-score on a particular task that falls within the bottom 10% of healthy Controls

When neuropsychological performance was calculated in this way (z-score covaried for age and BPVS), there were no longer statistical differences between HKD and Control groups on three variables that had previously distinguished between the groups (Stockings of Cambridge solved in minimum moves, Intradimensional – Extradimensional Shift total trials and 5 Choice Reaction Time). For these three variables, the proportion of HKD subjects with a "deficit" was around the level of 10% and therefore at the rate, which would be expected in the normal population.

For the other variables, the Cohen's effect sizes (d) ranged between 0.33 and 0.84, the partial eta squared (η^2_p) indicated that each of these variables accounted for less than 15% of the overall variance (range 5 to 14.9%). The overall proportion of HKD subjects with any particular "deficit" between ranged between 8 and 39%. Delayed Matching to Sample was associated with the largest effect size and partial eta squared and had the largest proportion of cases with "deficit" (39%).

If this data is looked at from a different perspective it suggests that for each task, between 89% and 61% of boys in the HKD group were performing within the expected range for healthy boys of a similar age and BPVS scores.

An alternative way to look at this data is to examine the number of different tasks for which each individual has a "deficit". These data are summarised in table 6.2.

Table 6.2: Overlapping distributions of impairment based on the percentage of individuals in HKD and healthy Controls who at baseline were impaired on a particular number of neuropsychological tasks

Number of tasks on which subject has a "deficit"[1]	0	1	2	3	4	5	6	7	8
Hyperkinetic Disorder (%)	18.7	29.3	18.7	9.3	14.7	1.3	1.3	4	2.7
Control (%)	44.3	28.6	14.3	7.1	0.0	2.9	2.9	0.0	0.0

[1] "Deficit" is defined as having an age and BPVS adjusted z-score on a particular task that falls within the bottom 10% of healthy Controls for that task

A significant minority (18.7%) of the HKD group did not have a “deficit” on any of these tasks. Of those subjects with HKD who had at least one “deficit”, the majority (59.0 %) had deficits on only one or two of the tasks and only 11.4% had 5 or more “deficits”. The majority of the Control group (55.7%) also had at least one “deficit” and similar proportions of this group had 1 or 2 “deficits” as the HKD group.

The tasks were separated into so-called “executive” (Spatial Working Memory, Stockings of Cambridge, Intradimensional – Extradimensional Shift and Reaction Time)and “non-executive” (Spatial Span, Pattern and Spatial Recognition, Delayed Matching to Sample and Paired Associates Learning) task groups and the proportions who had a “deficit” on any of the tasks within each group were calculated (Table 6.3). Contrary to expectation, considerably more of the HKD subjects had ‘non-executive’ deficits than ‘executive’ deficits (66.7% vs. 41.3%, $F(1,143) = 13.7$, $p < .001$). Whilst overall more of the HKD group than the Control group showed executive “deficits”, this fails to reach statistical significance (41.3% vs. 34.3%, $F(1,143) < 1$) and the proportions of subjects with a “pure” executive “deficit” are very similar (HKD, 14.7% vs. Controls, 18.6%).

Table 6.3: Proportions of boys with HKD and healthy Controls with "executive[1] and non-executive[2] deficits"

	None	"Executive deficit"[1]	"Non-executive deficit"[2]	Both "Executive and non-executive "deficit"
Hyperkinetic Disorder	18.7	14.7	40.0	26.7
Control	44.3	18.6	21.4	15.7

[1] "Executive deficit" is defined as having an age and BPVS adjusted z-score on one or more of the tasks with high executive functioning demands (Spatial Working Memory, Stockings of Cambridge, Intradimensional – Extradimensional Shift and Reaction Time) that falls within the bottom 10% of healthy Controls for that task.

[1] "Non-executive deficit" is defined as having an age and BPVS adjusted z-score on one or more of the tasks with low executive functioning demands (Spatial Span, Pattern and Spatial Recognition, Delayed Matching to Sample and Paired Associates Learning) that falls within the bottom 10% of healthy Controls for that task.

Associations between tasks

It was intended to follow the methods described by Sonuga-Barke et al (Sonuga-Barke, Dalen, & Remington 2003) and to investigate whether neuropsychological measures independently predict HKD by conducting a discriminant analysis based on component scores from a principle components analysis. However, it was felt necessary to first investigate whether the associations between the tasks were similar or different in each of the two groups (HKD and Control) as both represent extremes of the normal population. Whilst the arguments for the HKD group being at the extreme end of the normal population are straight forward, those pertaining to the Control group are not as obvious but are equally important. The Control group for this study were selected after fairly intensive screening identified them as having no evidence for any psychopathology either at the time of enrolment into the study or at anytime previous to this. They are therefore "super healthy" with respect to psychopathology and at the other end of the continuum to the HKD group.

Two separate bivariate correlations were conducted on the age and BPVS adjusted z-scores for the 11 variables that had discriminated between the HKD and Control groups in the main baseline analysis. It was decided to include the measures from the Intradimensional-Extradimensional Shift, Stockings of Cambridge and 5 Choice Reaction Time, as even though these measures did not distinguish the two groups when the analyses were conducted using the z-scores, they had all previously been shown to distinguish between the groups in the original analyses using the raw data.

Table 6.4: Pearson correlations between baseline neuropsychological task performance on the various tasks – Healthy Control group

	ID/ED (Total Trials)	PAL (Total Trials)	PAL (Total Errors)	Pattern Recognition (% correct)	Spatial Recognition (% correct)	Spatial Span	5 choice Reaction Time	Spatial Working Memory (BSE)	Spatial Working Memory (Strategy Score)	Stockings of Cambridge (Solved in Minimum Moves)
PAL Total Trials	.282*									
PAL Total Errors	.231	.854**								
Pattern Recognition	-.180	-.415**	-.519**							
Spatial Recognition	.038	-.157	-.154	.336**						
Spatial Span	-.050	-.288*	-.283*	.266*	.423**					
5 choice Reaction Time	-.045	.324**	.078	.015	.008	-.008				
SWM BSE	.166	.074	.097	-.107	-.191	-.317*	-.036			
SWM Strategy Score	.095	.210	.237*	-.145	-.086	-.102	.029	.482**		
Stockings of Cambridge	.051	-.282*	-.314**	.311**	.256*	.216	-.144	-.116	-.108	
Delayed Matching to Sample	1.196	-.422**	-.469**	.292**	.263*	.318**	-.077	-.252*	-.222	.226

***Correlation is significant at the 0.05 level, ** Correlation is significant at the 0.05 level. (ID/ED. Intradimensional – Extradimensional Set-shifting; PAL, Paired Associates Learning; BSE, between-search errors, SWM, Spatial Working Memory)**

Table 6.5: Pearson correlations between baseline neuropsychological task performance on the various tasks – Drug naïve boys with hyperkinetic disorder

	ID/ED (Total Trials)	PAL (Total Trials)	PAL (Total Errors)	Pattern Recognition (% correct)	Spatial Recognition (% correct)	Spatial Span	5 choice Reaction Time	Spatial Working Memory (BSE)	Spatial Working Memory (Strategy Score)	Stockings of Cambridge (Solved in Minimum Moves)
PAL Total Trials	.232*									
PAL Total Errors	.197	.943**								
Pattern Recognition	-.232*	-.454**	-.385**							
Spatial Recognition	.038	-.232*	-.225	.283*						
Spatial Span	-.243*	-.297**	-.220	.253*	-.011					
5 choice Reaction Time	.267*	.175	.141	-.473**	-.058	-.303**				
SWM BSE	.210	.273*	.182	-.241*	-.175	-.246*	.170			
SWM Strategy Score	.026	.292*	.260*	-.130	-.204	-.221	-.085	.447**		
Stockings of Cambridge	-.158	-.089	-.038	.331**	.181	.234*	-.197	-.327**	-.321**	
Delayed Matching to Sample	.073	-.080	-.072	.352**	.119	.069	-.119	-.018	-.035	.052

***Correlation is significant at the 0.05 level, ** Correlation is significant at the 0.05 level. (ID/ED. Intradimensional – Extradimensional Set-shifting; PAL, Paired Associates Learning; BSE, between-search errors, SWM, Spatial Working Memory)**

The results of these analyses are described in tables 6.4 and 6.5.Whilst there were significant correlations in both samples, most of these were only moderate in strength.

There were several similarities between the samples;

- As predicted, the two Paired Associates Learning measures and the two Spatial Working Memory scores were strongly correlated with each other in both samples.
- The two Paired Associates Learning measures and the Spatial Working Memory - Between-search Errors were also significantly correlated with Pattern Recognition, and the Spatial Working Memory -Between-search Errors was significantly correlated with Paired Associates Learning (Total Trials) in both samples
- Pattern Recognition, Spatial Working Memory - Between-search Errors and Paired Associates Learning – Total Trials were significantly correlated with Spatial Span in both samples.
- Pattern Recognition was also significantly correlated with Delayed matching to Sample and Stockings of Cambridge in both.
- There were also a range of variables in both samples, which uncorrelated with each other

However, whilst there were these similarities between the two analyses there were also several differences.

- Intradimensional – Extradimensional Set-shifting was significantly correlated with Pattern Recognition, Spatial Span and 5 Choice Reaction Time in the HKD group but not the Control group.

- Paired Associates Learning (Total Trials) was significantly correlated with 5 Choice Reaction Time, Stockings of Cambridge and Delayed Matching to Sample in the Control group but not the HKD group.

- Paired Associates Learning (Total Errors) was significantly correlated with Spatial Span, Stockings of Cambridge and Delayed Matching to Sample in the Control group but not the HKD group.

- Delayed Matching to Sample was significantly correlated with Spatial Recognition, Spatial Span and Spatial Working Memory - Between-search Errors in the Control group but not the HKD group.

- Spatial Recognition was significantly correlated with Spatial Span and Stockings of Cambridge in the Control group but not the HKD group.

- Paired Associates Learning (Total Trials) was significantly correlated with Spatial Recognition, Spatial Working Memory - Between-search Errors and Strategy Score in the HKD group but not the Control group.

- Stockings of Cambridge was significantly correlated with Spatial Span and Spatial Working Memory - Between-search Errors and Strategy Score in the HKD group but not the Control group.

- Spatial Span and 5 Choice were significantly correlated with each other in the HKD group but not the Control group.

In view of these apparent differences in association, the component structures of the two groups were explored using principal components analyses (PCA). Separate analyses were conducted for each group (tables 6.6 and 6.7). In addition to further describing the relationships between the neuropsychological measures, the PCA reduces measurement

error, which is inherent in the individual measures and which may constrain their predictive power. By deriving several latent traits, each of which represents the shared variance among the constituent tasks, PCA eliminates error variance that is specific to each task and thus provides a more reliable measure of the underlying construct of interest. This method is also useful in investigating heterogeneity as by using the Anderson-Rubin method of producing components, it is possible to ensure that the resulting components are uncorrelated with each other and therefore that each measures a distinct aspect of functioning unrelated to those measured by the other components (Field 2005).

Table 6.6: Principle Components Analysis of baseline neuropsychological performance data: Healthy Control Group

	Component			
	1	2	3	4
Total Variance Explained (%)	30.7	13.2	11.4	10.2
Paired Associates Learning Total Errors	.872			
Paired Associates Learning Total Trials	.856			
ID/ED Shift Total Trials	.604			
Pattern Recognition, Percent Correct	-.547			
Delayed Matching to Sample, Total Percent Correct	-.500			
Spatial Working Memory Between-search Errors		-.858		
Spatial Working Memory Strategy Score		-.836		
Spatial Recognition, Percent correct			.790	
Spatial Span			.674	
Stockings of Cambridge Solved in Minimum Moves			.527	
5-Choice Reaction Time				.861

Extraction Method: Principal Component Analysis. Rotation Method: Oblimin with Kaiser Normalization. Rotation converged in 12 iterations.
(ID/ED, Intradimensional-Extradimensional Set-shifting)

Table 6.7: Principle Components Analysis of baseline neuropsychological performance data: Drug naïve boys with hyperkinetic disorder

	Component			
	1	2	3	4
Total Variance Explained (%)	29.6	12.9	12.6	11.4
Paired Associates Learning Total Errors	.972			
Paired Associates Learning Total Trials	.943			
5-Choice Reaction Time		-.737		
ID/ED Shift Total Trials		-.675		
Spatial Span		.533		
Spatial Working Memory Strategy Score			-.794	
Spatial Working Memory Between-search Errors			-.732	
Stockings of Cambridge Solved in Minimum Moves			.701	
Delayed Matching to Sample, Total Percent Correct				.780
Pattern Recognition, Percent Correct				.619
Spatial Recognition, Percent correct				.476

Extraction Method: Principal Component Analysis. Rotation Method: Oblimin with Kaiser Normalization. Rotation converged in 20 iterations.
(ID/ED, Intradimensional-Extradimensional Set-shifting)

Both of the PCAs generated 4 components. Whilst these components were, in the main interpretable, their structures were different for the two groups, suggesting that these neuropsychological tasks are indeed associated (and possibly mediated) in different ways in the two groups.

For the Control group the four components comprised;

- Component 1: “Recognition Memory and Set-shifting ”, which included; Both Paired Associates Learning measures, Intradimensional-Extradimensional Set-shifting, Pattern Recognition and Delayed Matching to Sample.
- Component 2: “Spatial Working Memory”, which included; Both Spatial Working Memory Measures.
- Component 3: “Spatial memory and Planning”, which included; Spatial Recognition, Spatial Span and Stockings of Cambridge
- Component 4: “Reaction time”, which included, 5 Choice Reaction Time

For the HKD group the four components comprised;

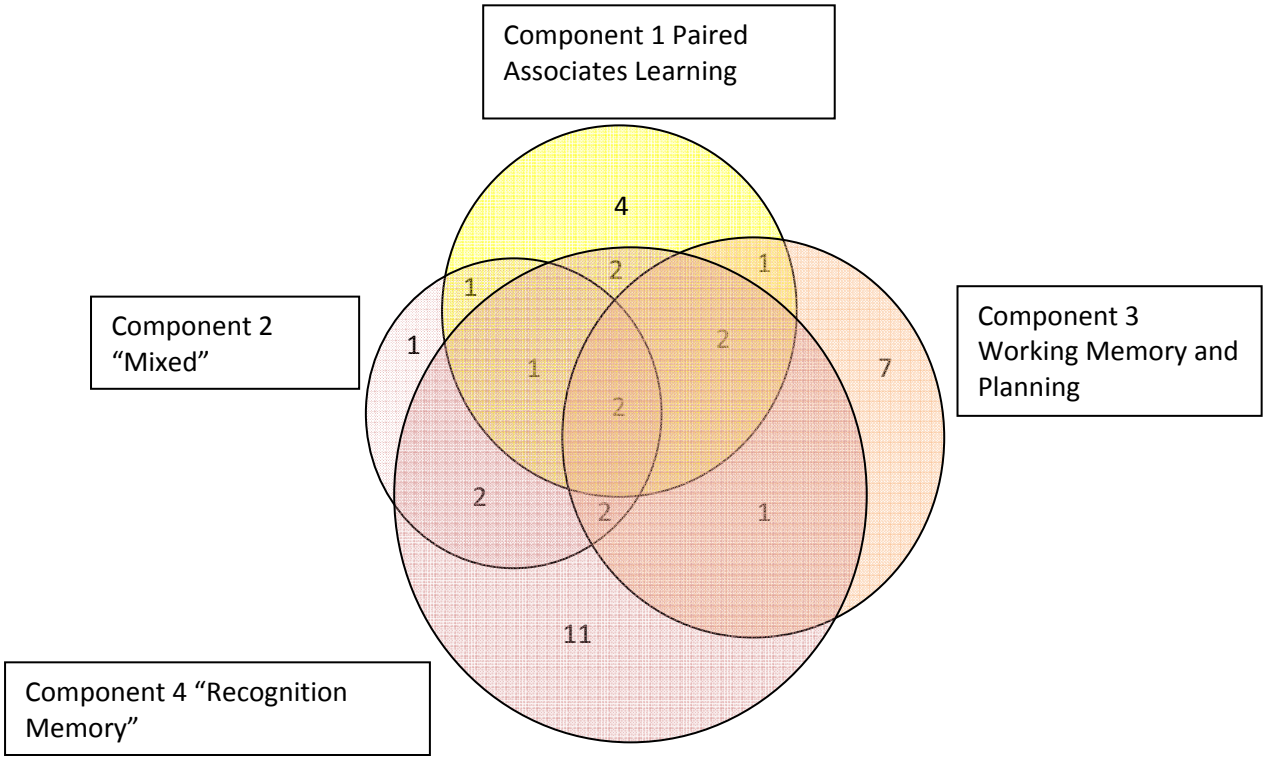
- Component 1: “Paired Associates Learning”, which included both Paired Associates Learning measures
- Component 2: A “Mixed” component, which was difficult to interpret in a meaningful way and which included; 5 Choice Reaction Time, Intradimensional-Extradimensional Set-shifting and Spatial Span
- Component 3: “Working Memory and Planning”, which included; Both Spatial Working Memory Measures and Stockings of Cambridge

- Component 4: “Recognition Memory”, which included; Delayed Matching to Sample, Pattern Recognition and Spatial Recognition

Interestingly, the component structure for the HKD group resembles the theoretical structure of the CANTAB battery more closely than that of the Control group. Specifically, the “executive” and “non-executive tasks were more clearly separated in the HKD group than they were in the Control group. In view of the differences in structure between the Control group and the HKD group, it was decided not to conduct a Principal Components Analysis of the combined groups. Unfortunately this meant that it was not possible to investigate whether the components were able to distinguish between the two groups.

It was, however, possible to calculate z-scores for each component for the HKD group. These were based on the mean z-scores for the HKD boys on the individual tasks and component loadings in table 6.7. These give an estimate of effect size for each component; Component 1, “Paired Associates Learning” = .42; Component 2, “Mixed” = .15; Component 3 “Spatial Working Memory and Planning” = .36; Component 4, “Recognition Memory” = .49. Using the component weighted z-scores for each individual it was also possible to calculate the number of HKD boys with “deficits” on each of the components were estimated (Figure 6.1). Deficit was again defined as having a component weighted z-score on one or more of the factors, which falls within the bottom 10% of healthy Controls for that task. Thirteen HKD boys (17.3%) had a “deficit” on the “Paired Associates Learning” component (Component 1), 9 (12%) had a “deficit” on the “Mixed” component (Component 2), 15 (20%) on the “Working Memory and Planning” component (Component 3) and 24 (32%) on the “Recognition Memory” component (Component 4). Around half of the HKD subjects, 39 (50.7%), have no “deficit” by this definition, 23 (30.7%) have a “deficit” on one component, 7 (9.3%) have a “deficit” on two components, 5 (6.7%) have a “deficit” on three and 2 (2.7%) have a “deficit” on all four components (Figure 6.1).

Figure 6.1: Distribution of and overlap between "deficits"[1] in the drug naïve boys with hyperkinetic disorder on each of the four components identified by the principle components analysis. Numbers represent the number of subjects with "deficit" on each component or overlapping components. Only those subjects with at least one deficit (n = 37) are included (39 HKD subjects have no deficit by this method and are therefore not included here).



[1] "Deficit" is defined as having a component weighted z-score on one or more of the components that falls within the bottom 10% of healthy controls for that task

Discriminant abilities of neuropsychological tasks

As it was not possible to conduct a discriminant function analysis based on the results of a PCA, this analysis was instead conducted using the age and BPVS corrected z-scores for those variables that had discriminated between HKD and Controls (see table 6.1). Separate analyses were conducted for each of these variables in order to determine the percentage of subjects correctly assigned to the HKD group (sensitivity), the percentage correctly assigned to the Control group (specificity) and the overall percentage correctly allocated (Table 6.8).

These analyses suggest that the neuropsychological measures are, at best, moderate discriminators between HKD boys and Controls. For the Intradimensional – Extradimensional Shift, Stockings of Cambridge, Paired Associates Learning and 5 choice reaction time discrimination is no better than chance. The findings for the 5-choice reaction time are, however, particularly striking. This task had a very high specificity of 95.7% but a very low sensitivity at only 8%. Thus if you had a "deficit" on 5-choice reaction time you were very likely to have HKD, but if you did not, it was not a good indicator that you did not have HKD as most of those with HKD did not have a "deficit" on this task. The other measures performed slightly better, with sensitivity ranging between 58.7% and 66.7%, specificity between 54.3% and 72.9% and overall correct classification between 57.9% and 66.2%.

In order to assess whether discrimination is increased by using more than one measure, the better predictors (Spatial Span, Spatial Working Memory BSE and Strategy, Pattern Recognition, Spatial Recognition and Delayed Matching to Sample) were entered into the analysis together. This improved the sensitivity to 70.7 %, the specificity to 72.9% and the overall correct classification to 71.7%. These same predictors were all also entered in separate analysis in a stepwise fashion. Only Delayed Matching to Sample and Spatial

Working Memory-Between-search Errors were retained in the analysis. The specificity for this analysis (sensitivity, 66.7%; specificity, 68.6%; and overall correct classification 67.6%) was greater than those of the individual measures but not quite as large as that for all eight variables entered together.

Table 6.8: Abilities of neuropsychological measures to discriminate between the drug naïve boys with HKD and the healthy Controls at baseline

Task	Sensitivity (%)	Specificity (%)	Overall Correct (%)
Intradimensional – Extradimensional Shift	40.0	58.6	49.0
Spatial Span	62.7	62.9	62.8
Spatial Working Memory BSE	61.3	54.3	57.9
Spatial Working Memory Strategy	66.7	57.1	62.1
Stockings of Cambridge	57.3	48.6	53.1
Pattern Recognition	58.7	71.4	64.8
Spatial Recognition	61.3	71.4	66.2
Delayed Matching to Sample	58.7	70.0	64.1
Paired Associates Learning Total Trials	45.3	72.9	58.6
Paired Associates Learning Total Errors	44.0	62.9	53.1
5 Choice Reaction Time	8.0	95.7	50.3
Spatial Span+ Spatial Working Memory BSE + Spatial Working Memory Strategy + Pattern Recognition + Spatial Recognition + Delayed Matching to Sample (entered together)	70.7	72.9	71.7
Delayed Matching to Sample + Spatial Working Memory BSE (stepwise)	66.7	68.6	67.6

Discussion

Neuropsychological heterogeneity in HKD.

These data do not support a single cause model for hyperkinetic disorder (HKD). The hypothesis that drug naïve boys with hyperkinetic disorder would demonstrate a lesser degree of neuropsychological heterogeneity than has been previously found with ADHD samples (Nigg, Willcutt, Doyle, & Sonuga-Barke 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington 2005) was also not supported. Rather, these data suggest that, from a neuropsychological perspective at least, the heterogeneity in HKD is very similar to that described for ADHD. Overall measures of effect size and the partial eta squared measure of overall variance were both in the small to moderate range, indicating a moderately high level of overlap in neuropsychological performance between the HKD and Control groups. None of the effect sizes for the individual neuropsychological measures (0.12 – 0.84) could account for the effect sizes associated with the baseline scores on the Conners' questionnaires, which were 3.3 – 6.7 for parent ratings and 1 – 2.1 for teacher ratings. This would suggest that none of these "deficits" on their own are anywhere near 'sufficient' to cause a clinical presentation of HKD.

Even with the fairly liberal cut-off of 10%, which was used to define "deficit", there were a significant minority of HKD boys for whom there was no evidence, using a fairly broad battery of tasks, for any neuropsychological "deficit". This, of course, does not mean that these boys did not have any neuropsychological difficulties. There are several aspects of neuropsychological functioning that have been implicated in AD-HKD, which were not tested by this battery of tasks (for example delay aversion and other motivational problems and timing problems). These data do, however, indicate that having a "deficit" on any of the included tasks it not a prerequisite for HKD i.e. a "deficit" on these tasks is not necessary for a diagnosis of HKD. The spread of "deficits" across subjects suggests that

most subjects with at least one “deficit” had “deficits” in no more than two tasks and very few subjects had problems on 5 or more tasks. This means that many of the HKD boys scored within the normal range on many of the tasks.

The pattern of findings reported here is very similar to that reported by Nigg et al. (Nigg, Willcutt, Doyle, & Sonuga-Barke 2005), with respect the proportion with no “deficit” and the effect sizes, partial eta squared, and spread of “deficits” across the sample (Table 6.9). This would be a very positive finding if the analyses were based on a similar sample and similar battery of tasks but is, perhaps, even more so when one considers that the samples reported on by Nigg and colleagues were diagnosed to DSM criteria and were a mixture of community and clinic samples, many of whom had previously been medicated (Nigg, personal communication). The sample reported on here was designed to be as homogeneous as possible, they had all been referred to clinical services, were all diagnosed using the more restrictive ICD 10 HKD criteria (which tends to identify those with the most severe AD-HKD), were all male and were all drug naïve.

Table 6.9; Comparison between current sample and the samples described in Nigg et al (2005)

Number of tasks on which subject has a "deficit"	0	1	2	3	4	≥5
Current Sample HKD (%)	18.7	29.3	18.7	9.3	14.7	7.3
Nigg et al (2005) ADHD (%)	21	26	22	13	8	10

That performance deficits on these neuropsychological tasks are neither necessary, nor sufficient, to cause AD-HKD does not mean they are not important. As with the samples reported on by Nigg et al (Nigg, Willcutt, Doyle, & Sonuga-Barke 2005), it appears that each individual neuropsychological "deficit" is being carried by only a small proportion of the cases i.e. despite robust differences between groups, relatively few subjects had a "deficit" on any one particular measure, and any one measure only accounts for a relatively small portion of the overall variance. This may be particularly so for those tasks that separated the HKD and Control groups but for which the proportion of HKD boys with a "deficit" was at the level of chance (around 10%). It would be easy to dismiss performance on these tasks as irrelevant to the HKD presentation as so few of the HKD boys had a "deficit". However those that did clearly had enough of a difficulty to account for the separation between the groups. The potential importance of these tasks can be demonstrated in different ways for different tasks. For Spatial Span the effect size was moderate at 0.52 even though only 11% of HKD boys had scores in the bottom 10% of Controls. On the other hand, the 5-choice reaction time, on which only 8% of HKD boys had a "deficit" and for which the sensitivity was only 8%, had a very high degree of specificity for HKD at 95.7%.

Between task associations for HKD and Control boys

The hypothesis that HKD would be more strongly associated with executive rather than non-executive deficits in neuropsychological functioning was not supported. Indeed the reverse was true. This finding that non-executive "deficits" were more common than executive "deficits" was unexpected at the outset of the study and has not previously been reported. These data do, however, fit with those reported in Chapter 5 where it was found that the largest effect sizes at baseline were for three low executive recognition memory tasks (Pattern and Spatial Recognition and Delayed Matching to Sample). Whilst these data do not indicate that executive deficits are unimportant, they do suggest that they need to

be considered within the context of underlying non-executive processes. It is, for example, possible that the "deficits" demonstrated on working memory tasks are a consequence of underlying non-executive memory problems and do not reflect an actual deficit in central executive processes. It is not possible to be certain about this from the results of the CANTAB Spatial Working Memory task as it does not allow one to fractionate the central executive aspects of performance from those aspects that may reflect difficulties with the visuospatial sketchpad (Baddeley 1992). It was, however, possible to investigate this issue indirectly by looking at the associations between tasks.

The hypothesis that there will therefore be different patterns of between task association for HKD and Control boys was supported although this was probably for different reasons than had been anticipated. Prior to the study it was predicted that the different inter-relationships between neuropsychological measures in the two groups would be driven by the executive tasks, whereas it was the non-executive memory tasks, and in particular Delayed Matching to Sample, that were most important.

Whilst there were some similarities between the Control and HKD groups with respect to the interrelationships between the different neuropsychological measures, there were also differences. These differences were seen in both the simple correlations and in the PCA and were particularly noticeable in the relationship between the Delayed Matching to Sample task and the other variables. This is of particular interest as Delayed Matching to Sample was the measure that was consistently associated with the strongest effects across all of the analyses. These differences between HKD boys and Controls have not been described before and have not been taken into account in previous factorial and principal components analyses of ADHD samples (e.g. (Sonuga-Barke, Dalen, & Remington 2003; Willcutt, Doyle, Nigg, Faraone, & Pennington 2005). By combining the two samples into one analysis, these groups may have derived factors or components, which whilst valid for the

whole group, did not actually reflect the true factorial structures within the two subsamples (cases and controls). This would complicate the interpretation of the results of all subsequent analyses, which used these component scores as variables.

The results of the separate PCAs are, however, of interest. For the HKD boys the 4 components with eigenvalues greater than 1 were consistent with the presumed structure of the CANTAB and had several similarities to the structure reported for a similar analysis of the CANTAB battery tasks conducted by Robbins et al. (1998) in a group of healthy adults aged 21 – 79 years. Two separate components were identified that were exclusively non-executive in nature ("Paired Associate Learning" and "Recognition Memory"), both of which were theoretically sound in that they included measures that would be expected to sit together, and one executive component that had a similarly predictable structure (Working Memory and Planning") as well as one "mixed" component that was less predictable and easy to reconcile. This suggests that, in general, the executive and non-executive contributions to HKD are relatively independent of each other, strongly supporting the presence of a neuropsychological heterogeneity, and that these different types of neuropsychological deficits may contribute to separate pathways.

It was interesting that the PCA for the Control boys reflected the presumed structure of the CANTAB battery less well than that for the HKD group and was very different to that reported for a similar analysis of the CANTAB battery tasks conducted by Robbins et al. (1998) in a group of healthy adults aged 21 – 79 years. The reasons for this are unclear. One possibility is that it is a consequence of the relative developmental immaturity of the sample. The neuropsychological functions being tested may relate differently to each other in children and adolescents than they do in adulthood. Alternatively, the tasks may be tapping into different aspects of neuropsychological functioning at different developmental stages. This could arise, for example, if a particular skill was not well developed at the time

of testing and the child may need to utilize a different strategy to complete the task than is traditionally used in the adult. A major weakness in this argument is that whilst the HKD group would be expected to be even further behind developmentally than the Control boys, the component structure of their neuropsychological functioning was more similar to the theoretical CANTAB structure, and indeed, the actual structure described in an adult sample by Robbins et al (1998), than that of the Control boys. The issue of development is the focus of Chapter 7. Clearly the component structure of the CANTAB battery and the impact of disorder and development on this structure warrant further investigation.

One of the most important benefits of the principal components analysis methodology is its potential to reduce measurement error and increase the predictive power of the neuropsychological measures. It was, therefore, somewhat surprising that the mean z-scores for the resultant components from the PCA reported here were lower rather than higher than those for the component neuropsychological measures. Similarly, it was disappointing that the component scores identified fewer subjects as having a "deficit" than did the scores for the separate tasks. This is in direct contrast to the findings reported by Willcutt et al (2005) who found that the effect size for their response inhibition/excitation factor score (d = 1.19) was substantially higher than that for any of the individual measures that loaded on this factor (d = 0.5 – 0.89). The reason for this finding is unclear.

Using neuropsychological deficits to discriminate between HKD and Controls.

Another potential benefit of the PCA is that the derived components are uncorrelated and therefore independent of each other. This means that, if the component scores are able to discriminate between groups (e.g. cases and Controls, responders and non-responders), they are doing so independently, which would be indicative of a heterogeneity within the

sample. Unfortunately, as it was not possible to justify conducting a PCA on the whole sample due to the differing patterns of association in the two groups, it was not possible to conduct a discriminant analysis on the components. It was, however, possible to use them as predictors of medication response (described in Chapter 9).

The results of the discriminant analysis using the z-scores of the tasks supported the hypothesis that both executive and non-executive neuropsychological deficits make independent contributions to HKD. The overall ability of the CANTAB tasks to discriminate between the groups was only moderate. There was some improvement in both sensitivity and specificity when multiple measures were entered together. The hypothesis that executive tasks would discriminate HKD and Controls more effectively than the non-executive tasks was not supported. When the tasks were entered separately it was the non-executive memory tasks (Spatial Recognition, Pattern Recognition, Delayed Matching to Sample and Spatial Span) along with the executive Spatial Working Memory task that discriminated most effectively. When tasks were entered into a multivariate analysis in a stepwise manner, the two tasks that were retained in the best fit model were the Between-search Errors measure of the executive Spatial Working Memory task and the Percent Correct across all Delay Conditions measure of the non-executive Delayed Matching to Sample task. The finding that both of these measures made significant but independent contributions to the discrimination between HKD boys and Controls provides further support for heterogeneity and for a hypothesis that executive and non-executive tasks may make independent contributions to the development of AD-HKD. This is similar to the argument made by Solanto et al. (2001) and subsequently by Sonuga-Barke (2003) in his dual pathway model of AD-HKD. They demonstrated that response inhibition and delay aversion separately contributed to the discrimination between children with and without ADHD. Taking these findings together with those of the current Chapter raises the

possibility of a “quadruple” pathway including response inhibition, delay aversion, non-executive memory and working memory. This is clearly a very speculative proposal but does highlight the need for more “head to head” studies comparing different theoretical approaches, rather than reliance on indirect evidence and comparisons.

In a similar vein, these data also suggest that our conceptualisation of ADHD as a disorder of frontal lobe functioning may need to be reconsidered. Although it is not possible to simply map deficits in neuropsychological performance on to specific neuroanatomical and pathophysiological processes, there is a considerable body of evidence available, which describes various structural and functional correlates of many of the CANTAB tasks (e.g. Baker, Rogers, Owen, Frith, Dolan, Frackowiak, & Robbins 1996; Mehta, Owen, Sahakian, Mavaddat, Pickard, & Robbins 2000; Morris, Ahmed, Syed, & Toone 1993; Owen, Sahakian, Semple, Polkey, & Robbins 1995; Owen et al. 1996b; Owen, Doyon, Petrides, & Evans 1996a; Robbins, James, Owen, Sahakian, Lawrence, McInnes, & Rabbitt 1998; Rogers, Andrews, Grasby, Brooks, & Robbins 2000). Whilst many of these tasks are dependent on intact frontal lobe functioning, performance on two of the tasks most strongly associated with HKD in this sample, Delayed Matching to Sample and Pattern Recognition, were not impaired in subjects who had undergone a frontal lobe resection but were in those with either temporal lobe or amygdale/hippocampal damage (Owen, Sahakian, Semple, Polkey, & Robbins 1995). As the deficits on these tasks were independent of those on other tasks it suggests that, at least in a proportion of cases, HKD is associated with sub-optimal functioning of the temporal lobe and/or the amygdale/hippocampus.

Summary and Conclusions

The data presented here suggests that drug naïve boys with HKD are heterogeneous with respect their neuropsychological functioning and that the pattern of neuropsychological heterogeneity in this sample is similar to that previously demonstrated in children with

DSM IV defined ADHD. It also strengthens the argument that deficits in both non-executive and executive memory function play an important role in HKD, that these may be independent of each other and that the importance of non-executive deficits has been underestimated past accounts of the pathogenesis of AD-HKD. This data also warns against the assumption that the inter-relationships between different aspects of neuropsychological functioning are the same in those with and without AD-HKD. In Chapter 7, I will investigate whether the neuropsychological heterogeneity identified and described in this Chapter is a consequence of developmental changes. In Chapter 8, I will investigate whether this heterogeneity is associated with patterns of comorbidity with oppositional defiant disorder or conduct disorder.

Chapter 7

Development of Neuropsychological Functioning In Hyperkinetic Disorder

Background

In recent years there has been increasing interest and focus on developmental aspects of neuropsychological functioning and on the parallels between the functional emergence of neuropsychological capabilities and structural maturation of the brain. Both have been demonstrated to be in an immature state in the young child and to have a protracted period of development through adolescence and into adulthood (De Luca & Leventer 2008). Whilst considerable effort has been made to understand the differences in brain development between those with and without AD-HKD, little is known about the development of neuropsychological functioning in AD-HKD.

Normally developing children

Normal Brain Development in Childhood and Adolescence

Recent longitudinal studies have highlighted the continuing development of the brain throughout childhood and adolescence and into adulthood. In particular, the ongoing National Institute of Mental Health study of human brain development (Giedd 2004; Gogtay et al. 2004; Gogtay, Giedd, & Rapoport 2002), has clearly described many of the changes that occur in normal brain development during the second decade of life and has demonstrated that the brain of an early adolescent differs measurably in anatomy, biochemistry, and physiology when compared with that of a late adolescent. This, and other studies such as the National Institute of Health funded Magnetic Resonance Imaging (MRI) study of normal brain development (Almli, Rivkin, & McKinstry 2007; Evans 2006;

Waber et al. 2007) and studies utilizing PET scanning techniques (Chugani, Phelps, & Mazziotta 1987), functional MRI and diffusion tensor imaging (Olesen et al. 2003) and electroencephalography (Segalowitz & Davies 2004) have demonstrated that, in addition to the well recognised periods of rapid growth, which take place in utero, between birth and three years and between 10 and 13 years and which result in significant increases in the number of neurons and synapses giving the brain enormous potential , there are also periods of neuronal pruning through which the brain refines and organises its neural pathways. This pruning occurs at different times and progresses at different rates across the various brain regions. It seems to proceed on a "use-it-or-lose-it" basis, which is associated with learning and whereby only the most efficient and "strong" of the synapses are retained. This pruning process is also associated with myelination and whilst the majority of pathways in the human brain have completed myelination by the end of the second year of life, the prefrontal cortex, and in particular the dorsolateral regions, continue to myelinate into the third decade (Klingberg et al. 1999). The NIMH group have demonstrated that the higher-order and phylogenetically older association cortices mature only after the lower-order somatosensory and visual cortices (Gogtay, Giedd, Lusk, Hayashi, Greenstein, Vaituzis, Nugent, III, Herman, Clasen, Toga, Rapoport, & Thompson 2004). Whilst the prefrontal cortex, widely regarded as the seat of the executive functions, was one of the latest regions to develop, it was the superior temporal cortex, which contains association areas that integrate information from several sensory modalities that was shown to matured last of all regions.

Development of neuropsychological functioning in healthy children and adolescents

Studies of neuropsychological development have demonstrated a general pattern by which the more basic non-executive skills, such as recognition memory, tend to develop earlier than the more complex executive functions such as working memory and planning, which

do not fully mature until well into the third decade of life (De Luca et al. 2003; Luciana et al. 2005; Luciana & Nelson 1998; Luciana & Nelson 2002)

These findings are important in contextualizing our understanding of normal adolescent development;

- Impulse control, planning, and decision making, aspects of functioning, which are all largely dependent on the prefrontal cortex, are still maturing during adolescence.

- Whilst adults tend to respond to stimuli in an “intellectual” manner, a teenager’s response is often more "from the gut“. Thus, whilst the changeability/plasticity of the adolescent brain may be well suited to meet many of the demands of teen life, support and guidance from adults is essential while this decision-making circuitry is being formed.

- The ability for the brain to plan, to adapt to the social environment, and to imagine the possible future consequences of an action or to appropriately gauge its emotional significance, is still developing throughout adolescence.

- The brain circuitry that enhances a teen’s ability to connect their “gut feelings” with an ability to help retrieve memories in order that situations can be placed in context, and that permits them to remember salient details about a past situation, is also undergoing a major construction during adolescence.

From the opposite perspective, it was for many years assumed that the executive functions were adult capacities that did not appear until puberty. This was in line with, and in part a consequence of, Piaget’s “stage” model transformation from concrete to formal operational thinking (Travis 1998). More recently it has been realised that the failure to

demonstrate executive functioning in pre-adolescents was largely due to the use of age inappropriate tasks (Anderson 1998). When age appropriate tasks are used, executive skills can be detected early in childhood (Anderson, Jacobs, & Anderson 2008; Anderson et al. 2001; Hughes 1998; Hughes, Dunn, & White 1998). For example, the first signs of working memory and inhibitory control arise around 7 months at which age infants can correctly retrieve objects on a delayed response task when the delay is limited to 1 – 2 seconds (Diamond 1985). By 12 months, a delay of 10 seconds was necessary to elicit perseverative errors. Further gains in performance are seen between 3 and 4 years and by 5 years of age a normally developing child can be expected to manage delays of up to 30 seconds without making an error (Espy et al. 1999; Espy, Kaufmann, & Glisky 2001). Working memory continues to develop through childhood and adolescence and begins to take on an adult form in late adolescence or early adulthood (Luna et al. 2004).

Using the CANTAB test battery, Luciana and Nelson (1998) found a general age-related progression from 4 to 8 years in ability levels on executive functioning tests. Specifically, they reported improvements on the Spatial Working Memory Between-search Error score and strategy formation, the Intradimensional-Extradimensional Set-shifting Task and the Stocking of Cambridge planning task. Young children (4-8 years) showed most difficulties when task performance required them to integrate behaviours, suggesting that EF abilities had not fully developed. There was, however, an interaction between age and difficulty with degree of improvement being dependent on task difficulty. By the age of 7 years the children had reached adult levels of performance on the simpler 2 and 4 box searches on the Spatial Working Memory task, but compared with a small group of teens, there were further improvements from 8 years to adolescence, which were at least as great as the improvements between 4 and 8 years on the more difficult stages of this task. In a later study, performance on the Spatial Working Memory task was found to improve across the

age range from 9 to 20 years, with strategy use reaching maturity between 16 and 17 years of age (Luciana, Conklin, Hooper, & Yarger 2005). Similar findings were also reported for the Stockings of Cambridge tasks. De Luca et al. (2003) confirmed many of these findings in their study of 194 participants aged between 8 to 64 years of age. They reported peak performance on the Spatial Working Memory task between 20 – 29 years of age and on the Stockings of Cambridge between 15 – 19 years of age.

In contrast to their performance on these tasks, performance on the Intradimensional/ Extradimensional Set-shifting task and the non-executive recognition memory tasks such as Pattern and Spatial Recognition developed much earlier with children typically reaching adult performance levels by the age of 7 or 8 years (De Luca, Wood, Anderson, Buchanan, Proffitt, Mahony, & Pantelis 2003; Luciana, Conklin, Hooper, & Yarger 2005; Luciana & Nelson 1998).

Combining structure and function

Unfortunately, whilst there are many studies linking various neuropsychological processes with potential neuroanatomical substrates, few of these have used a developmentally sensitive design. This is particularly relevant as it has been hypothesised that brain structure and function may be more fluid in children than in adults and that this may diminish the role of the prefrontal cortex as the primary anatomical substrate of executive functioning in children. Several authors have postulated that the accurate and effective performance of executive tasks is, in fact, dependent on the integrity of the whole brain (Anderson et al. 2005; Grady, McIntosh, & Craik 2005; Jacobs & Anderson 2002).

Whilst describing the developmental relationships between structure and function is one of the main aims of the ongoing National Institute of Health funded Magnetic Resonance Imaging (MRI) study of normal brain development (Evans 2006), to date only the

neuropsychological data has been made available (Waber, De Moor, Forbes, Almli, Botteron, Leonard, Milovan, Paus, & Rumsey 2007).

Schweinsburg et al. (2005) conducted an elegant study examining the relationship between fMRI findings and task performance during the CANTAB Spatial Working Memory task across early adolescence (12 – 14 years). Interestingly, whilst no age differences were found for task performance, age was *positively* associated with Spatial Working Memory brain response in the left prefrontal and bilateral inferior posterior parietal regions and *negatively* associated with Spatial Working Memory activation in bilateral superior parietal cortex. These findings support the notion that the frontal and parietal neural networks involved in spatial working memory are changing over the course of adolescence. Whilst the relevance of these changes remains unclear, they may represent evolving mnemonic strategies subserved by ongoing adolescent brain development.

Killgore, Oki & Yurgelun-Todd (2001) also found evidence to support a switch in the pathways utilised in a task designed to assess emotional functions. Children were demonstrated to be using the more 'primitive' amygdale-based circuits whilst adults utilised more frontal-related circuitry.

Children with AD-HKD

Brain development in children and adolescents with AD-HKD

Neuroimaging studies have consistently found differences in brain structure (and more recently brain development) between those with and without AD-HKD. Studies with a developmentally sensitive design have yielded particularly interesting findings. Castellanos et al (2002a) described the developmental trajectories of several brain regions that distinguished between ADHD and Control children at some point in development. They found that for total brain volume, frontal and temporal grey matter and cerebellum these

differences between the ADHD and Control groups remained stable over time. For the caudate nucleus, however, the differences, which were significant for the younger children, diminished and eventually disappeared in adolescence and early adulthood. This may relate to the reduction in overt hyperactivity symptoms in adolescence, which is often described clinically. However, the interpretation may be more complex than originally thought. Whilst it is true that adolescents with AD-HKD are less obviously hyperactive than their peers, they very often remain fidgety and report significant inner restlessness.

Recent work by the same group has described the developmental progression in brain architecture over time in more detail (Shaw, Eckstrand, Sharp, Blumenthal, Lerch, Greenstein, Clasen, Evans, Giedd, & Rapoport 2007). They used computational techniques to estimate cortical thickness at >40,000 cerebral points from 824 magnetic resonance scans of 223 children with ADHD and 223 typically developing controls. They calculated the mean growth trajectory of each cortical point, and found an overall phase of increased cortical thickening in childhood, which is followed by a decrease in thickness in adolescence. Using the age at which peak cortical thickness was attained as an index of cortical maturation they found that the brains of both groups matured in a similar manner regionally. However, there was a marked delay, of around 3 years, in the ADHD group attaining peak thickness. This delay was most prominent in prefrontal regions.

Development of neuropsychological functioning in children and adolescents with AD-HKD

There are currently no published descriptions of neuropsychological development in AD-HKD. Brophy, Taylor and Hughes (2002) did, however, conduct a 3 year follow up of 40 children who had initially been identified as being “hard to manage” at the age of 4 years and who had, at this first assessment, been identified as having marked deficits in inhibitory control and planning but no deficits in either set-shifting or working memory

(Hughes, Dunn, & White 1998). At follow-up interviews when the children were aged 6 years, around two thirds (64%) of the children in the "hard to manage" group were reported to have "clinically significant levels of either hyperactivity or conduct disorder", suggesting that between age 4 and 7 years around one third had made significant behavioural improvements. Compared with a healthy control group, the "hard to manage" children continued to demonstrate deficits in inhibitory control but had intact planning, working memory and set-shifting. This study supports the notion that some children with disruptive behaviours will grow out of these problems over time and that for some aspects of neuropsychological functioning at least some children with early onset behaviour problems will catch up with healthy children. Although these findings are important, the fact that the study focused on a group of children with a broader definition of difficulty means that extra caution is required when considering whether the findings will generalise to the whole AD-HKD population. It is not yet possible to describe with any certainty how the neuropsychological performance of children with AD-HKD changes over time and whether it matures at the same rate in as it does in healthy children.

This is an important question with respect to the investigation of heterogeneity in AD-HKD. It is possible that the heterogeneity seen within samples simply reflects the fact that different neuropsychological deficits appear and disappear at different stages in development and therefore what appears to be neuropsychological heterogeneity is simply a function of the developmental differences between children within or between samples. Of course such a finding, if true, could go a long way to explaining any lack of replication between different research groups if their samples were of different ages.

The aim of the current Chapter, therefore, is to compare and contrast the development of performance of boys with HKD and healthy children on a Go/NoGo task and a range of

neuropsychological tasks from the CANTAB battery. The CANTAB is particularly suited to such a study as identical versions of the tasks can used right across development.

The specific research questions are;

- What are the patterns of development of the various aspects of neuropsychological functioning?

- Are there differences in the rates and patterns of development of neuropsychological functioning between drug naïve boys with and without HKD?

The hypotheses to be tested are;

- In healthy children the timing and rate of development will differ between the different aspects of neuropsychological functioning, with non-executive memory developing earlier than executive functioning.

- Children with HKD will show similar patterns of neuropsychological development to those seen in healthy children, with non-executive processes developing earlier than executive processes, but their overall development will be significantly delayed compared with these healthy Controls.

Statistical Considerations

Analyses were conducted on the raw baseline performance data. Data for each task were first plotted as a scatter plot with age as a continuous variable and explored using curve fit analysis to investigate which regression curve best fitted the data.

Subjects were then grouped into four two-year age bandings to ensure maximum power in analyses (i.e. 7 – 8 years, 9 – 10 years, 11 – 12 years, and 13 – 14 years). Children older than 14 years were excluded from this analysis as numbers were too small [n = 3]. Descriptive data for task performance by age band is presented. Data were then analysed using univariate or repeated-measures ANOVA with a between-subject factors of AGE BAND and

of GROUP (HKD vs. Controls). Repeated-measures ANOVA was conducted on the following measures with DIFFICULTY level included as a within subject factor: Go/NoGo (Blocks 1 and 2), Spatial Working Memory Between-search Errors (3, 4, 6, 8 boxes), Stockings of Cambridge Average Moves (2-5 moves), Delayed Matching to Sample delay conditions (0, 4, 12 seconds delay) and Reaction Time (simple and 5-choice). BPVS Percentile Rank was used as a covariate in all analyses. Following ANOVA, further exploration of the data was conducted using pairwise comparisons.

Results

Neuropsychological performance organised by age-band is detailed in table 7.1.

There was an effect of GROUP (HKD vs. Control) ($F(1,135) = 29.5$, $p < 0.001$) and AGE BAND ($F(3,135) = 3.0$, $p < 0.033$) on BPVS percentile rank with Control boys and younger boys having a greater BPVS rank score. There was no GROUP x AGE BAND interaction.

Table 7.6: The effects of age on BPVS and neuropsychological functioning in drug naïve boys with hyperkinetic disorder and healthy Controls.

	Hyperkinetic Disorder				Controls			
Age Band (years)	7 – 8 (n = 19)	9 – 10 (n = 16)	11 – 12 (n = 12)	13 – 14 (n = 27)	7 – 8 (n = 18)	9 – 10 N = 16)	11 – 12 (n = 14)	13 – 14 (n = 21)
BPVS (% Correct)	49.1 (25.0)	37.3 (27.9)	33.3 (29.0)	27.8 (26.9)	66.7 (24.4)	59.4 (22.9)	64.8 (18.0)	54.3 (32.2)
Go/NoGo								
Errors for Distractors Block 1	*3.50 (1.50)*	*2.16 (1.29)*	*2.42 (1.31)*	*1.58 (1.18)*	*3.32 (1.63)*	*1.98 (1.01)*	*1.96 (1.21)*	*1.68 (0.91)*
Errors for Distractors Block 2	3.55 (1.89)	*1.91 (1.52)*	*1.98 (1.02)*	*1.59 (1.31)*	*3.06 (2.12)*	*1.92 (0.72)*	*1.71 (1.21)*	*1.19 (0.62)*
Reaction Time to targets Block 1	*516 (108)*	*487 (70)*	*416 (101)*	*429 (46.6)*	*505 (96.7)*	*472 (63.0)*	*408 (53.4)*	*404 (45.1)*
Reaction Time to targets Block 2	*526 (117)*	*486 (48)*	*445 (73.2)*	*419 (50.3)*	*496 (91.0)*	*484 (71.3)*	*414 (58.8)*	*411 (38.9)*
Spatial Span								
Span Score	*4.11 (1.24)*	*4.94 (0.54)*	*5.42 (1.38)*	*5.70 (1.14)*	*4.72 (1.36)*	*5.75 (1.00)*	*6.79 (1.12)*	*6.43 (1.57)*
Spatial Working Memory								
Total Between-search Errors	*66.0 (9.77)*	*56.0 (12.8)*	*46.3 (19.6)*	*40.2 (19.8)*	*52.1 (18.9)*	*37.8 (18.1)*	*27.9 (17.9)*	*23.3 (16.1)*
Strategy Score	*38.3 (3.96)*	*37.3 (3.24)*	*35.0 (5.10)*	*35.1 (4.89)*	*34.3 (5.16)*	*34.9 (3.79)*	*32.0 (4.13)*	*30.1 (5.80)*
Stockings of Cambridge								
No. Solved in Minimum Moves	*5.63 (1.34)*	*7.06 (2.32)*	*7.92 (1.31)*	*7.81 (2.04)*	*6.83 (2.18)*	*7.94 1.73)*	*8.71 (1.64)*	*8.90 (2.02)*
Average Moves (5 move problems)	*8.44 (1.27)*	*7.72 (1.58)*	*7.81 (1.31)*	*6.84 (1.28)*	*7.63 (1.29)*	*7.28 (1.29)*	*6.82 (1.07)*	*6.66 (1.55)*
Pattern Recognition								
% Correct	*79.9 (15.6)*	*81.9 (12.7)*	*79.5 (8.96)*	*82.8 (10.5)*	*91.4 (11.3)*	*88.0 (7.28)*	*90.2 (8.74)*	*93.0 (8.67)*
Spatial Recognition								
% Correct	*64.2 (13.6)*	*68.4 (11.2)*	*66.3 (16.7)*	*73.5 (14.0)*	*70.8 (13.3)*	*76.6 (13.0)*	*83.9 (6.56)*	*78.1 (14.4)*
Delayed Matching to Sample								
% Correct								
Simultaneous	*80.0 (18.9)*	*95.0 (13.7)*	*95.0 (12.4)*	*94.1 (12.2)*	*95.6 (8.56)*	*96.25 (8.06*	*98.57 (5.35*	*99.05 (4.36*
0 s delay	*58.8 (23.3)*	*67.5 (26.2)*	*70.8 (20.7)*	*80.0 (26.0)*	*65.6 (25.5)*	*76.2 (13.0)*	*75.1 (25.5)*	*89.5 (13.6)*
4 s delay	*48.4 (26.1)*	*51.25 (19.3*	*60.0 (17.1)*	*64.4 (26.2)*	*67.8 19.6)*	*65.6 (27.3)*	*88.6 (12.9)*	*81.0 (16.1)*
12 s delay	*35.8 (21.7)*	*48.8 (29.2)*	*51.7 (26.2)*	*62.2 (26.2)*	*63.3 (28.5)*	*73.8 (22.8)*	*80.0 (15.7)*	*77.1 (15.9)*
Paired Associates Learning								
Stage Reached	*7.95 (0.23)*	*8 (0)*	*8 (0)*	*7.93 (0.39)*	*8 (0)*	*7.87 (0.52)*	*8 (0)*	*8 (0)*
Total Errors	*18.7 (14.8)*	*14.2 (11.0)*	*6.50 (3.75)*	*6.70 (7.53)*	*9.29 (14.2)*	*9.27 (11.9)*	*5.77 (5.05)*	*5.86 (5.41)*
Total Trials	*15.0 (4.36)*	*13.6 (3.48)*	*10.8 (1.40)*	*11.1 (4.08)*	*11.2 (3.58)*	*12.1 (5.50)*	*10.2 (1.79)*	*10.3 (1.71)*
ID/ED								
Stage Reached Score	*7.0 (1.33)*	*7.63 (0.89)*	*7.58 (0.90)*	*7.85 (0.99)*	*7.50 (0.79)*	*7.81 (0.98)*	*7.57 (0.94)*	*8.62 (0.81)*
Pre-ED errors	*11.3 (7.71)*	*9.0 (2.88)*	*10.6 (7.88)*	*7.67 (5.53)*	*8.61 (5.47)*	*6.50 (2.22)*	*5.07 (1.07)*	*5.81 (2.79)*
Errors at ED shift	*25.2 (4.52)*	*19.3(9.58)*	*20.3 (8.90)*	*17.0 (11.7)*	*22.3 (9.07)*	*18.6 (9.82)*	*22.5 (9.94)*	*11.7 (10.3)*
Reaction Time								
Reaction Time Latency: Simple	*495 (178)*	*412 (152)*	*387 (150)*	*369 (168)*	*425 (141)*	*358 (78.3)*	*324 (56.9)*	*311 (41.2)*
Movement Time Latency: Simple	*408 (174)*	*414 (152)*	*439 (154)*	*444 (135)*	*479 (216)*	*423 (147)*	*366 (122)*	*371 (121)*
Reaction Time Latency: 5 choice	*550 (274)*	*397 (76.6)*	*442 (211)*	*372 (78.9)*	*522 (177)*	*378 (62.7)*	*332 (46.8)*	*336 (47.2)*
Movement Time Latency: 5 Choice	*436 (134)*	*463 (150)*	*394 (129)*	*424 (134)*	*408 (183)*	*420 (139)*	*374 (77.7)*	*380 (121)*

Go/NoGo

Reaction Time to Targets

Curve estimation for both Block 1 and 2 reaction time to targets identified the linear solution as the best fit for both Controls (RTT1 [r^2 = .34, F (1,69)=34.8, p<.001], RTT2 [r^2 = .29, F (1,69)=28.0, p<.001]) and HKD boys (RTT1 [r^2 = .17, F (1,73)=14.8, p<.001], RTT2 [r^2 = .26, F (1,73)=25.6, p<.001]). Repeated-measures ANOVA on reaction times to targets on the Go/NoGo task revealed a significant effect of age-band [F(3,134) = 15.8, p<.001] but no main effect of GROUP or BLOCK TYPE nor any interactions between AGE x BLOCK TYPE, AGE x GROUP or AGE x GROUP x BLOCK TYPE interactions. Pairwise comparisons revealed a developmental pattern of shorter reaction time to targets with increased age with significant differences between each age-band (except between the 7-8 and the 9 – 10 year olds and between the 11 – 12 and the 13 – 14 year olds), whereby the younger subjects showed the longest reaction times. The development of Go/NoGo Reaction Time is shown in Figure 7.1.

Errors to Distractors

Curve estimation for both Block 1 and 2 errors to distractors identified the linear solution as the best fit for both Controls (ERD1 [r^2 = .16, F (1,69)=13.2, p<.001], ERD2 [r^2 = .21, F (1,69)=18.0, p<.001]) and HKD boys (ERD1 [r^2 = .23, F (1,73)=21.6, p<.001], ERD2 [r^2 = .19, F (1,73)=16.7, p<.001]). Repeated-measures ANOVA on errors for distractors to targets on the Go/NoGo task revealed a significant effect of age-band [F(3,134) = 14.7, p<.001] but no main effect of GROUP or BLOCK TYPE nor any interactions between AGE x BLOCK TYPE, AGE x GROUP or AGE x GROUP x BLOCK TYPE interactions. Pairwise comparisons revealed a developmental pattern with reduced errors for distractors in the 7 – 8 year olds compared with the other age bands but not between the other age groups. The development of Go/NoGo Errors to Distractors is shown in Figure 7.2.

Figure 7.1: Development of Go/NoGo Reaction time to targets (means with standard deviation) in drug naïve boys with hyperkinetic disorder (n = 74) and healthy Controls (n = 69) aged between 7 and 14 years.

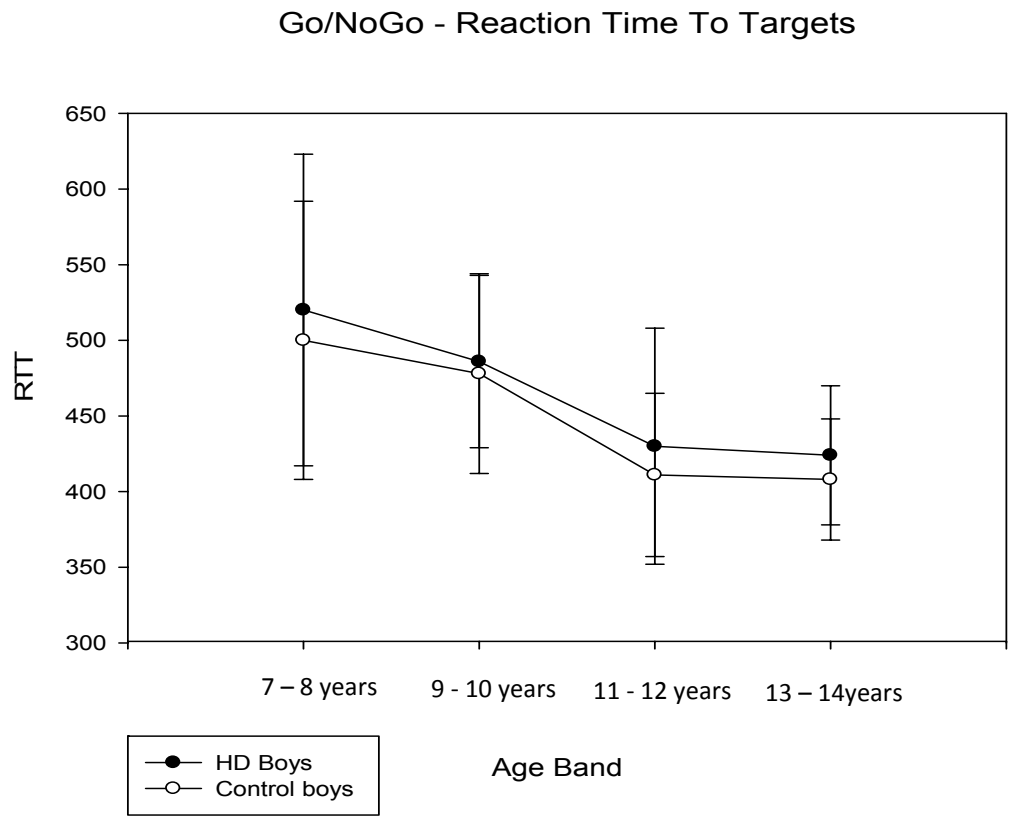
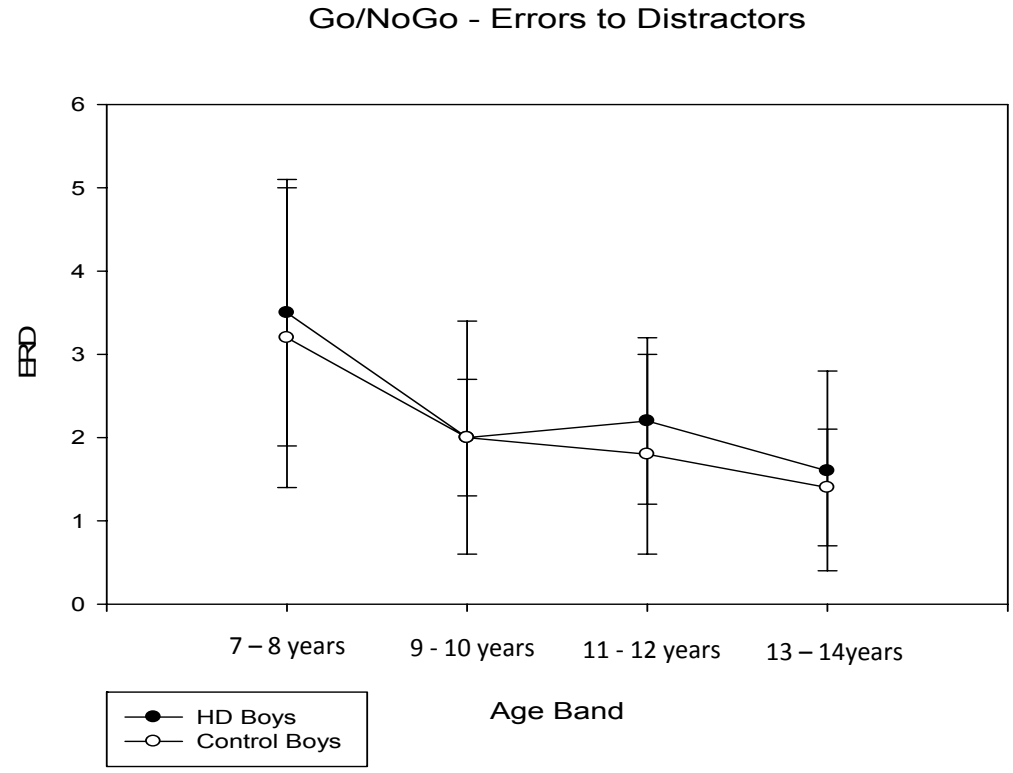


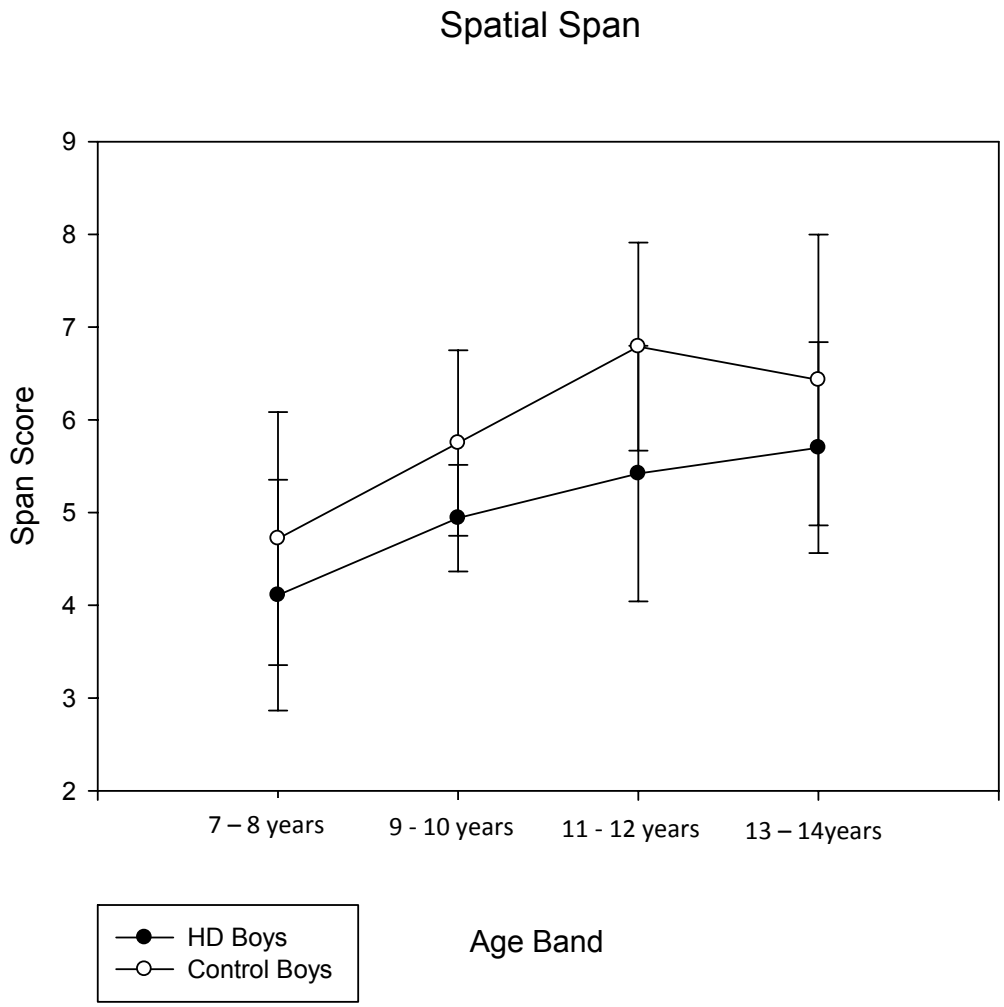
Figure 7.2: Development of Go/NoGo Errors to Distractors (means with standard deviation) in drug naïve boys with hyperkinetic disorder (n = 74) and healthy Controls (n = 69) aged between 7 and 14 years.



Span

Curve estimation for Span Score identified the linear solution as the best fit for both Controls [r^2 = .23, F (1,69)=20.2, p<.001] and HKD boys [r^2 = .23, F (1,73)=26.3, p<.001]. Univariate ANOVA on Spatial Span revealed a significant effect of age-band [F(3,134) = 16.4, p<.001] and of GROUP [F(1,134) = 10.3, p<.005] but no interaction between AGE x GROUP. Pairwise comparisons revealed increased span in the Control compared with HKD boys and increased span with increased age with significant differences between each age-band (except between 11 – 12 and 13 – 14 year olds). The development of Spatial Span is shown in Figure 7.3.

Figure 7.3: Development of Spatial Span (means with standard deviation) in drug naïve boys with hyperkinetic disorder (n = 74) and healthy Controls (n = 69) aged between 7 and 14 years.



Spatial Working Memory

Between-search Errors

Curve estimation for total Between-search Errors identified the linear solution as the best fit for both Controls [r^2 = .34, F (1,69)=34.8, p<.001] and HKD boys [r^2 = .34, F (1,73)=36.0, p<.001]. Repeated-measures ANOVA on Between-search Errors on the Spatial Working Memory task revealed a significant effect of age-band [F(3,134) = 22.3, p<.001] with pairwise comparisons demonstrating improved performance with increasing age and significant differences between each age-band (except between 11 – 12 and 13 – 14 year olds). There was also a significant effect of GROUP [F(1,134) = 21.5, p<.001] with Control boys performing better than HKD boys and DIFFICULTY [F(1,134) = 236.9, p<.001] with poorer performance as difficulty increased. There were also interactions between AGE x DIFFICULTY [F(3,134) = 15.6, p<.001] with younger subjects being affected more by difficulty than older subjects and GROUP x DIFFICULTY [F(1,134) = 20.3, p<.001] with HKD boys being more affected by difficulty than Control boys, but there were no AGE x GROUP or AGE x GROUP x DIFICULTY interactions. The development of Spatial Working Memory – Between-search Errors is shown in figure 7.4, 7.5 and 7.6.

Figure 7.4: Development of Spatial Working Memory - Between-search Errors (means with standard deviation) in drug naïve boys with hyperkinetic disorder (n = 74) and healthy Controls (n = 69) aged between 7 and 14 years.

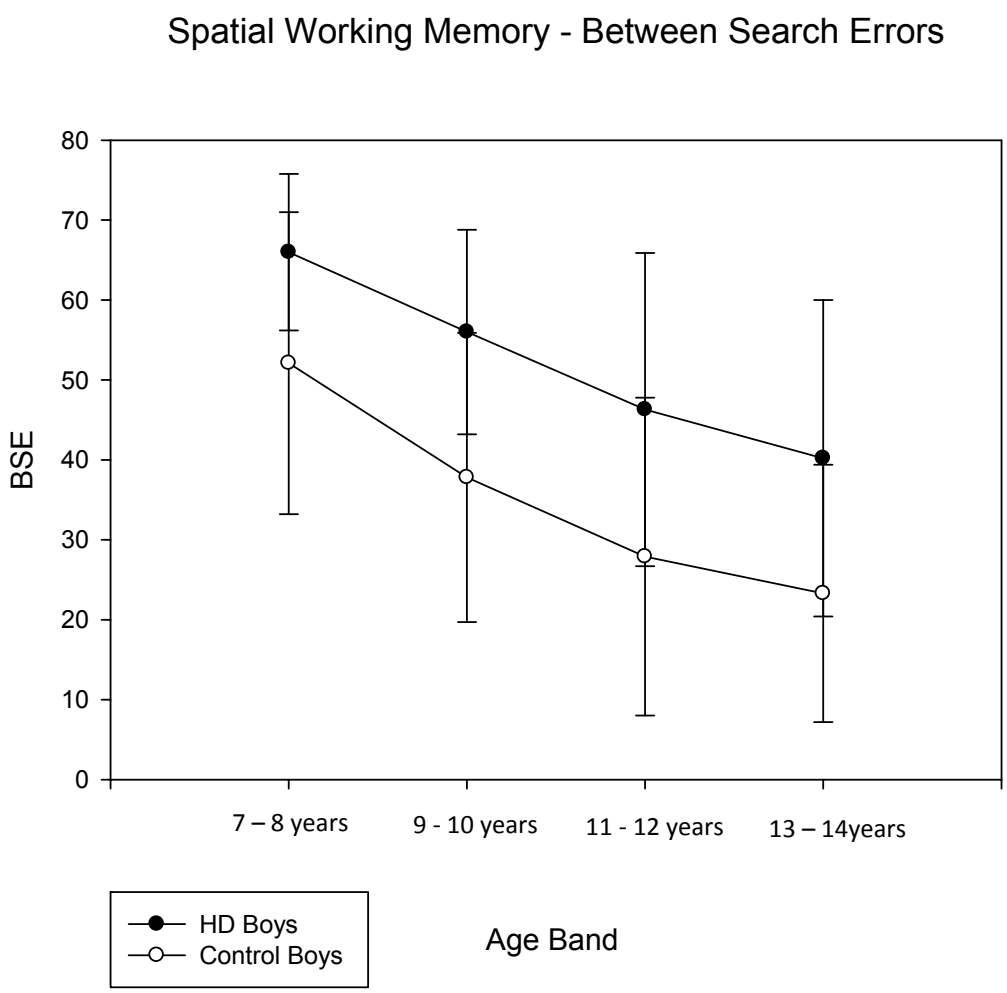


Figure 7.5: Interactions between difficulty and age in the development of Spatial Working Memory - Between-search Errors in (A) Drug naïve boys with hyperkinetic disorder (n = 74) and (B) healthy Controls (n = 69) aged between 7 and 14 years.

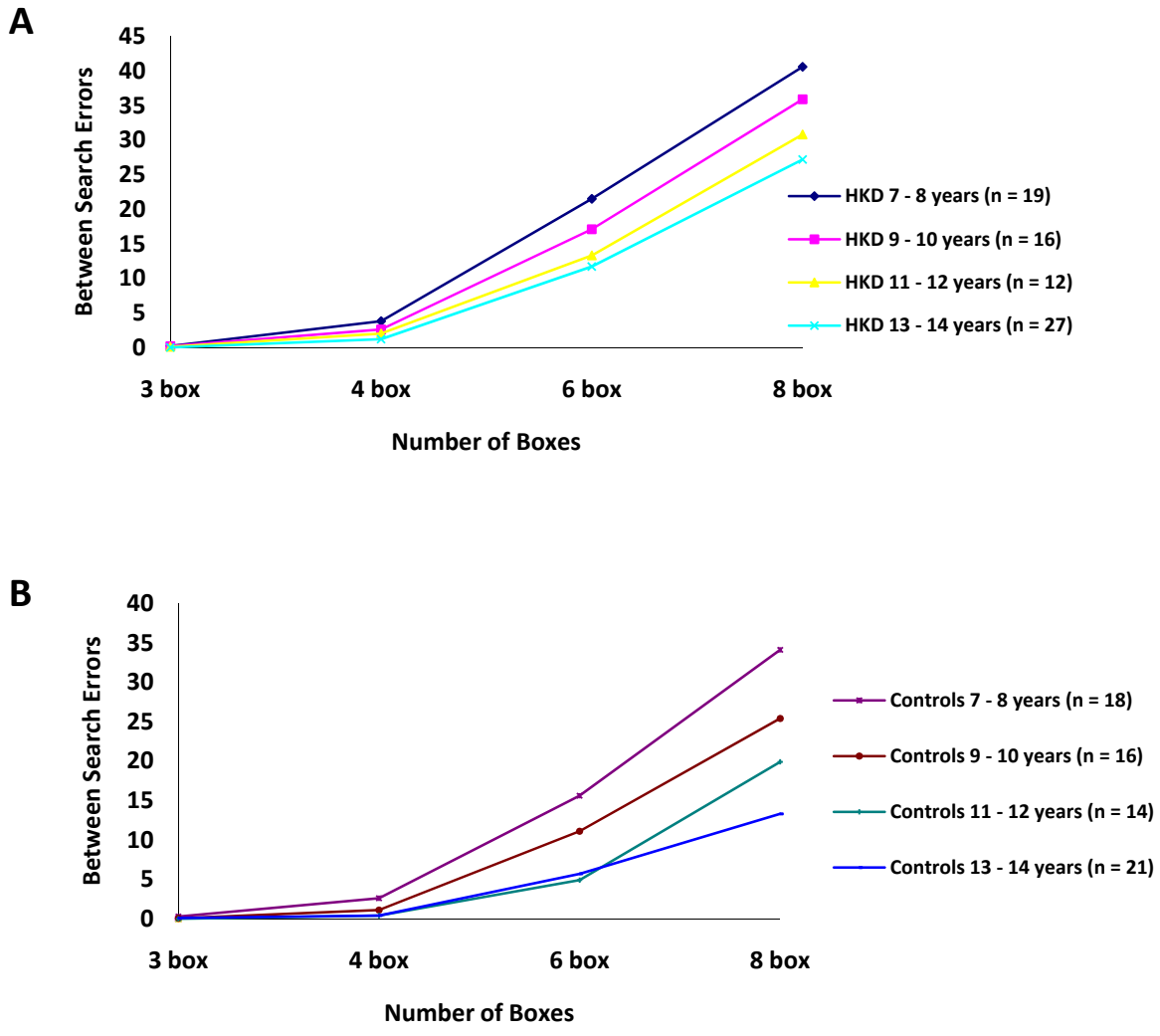
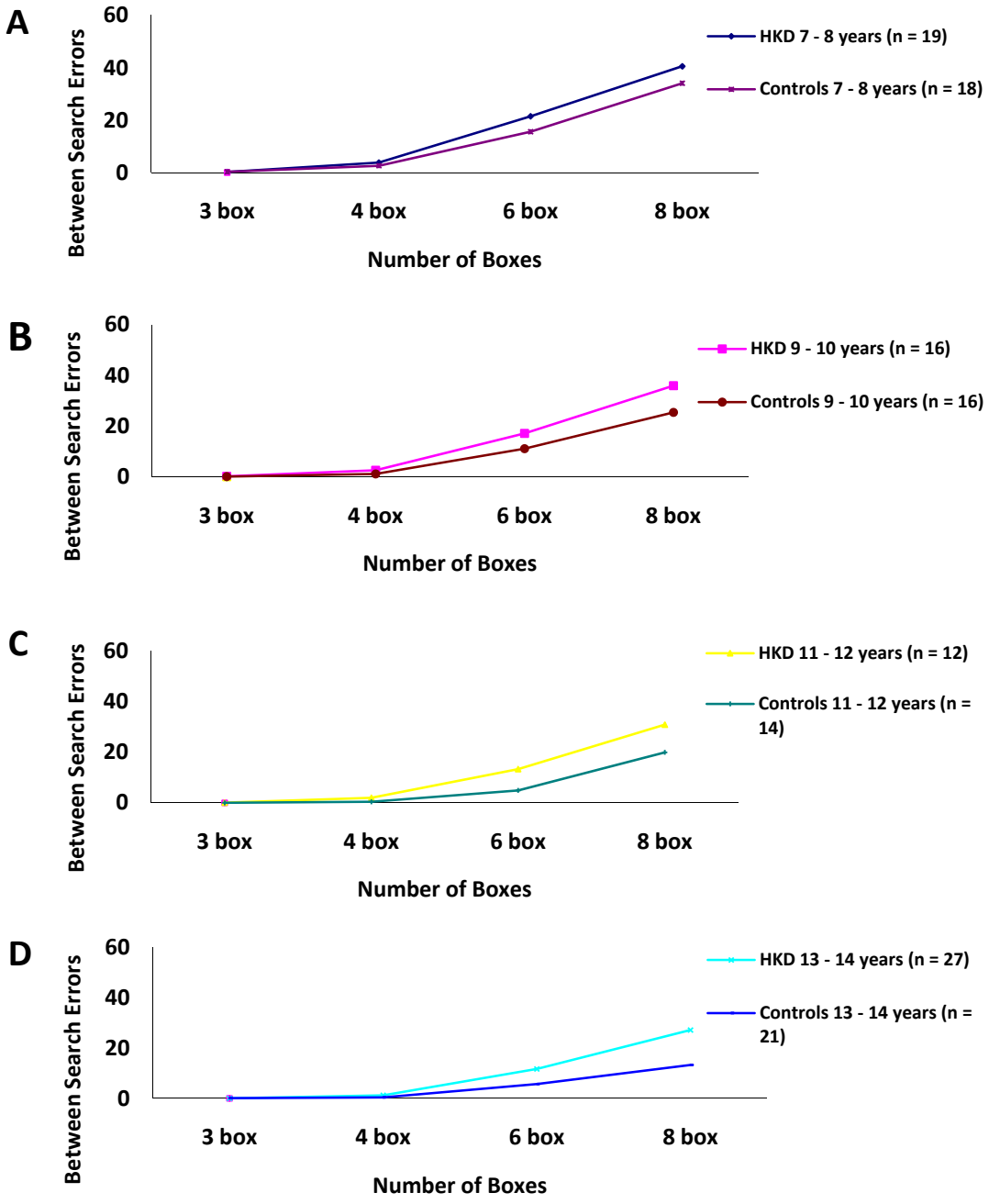


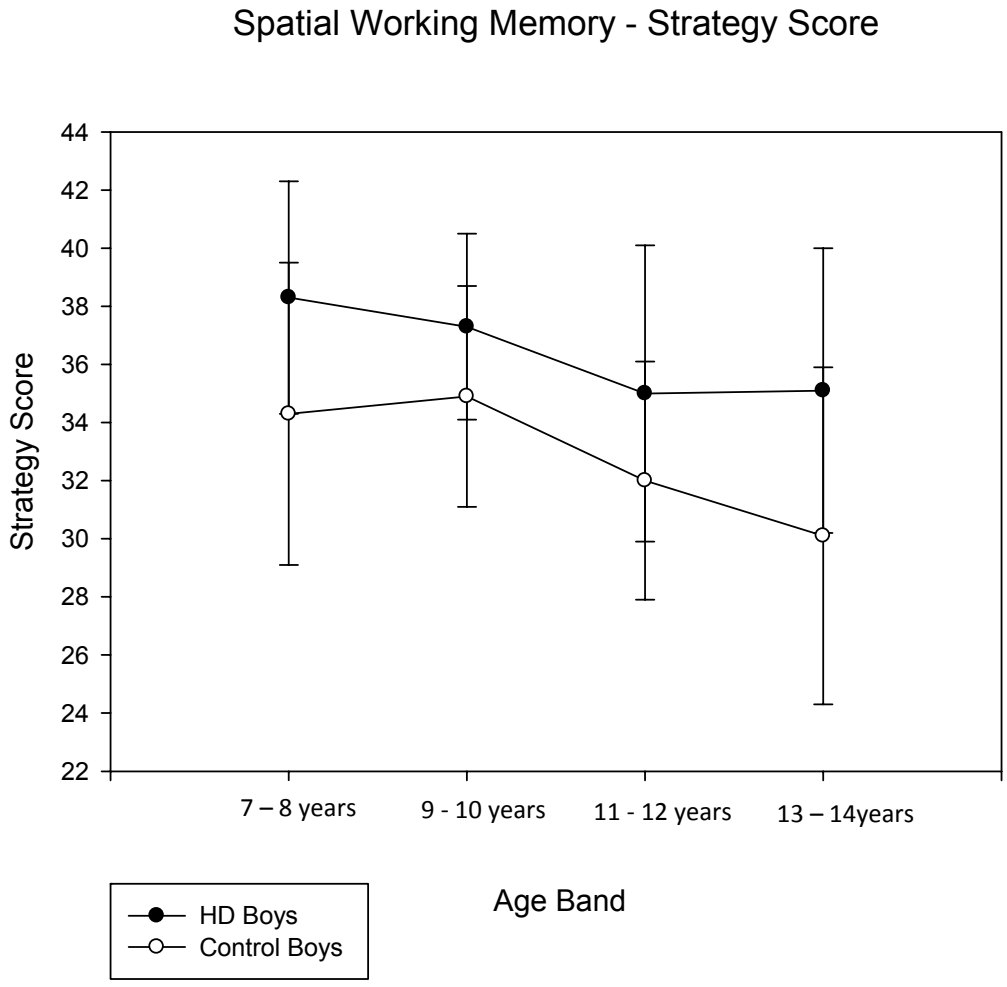
Figure 7.6: Interactions between difficulty and diagnostic status split by age in the development of Spatial Working Memory - Between-search Errors in drug naïve boys with hyperkinetic disorder (total n = 74) and healthy Controls (total n = 69) aged between 7 and 14 years. (A) boys aged 7 – 8 years (B) boys aged 9 – 10 years (C) boys aged 11 – 12 years (D) boys aged 13 – 14 years.



Strategy Score

Curve estimation for Spatial Working Memory Strategy Score identified the linear solution as the best fit for both Controls [r^2 = .11, F (1,69)=8.3, p<.005] and HKD boys [r^2 = .10, F (1,69)=8.2, p<.005]. Univariate ANOVA on Spatial Working Memory Strategy Score revealed a significant effect of age-band [F(3,134) = 6.4, p<.001] and of GROUP [F(1,134) = 13.8, p<.001] but no interaction between AGE x GROUP. Pairwise comparisons revealed improved use of strategy in the Control compared with HKD boys and increased use of strategy with increased age with significant differences between each age-band (except between the 7-8 and the 9 – 10 year olds and between the 11 – 12 and the 13 – 14 year olds). The development of Strategy is shown in Figure 7.7.

Figure 7.7: Development of Spatial Working Memory - Strategy Score (means with standard deviation) in drug naïve boys with hyperkinetic disorder (n = 74) and healthy Controls (n = 69) aged between 7 and 14 years.



Stockings of Cambridge

Curve estimation for Stockings of Cambridge problems solved in minimum moves identified the linear solution as the best fit for both Controls [r^2 = .16, F (1,69)=13.5, p<.001] and HKD boys [r^2 = .17, F (1,69)=14.5, p<.001]. Univariate ANOVA on problems solved in minimum moves revealed a significant effect of age-band [F(3,134) = 13.1, p<.001] but not GROUP and there was no interaction between AGE x GROUP. Pairwise comparisons revealed a developmental pattern of increased numbers of problems solved in minimum moves in the Control compared with HKD boys and an increased number of problems solved in minimum moves with increased age with significant differences between each age-band (except between the 9 – 10 year and the 11 – 12 year olds and between the 11 – 12 and the 13 – 14 year olds). The development of problems solved in minimum moves is shown in Figure 8.8.

Repeated-measures ANOVA on Stockings of Cambridge average moves revealed a significant effect of AGE BAND [F(3,134) = 10.3, p<.001] with pairwise comparisons demonstrating improved performance with increasing age and significant differences between each age-band (except between 9 – 10 year and 11 – 12 year olds and between 11 – 12 and 13 – 14 year olds). There was also a significant effect of DIFFICULTY [F(1,134) = 247.1, p<.001] with poorer performance as difficulty increased and an interaction between DIFFICULTY x AGE BAND [F(1,134) = 247.1, p<.001] with the performance of those in the younger age bands deteriorating to a greater degree as difficulty increased. There was no effect of GROUP and no interactions between AGE x GROUP, GROUP x DIFFICULTY or AGE x GROUP x DIFICULTY. The development of Stockings of Cambridge average moves is shown in figures 7.9 and 7.10.

Figure 7.8: Development of Stockings of Cambridge - Problems Solved in Minimum Moves (means with standard deviation) in drug naïve boys with hyperkinetic disorder (n = 74) and healthy Controls (n = 69) aged between 7 and 14 years.

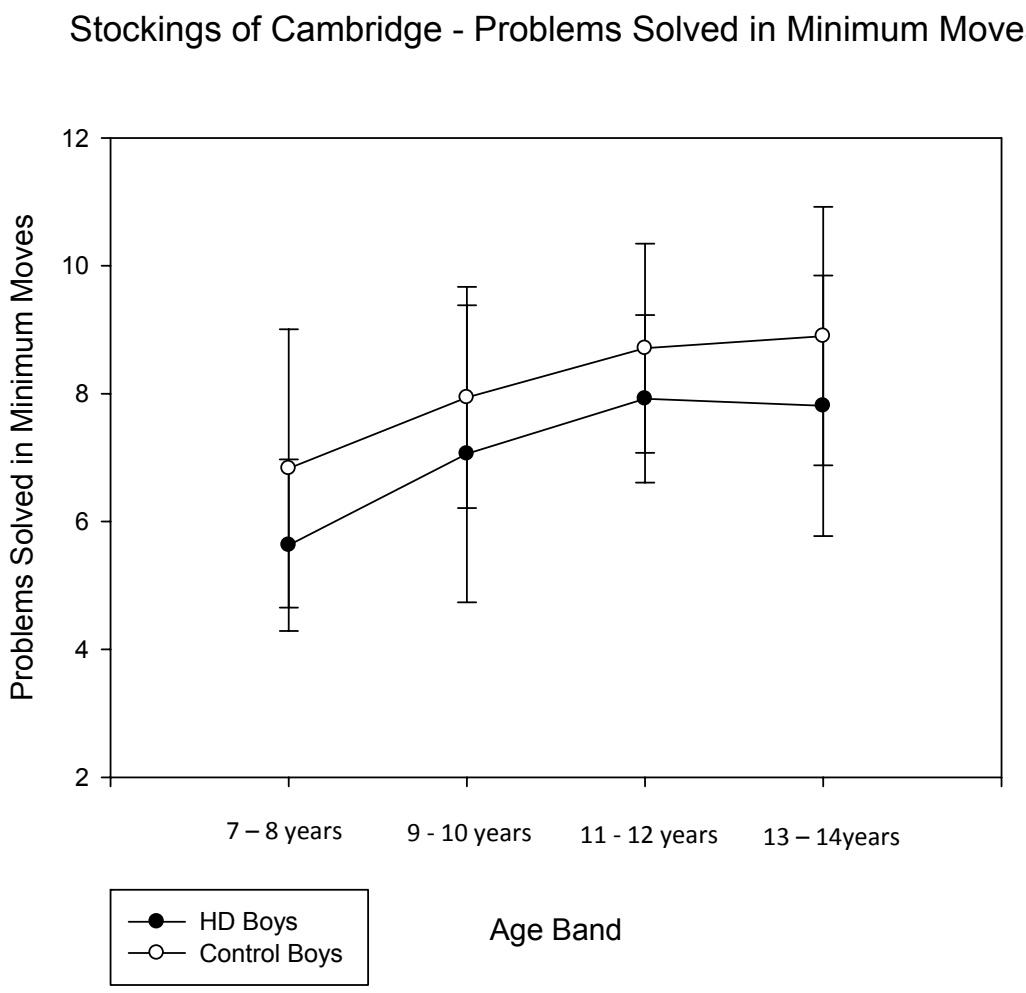
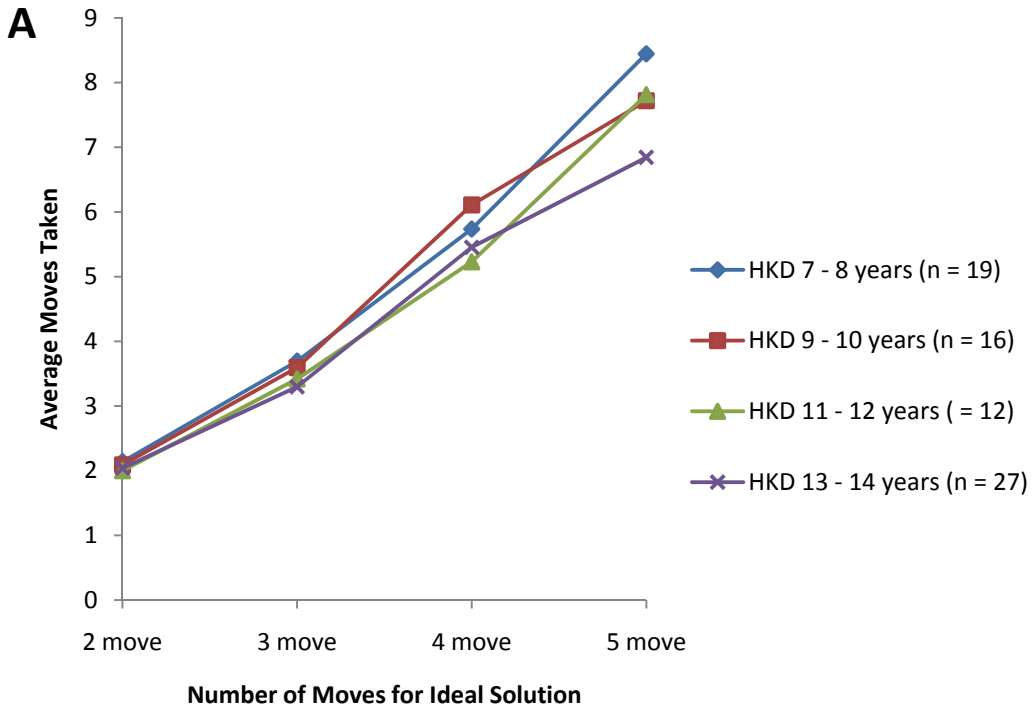


Figure 7.9: Interactions between difficulty and age in the development of Stockings of Cambridge – Average Moves in (A) Drug naïve boys with hyperkinetic disorder (n = 74) and (B) healthy Controls (n = 69) aged between 7 and 14 years.



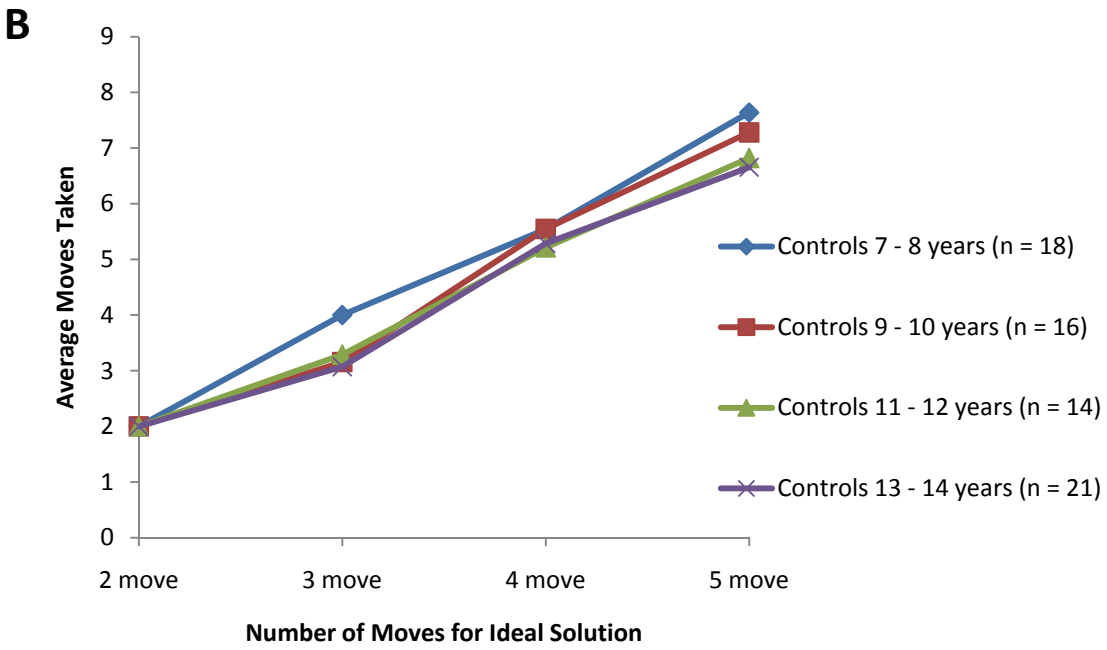
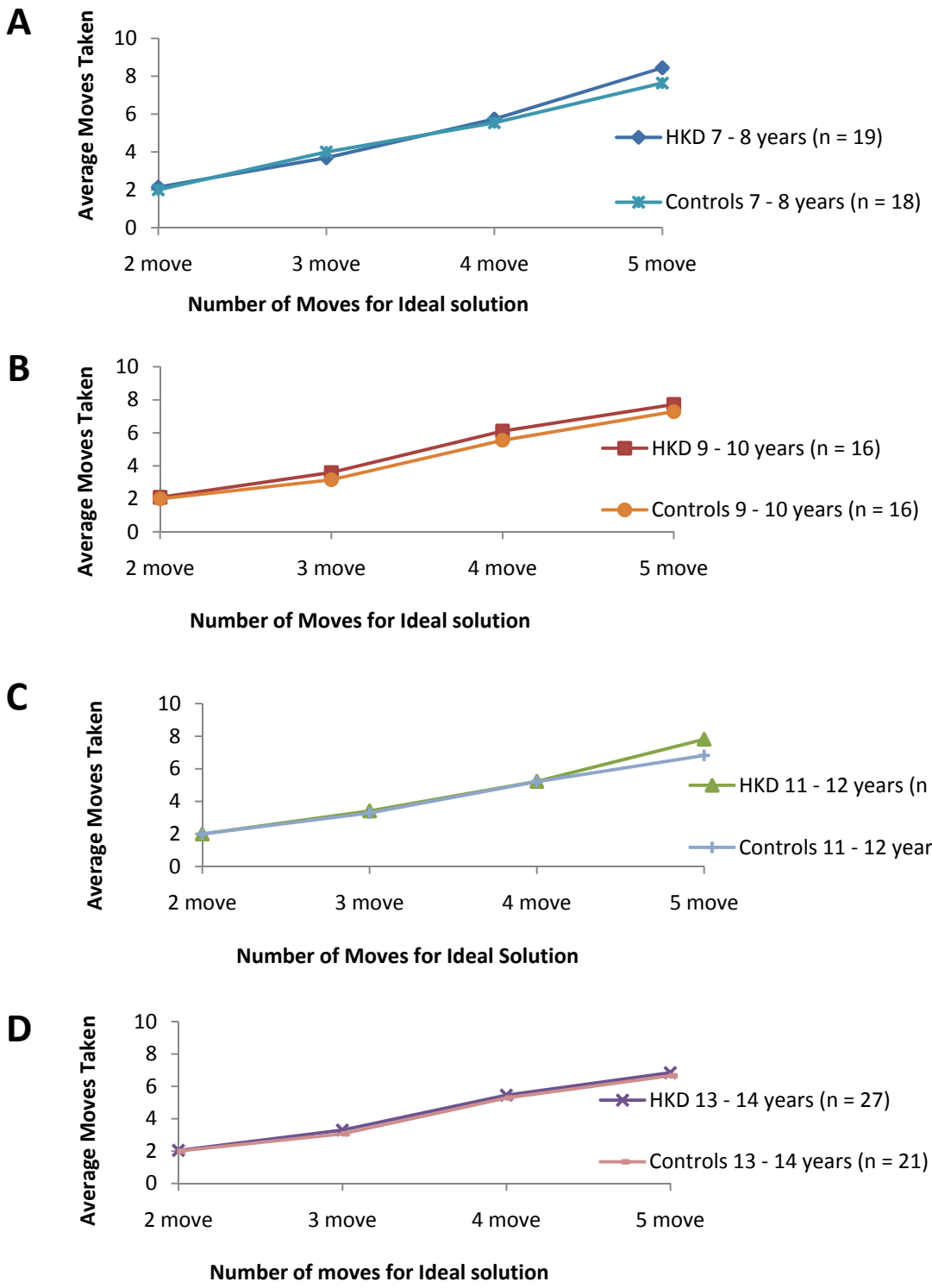


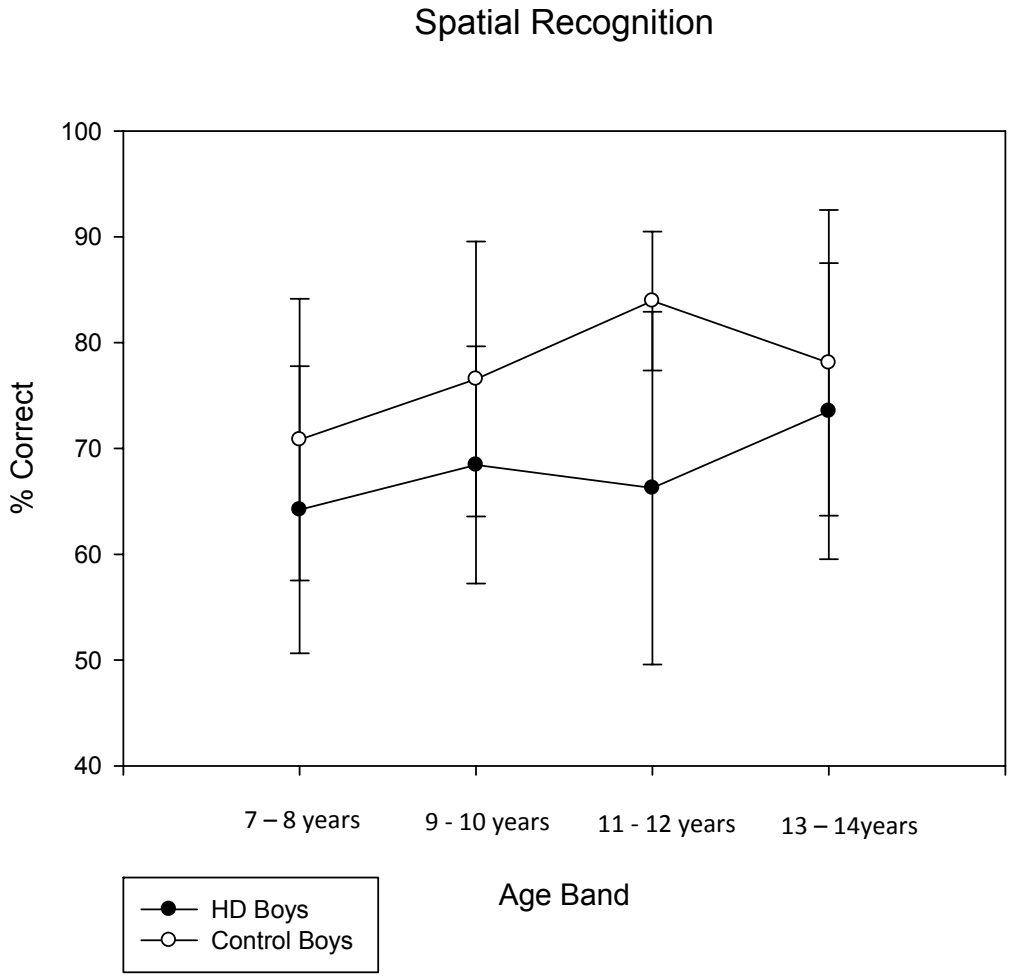
Figure 7.10: Interactions between difficulty and diagnostic status split by age in the development of Spatial Working Memory - Between-search Errors in drug naïve boys with hyperkinetic disorder (total n = 74) and healthy Controls (total n = 69) aged between 7 and 14 years. (A) boys aged 7 – 8 years (B) boys aged 9 – 10 years (C) boys aged 11 – 12 years (D) boys aged 13 – 14 years.



Spatial Recognition

Curve estimation for Spatial Recognition identified the linear solution as the best fit for both Controls [r^2 = .06, F (1,69)=4.5, p<.05] and HKD boys [r^2 = .06, F (1,73)=4.4, p<.05]. Univariate ANOVA confirmed that there was no effect of AGE BAND on Spatial Recognition performance. There was, however, an effect of GROUP [F(1,134) = 16.5, p<.001] but no interaction between AGE x GROUP. Pairwise comparisons revealed better Spatial Recognition in the Control boys compared with the HKD boys. The development of Spatial Recognition is shown in Figure 7.11.

Figure 7.11: Development of Spatial Recognition (means with standard deviation) in drug naïve boys with hyperkinetic disorder (n = 74) and healthy Controls (n = 69) aged between 7 and 14 years.



Pattern Recognition

Curve estimation for Pattern Recognition identified that none of the models tested reached significance. Observing the scatter plot and regression lines it is likely that this is due to a ceiling effect with many of the younger boys performing at ceiling and no evidence of improvement over time (fig. 7.12). Univariate ANOVA confirmed that there was no effect of AGE BAND on Pattern Recognition performance. There was, however, an effect of GROUP [$F(1,134) = 21.6$, $p<.001$] but no interaction between AGE x GROUP. Pairwise comparisons revealed better Pattern Recognition in the Control boys compared with the HKD boys. The development of Pattern Recognition is shown in Figure 7.13.

Figure 7.12: Scatterplot and regression lines for development of Pattern Recognition in drug naïve boys with hyperkinetic disorder (n = 74) and healthy Controls (n = 69) aged between 7 and 14 years.

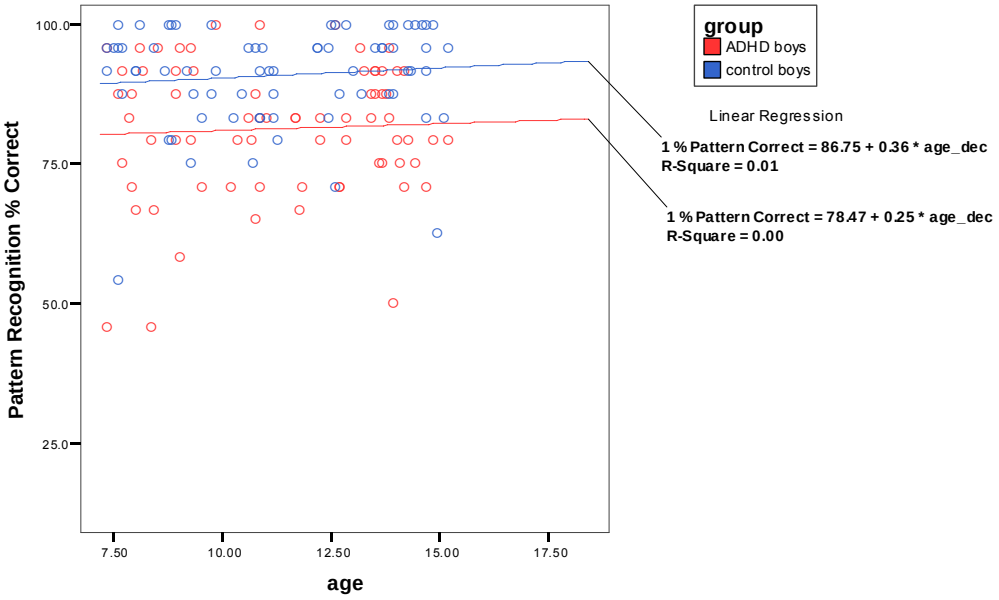
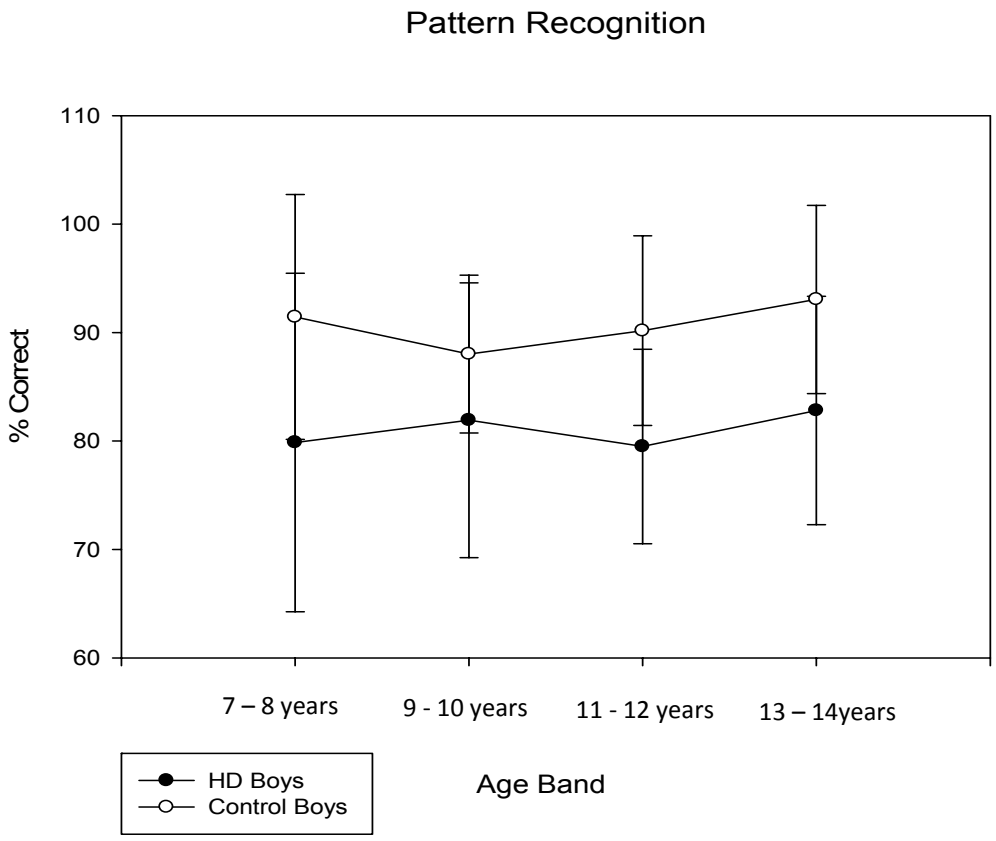


Figure 7.13: Development of Pattern Recognition (means with standard deviation) in drug naïve boys with hyperkinetic disorder (n = 74) and healthy Controls (n = 69) aged between 7 and 14 years.



Delayed Matching to Sample

Curve estimation for Delayed Matching to Sample percent correct across total delays identified the linear solution as the best fit for both Controls [r^2 = .19, F (1,69)=16.6, p<.001] and HKD boys [r^2 = .26, F (1,69)=25.1, p<.001]. Univariate ANOVA on percent correct across total delays revealed a significant effect of age-band [F(3,134) = 14.2, p<.001] and GROUP [F(1,134) = 28.4, p<.001] but no interaction between AGE x GROUP. Pairwise comparisons revealed improved performance in the Control compared with HKD boys and also with increased age with significant differences between each age-band (except between the 9 – 10 year and the 11 – 12 year olds and between the 11 – 12 and the 13 – 14 year olds). The development of Delayed Matching to Sample (total delays) is shown in Figure 7.14.

Repeated-measures ANOVA on Delayed Matching to Sample % correct across the different delay conditions revealed a significant effect of AGE BAND [F(3,134) = 12.9, p<.001] with pairwise comparisons demonstrating improved performance with increasing age and significant differences between each age-band (except between 9 – 10 year and 11 – 12 year olds and between 11 – 12 and 13 – 14 year olds). There was also a significant effect of GROUP [F(1,134) = 26.0, p<.001]with Control boys performing better than HKD boys and of DIFFICULTY [F(1,134) = 5.4, p<.05] with poorer performance as difficulty increased and an interaction between DIFFICULTY x GROUP [F(1,134) = 6.0, p<.05] with the performance of HKD boys deteriorating to a greater degree as difficulty increased. There were no interactions between AGE BAND x GROUP, AGE BAND x DIFFICULTY or AGE BAND x GROUP x DIFICULTY. The development of Delayed Matching to Sample is shown in figure 7.15.

Figure 7.14: Delayed Matching to Sample - Total Delays (means with standard deviation) in drug naïve boys with hyperkinetic disorder (n = 74) and healthy Controls (n = 69) aged between 7 and 14 years.

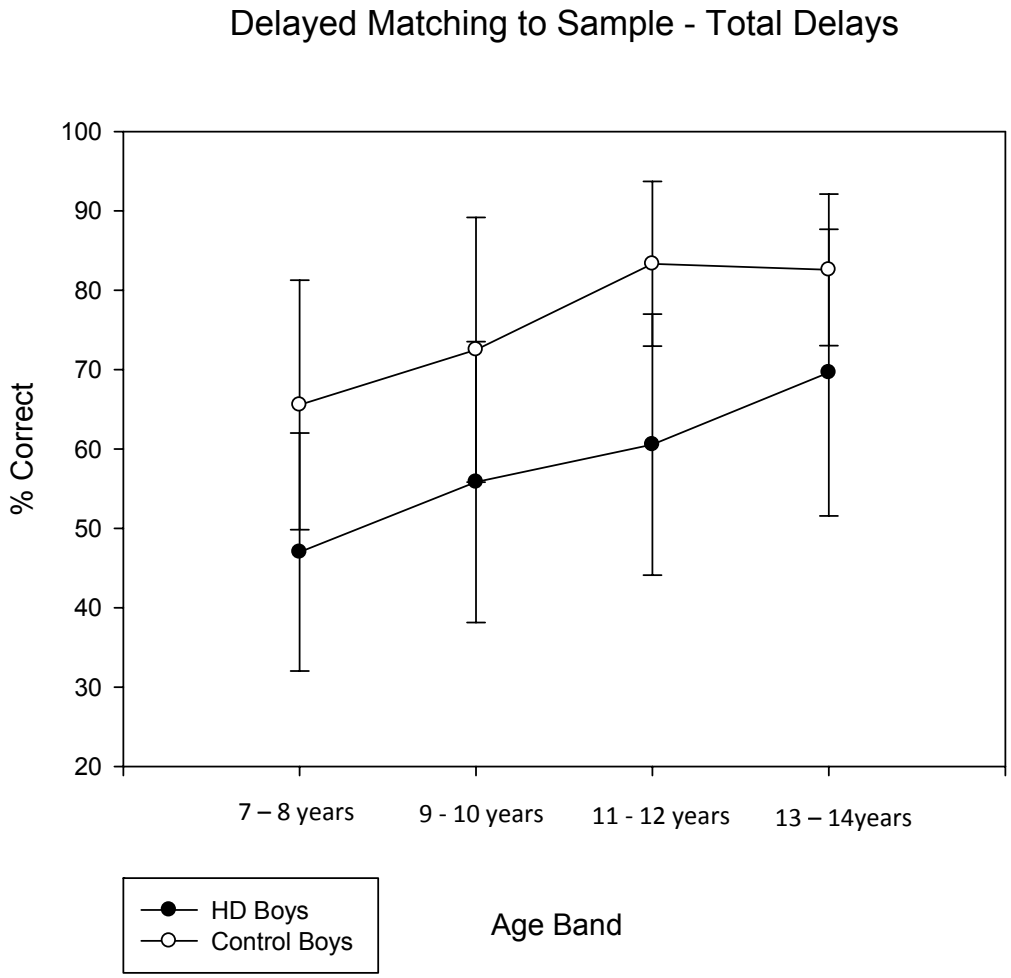
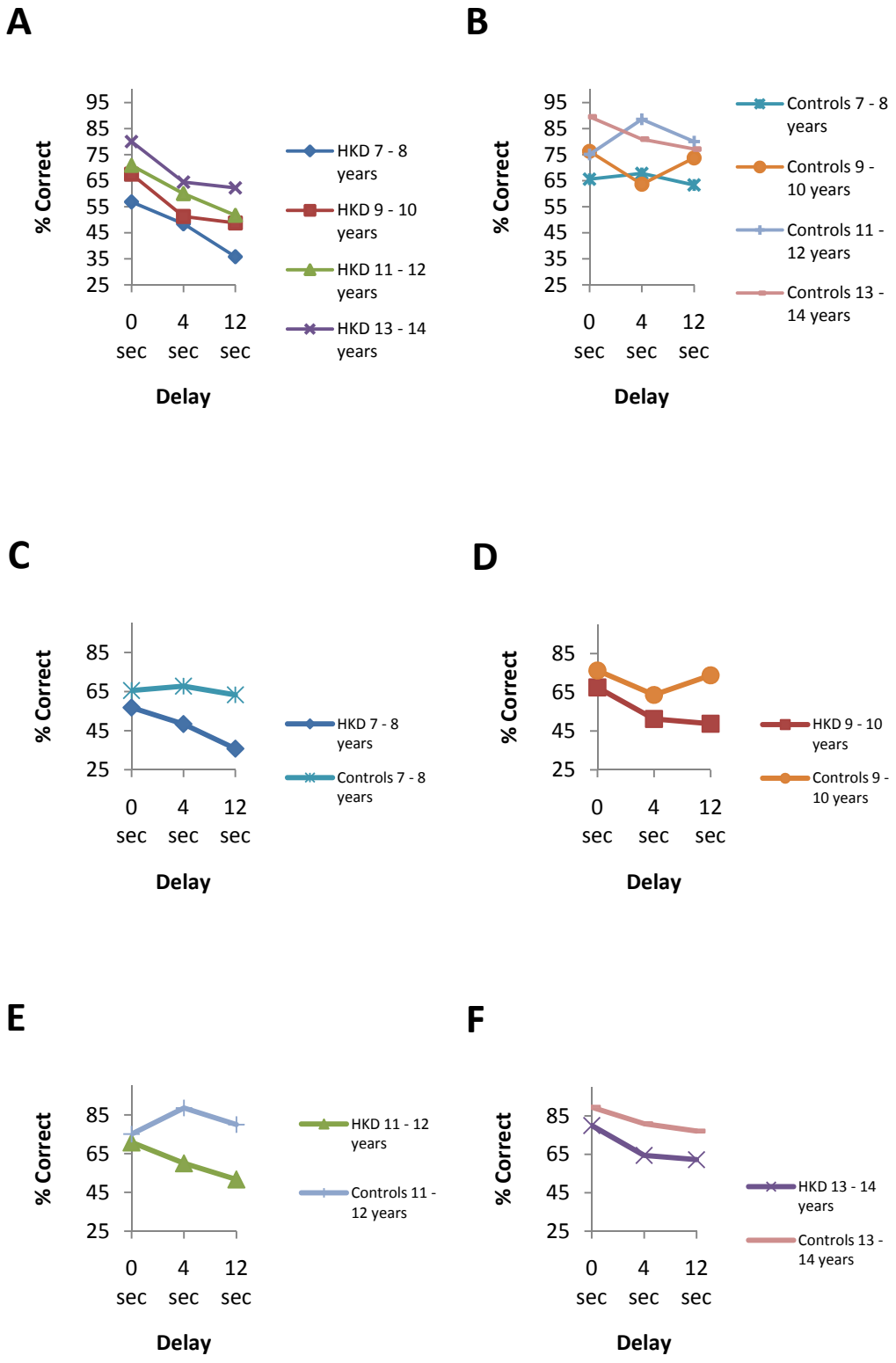


Figure 7.15: Interactions between difficulty and age in the development of Delayed Matching to Sample - % correct across total delays, in (A) Drug naïve boys with hyperkinetic disorder (n = 74) and (B) healthy Controls (n = 69) aged between 7 and 14 years, and interactions between difficulty and age and between difficulty and diagnostic status split by age for the same task in the same groups. (C) boys aged 7 – 8 years (D) boys aged 9 – 10 years (E) boys aged 11 – 12 years (F) boys aged 13 – 14 years.



Paired Associates Learning

Total Trials

Curve estimation for Paired Associates Learning total trials identified that none of the curves fitted for the Control boys. Observation of the scatter plot suggests that this was due to a floor effect with boys of all ages performing very well on the task (fig 7.16). For the HKD boys the linear solution was the best fit for the data [r^2 = .14, F (1,69)=11.5, p<.001].

Univariate ANOVA on Paired Associates Learning total trials revealed a significant effect of AGE BAND [F(3,134) = 5.3, p<.005] but not GROUP and no interaction between AGE x GROUP. Pairwise comparisons revealed improved performance with increased age with significant differences between each age-band (except between 7 - 8 year and 9 - 10 year olds and between 11 – 12 and 13 – 14 year olds). The development of Paired Associates Learning (total trials) is shown in Figure 7.17.

Figure7.16: Scatter plot and regression lines for Paired Associates Learning - Total Trials (means with standard deviation) in drug naïve boys with hyperkinetic disorder (n = 74) and healthy Controls (n = 69) aged between 7 and 14 years.

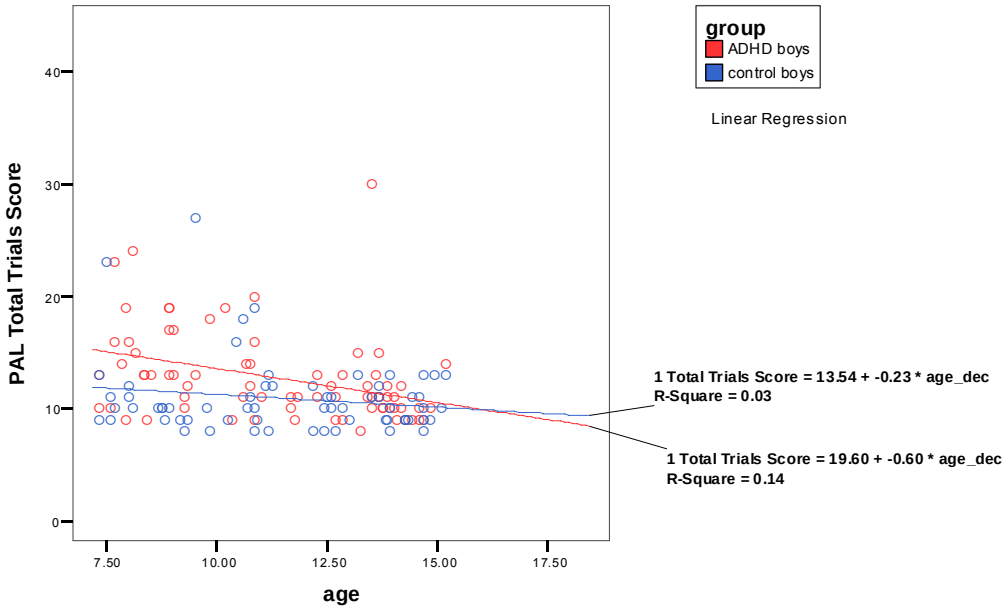
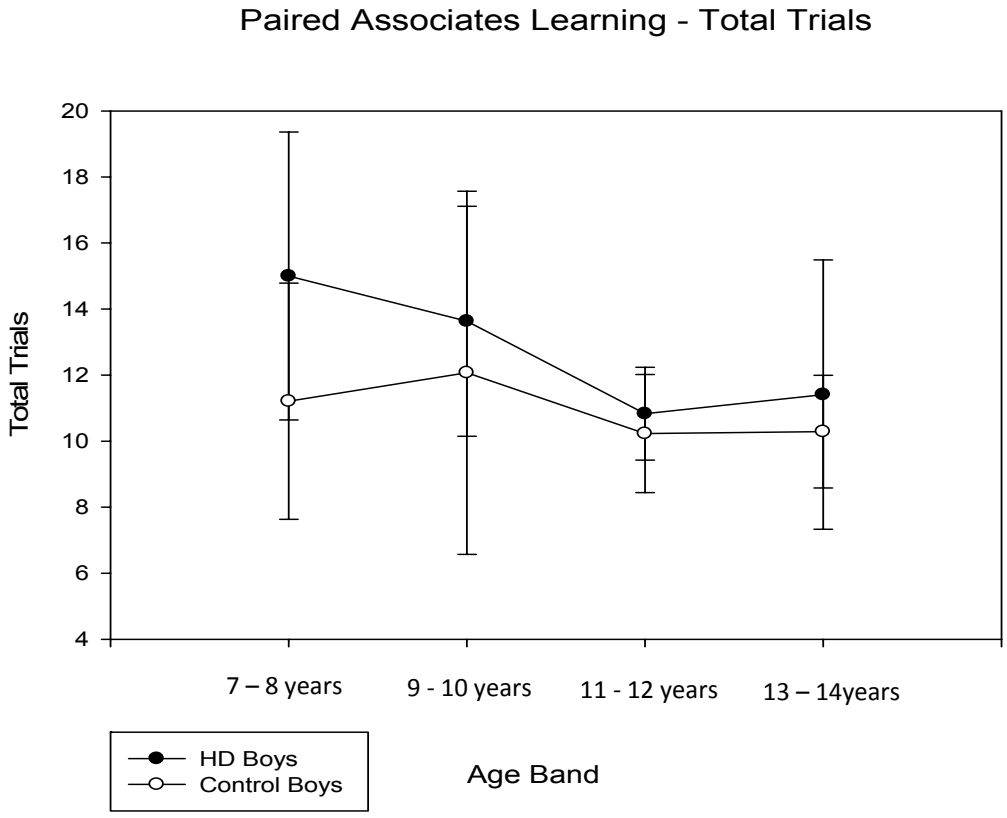


Figure7.17: Development of Paired Associates Learning - Total Trials (means with standard deviation) in drug naïve boys with hyperkinetic disorder (n = 74) and healthy Controls (n 69) aged between 7 and 14 years.



Total Errors

Curve estimation for Paired Associates Learning total errors identified that none of the curves fitted for the Control boys. Observation of the scatter plot suggests that this was due to a floor effect with boys of all ages performing very well on the task (fig 7.18) for the HKD boys the linear solution was the best fit for the data [r^2 = .18, F (1,69)=16.2, p<.001].

Univariate ANOVA on Paired Associates Learning total errors revealed a significant effect of AGE BAND [F(3,134) = 6.2, p<.001] but not GROUP and no interaction between AGE x GROUP. Pairwise comparisons revealed improved performance with increased age with significant differences between each age-band (except between 7 - 8 year and 9 - 10 year olds and between 11 – 12 and 13 – 14 year olds). The development of Paired Associates Learning (total errors) is shown in Figure 7.19.

Figure 7.18: Scatterplot and regression lines for Paired Associates Learning - Total Errors, in drug naïve boys with hyperkinetic disorder (n = 74) and healthy Controls (n = 69) aged between 7 and 14 years.

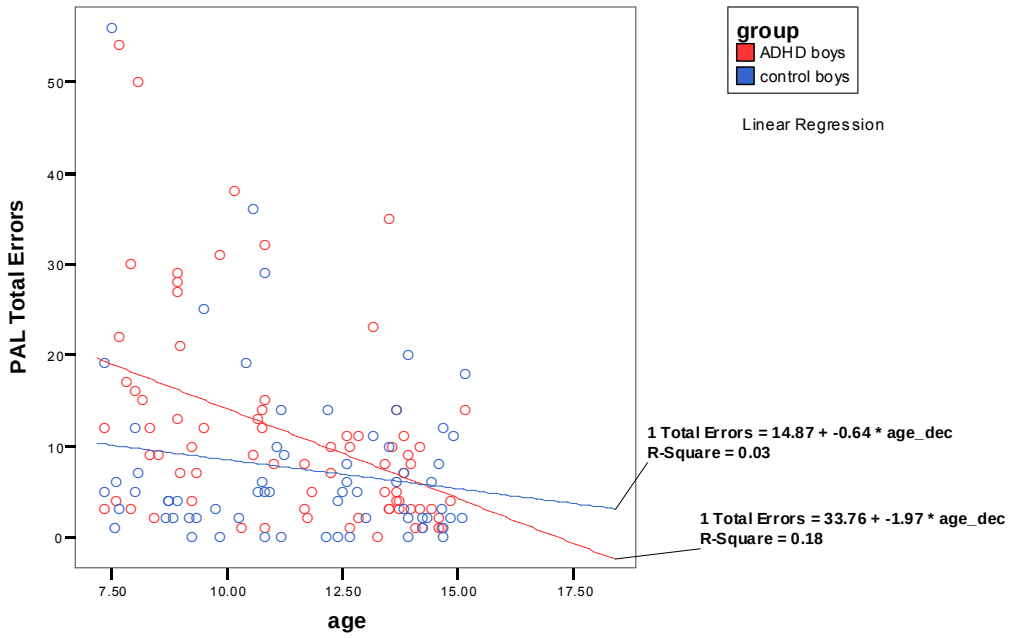
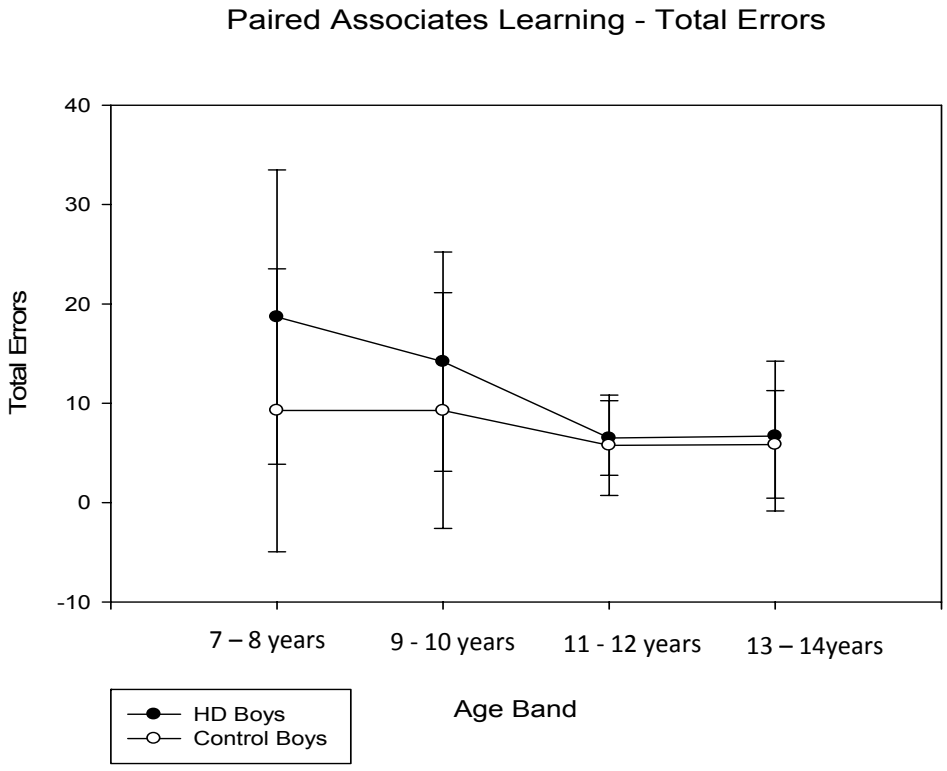


Figure 7.19: Development of Paired Associates Learning – Total Errors (means with standard deviation) in drug naïve boys with hyperkinetic disorder (n = 74) and healthy Controls (n = 69) aged between 7 and 14 years.



Intra-Dimensional/Extra-Dimensional Set-shifting

Curve estimation for Intra-dimensional/Extra-dimensional Set-shifting stage reached identified the linear solution as the best fit for both Controls [r^2 = .18, F (1,69)=14.9, p<.001] and HKD boys [r^2 = .11, F (1,69)=9.2, p<.005]. Univariate ANOVA revealed a significant effect of AGE BAND [F(3,134) = 7.2, p<.001] but not GROUP and no interaction between AGE x GROUP. Pairwise comparisons revealed improved performance with increased age with significant differences between each age-band (except between the 7 - 8 year and the 11 – 12 year olds and between the 9 – 10 year olds and the 11 – 12 year olds). The development of Intra-dimensional/Extra-dimensional Set-shifting stage reached is shown in Figure 7.20.

Curve estimation for Intra-dimensional/Extra-dimensional Set-shifting errors at ED shift identified the linear solution as the best fit for both Controls [r^2 = .12, F (1,69)=9.7, p<.001] and HKD boys [r^2 = .09, F (1,69)=7.0, p<.01]. Univariate ANOVA revealed a significant effect of AGE BAND [F(3,134) = 6.9, p<.001] but not GROUP and no interaction between AGE x GROUP. Pairwise comparisons revealed improved performance with increased age with significant differences between each age-band (except between the 7 - 8 year and the 11 – 12 year olds and between the 9 – 10 year olds and the 11 – 12 year olds). The development of Intra-dimensional/Extra-dimensional Set-shifting errors at ED shift is shown in Figure 7.21.

Figure 7.20: The development of Intra-dimensional/Extra-dimensional Set-shifting – Stage Reached (means with standard deviation) in drug naïve boys with hyperkinetic disorder (n = 74) and healthy Controls (n = 69) aged between 7 and 14 years.

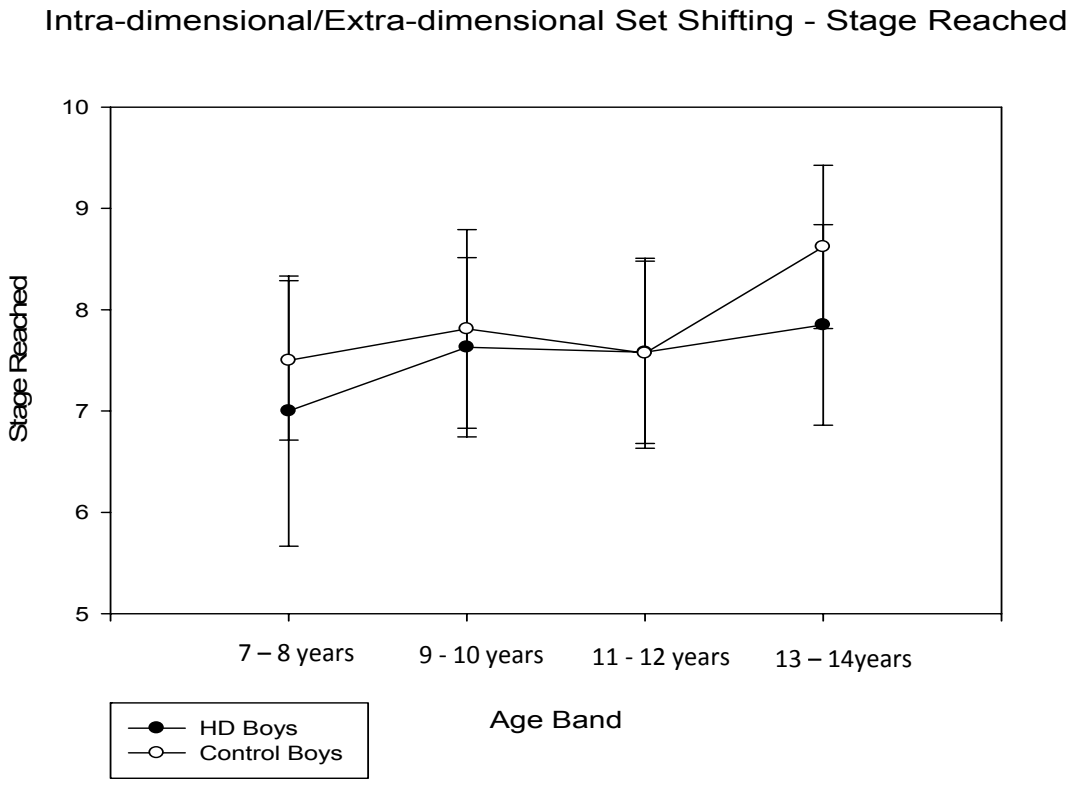
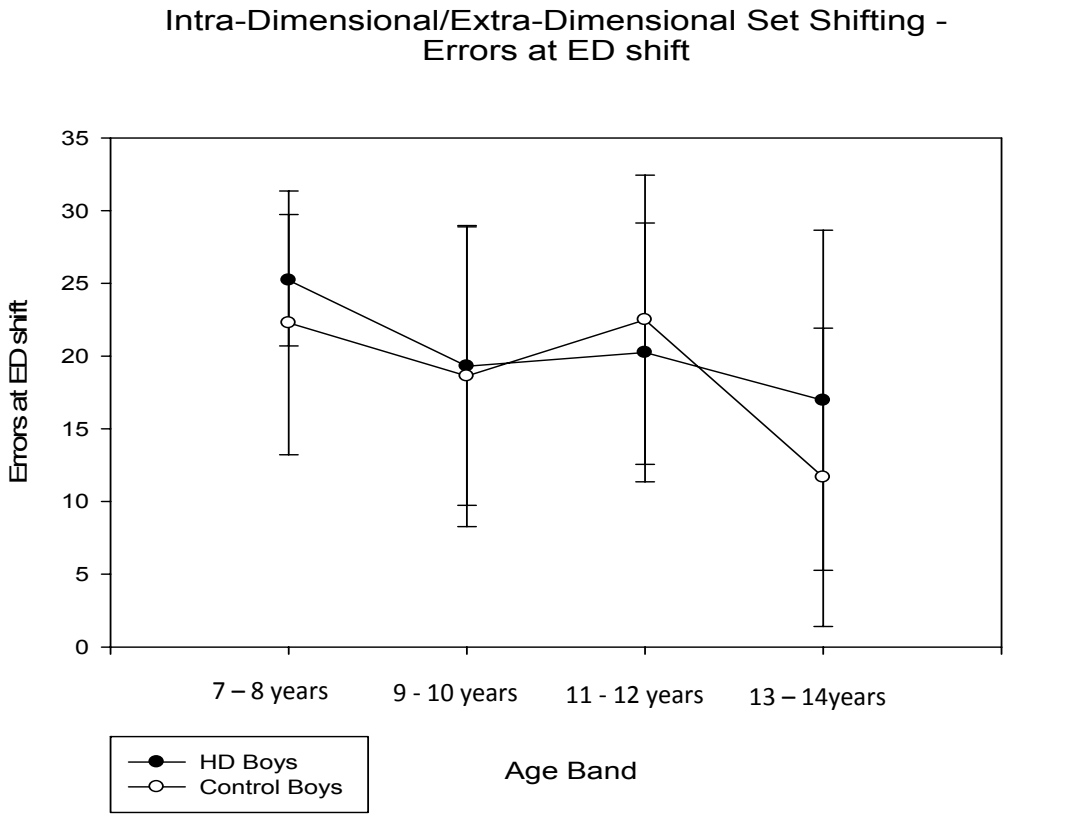


Figure 7.21: The development of Intra-dimensional/Extra-dimensional Set-shifting – Errors at ED Shift, in drug naïve boys with hyperkinetic disorder (n = 74) and healthy Controls (n = 69) aged between 7 and 14 years.



Reaction Time

Curve estimation for both simple and 5-choice Reaction time identified the linear solution as the best fit for both Controls (simple [r^2 = .23, F (1,69)=19.3, p<.001], 5-choice [r^2 = .31, F (1,69)=29.8, p<.001]) and HKD boys (simple [r^2 = .10, F (1,69)=7.8, p<.01], 5-choice [r^2 = .15, F (1,69)=12.0, p<.001]). Repeated-measures ANOVA on Reaction Time revealed a significant effect of AGE BAND [F(3,134) = 9.1, p<.001] with pairwise comparisons demonstrating shorter reaction times with increasing age and significant differences between each age-band (except between the 9 – 10 year and the 11 – 12 year olds, 9 – 10 year and 13 - 14 year olds and between the 11 – 12 and the 13 – 14 year olds). There was also a significant effect of GROUP [F(1,134) = 6.1, p<.05]with shorter reaction times for Control boys than for HKD boys. There were no interactions between AGE BAND x GROUP. There was no main effect of DIFFICULTY and no interactions between DIFFICULTY x GROUP, AGE BAND x DIFFICULTY or AGE BAND x GROUP x DIFICULTY. The development of Reaction Time is shown in figures 7.22, 7.23, & 7.24.

Figure 7.22: Development of Simple Reaction Time (means with standard deviation) in drug naïve boys with hyperkinetic disorder (n = 74) and healthy Controls (n = 69) aged between 7 and 14 years.

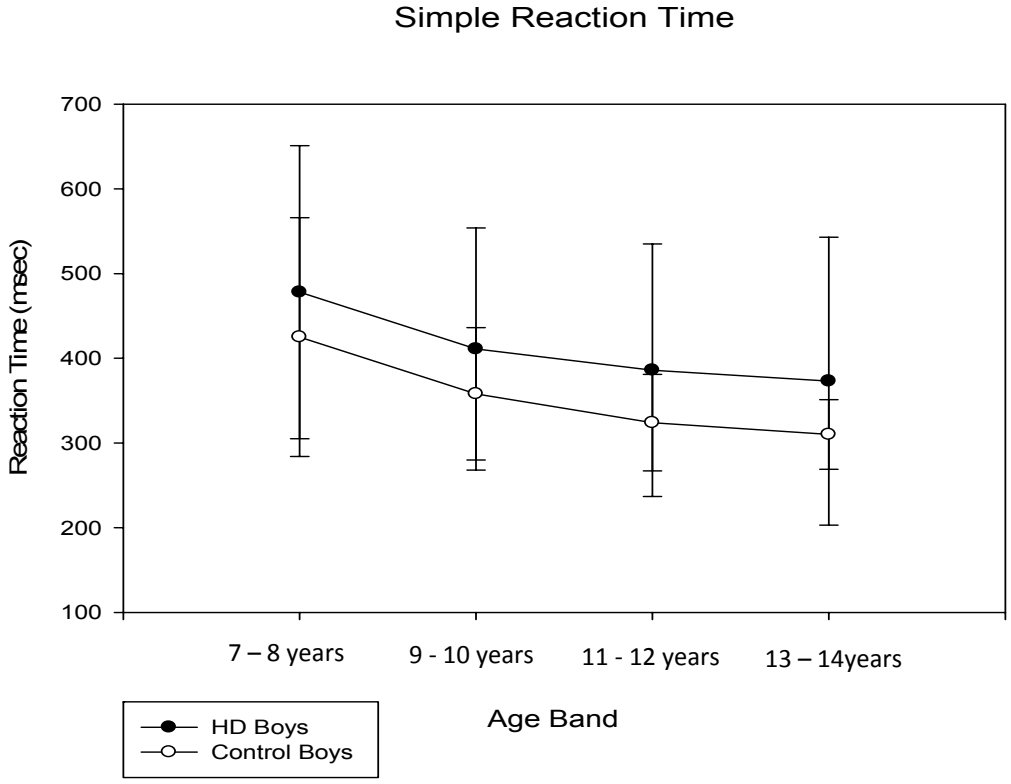


Figure 7.23: Development of 5-Choice Reaction Time (means with standard deviation) in drug naïve boys with hyperkinetic disorder (n = 74) and healthy Controls (n = 69) aged between 7 and 14 years.

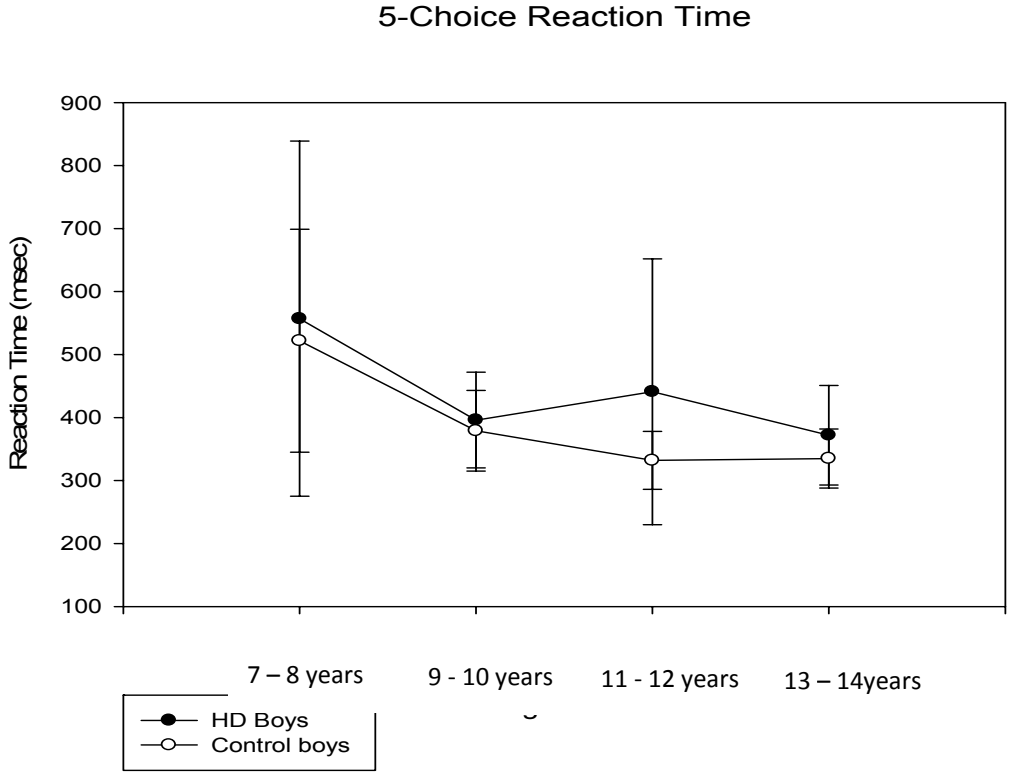
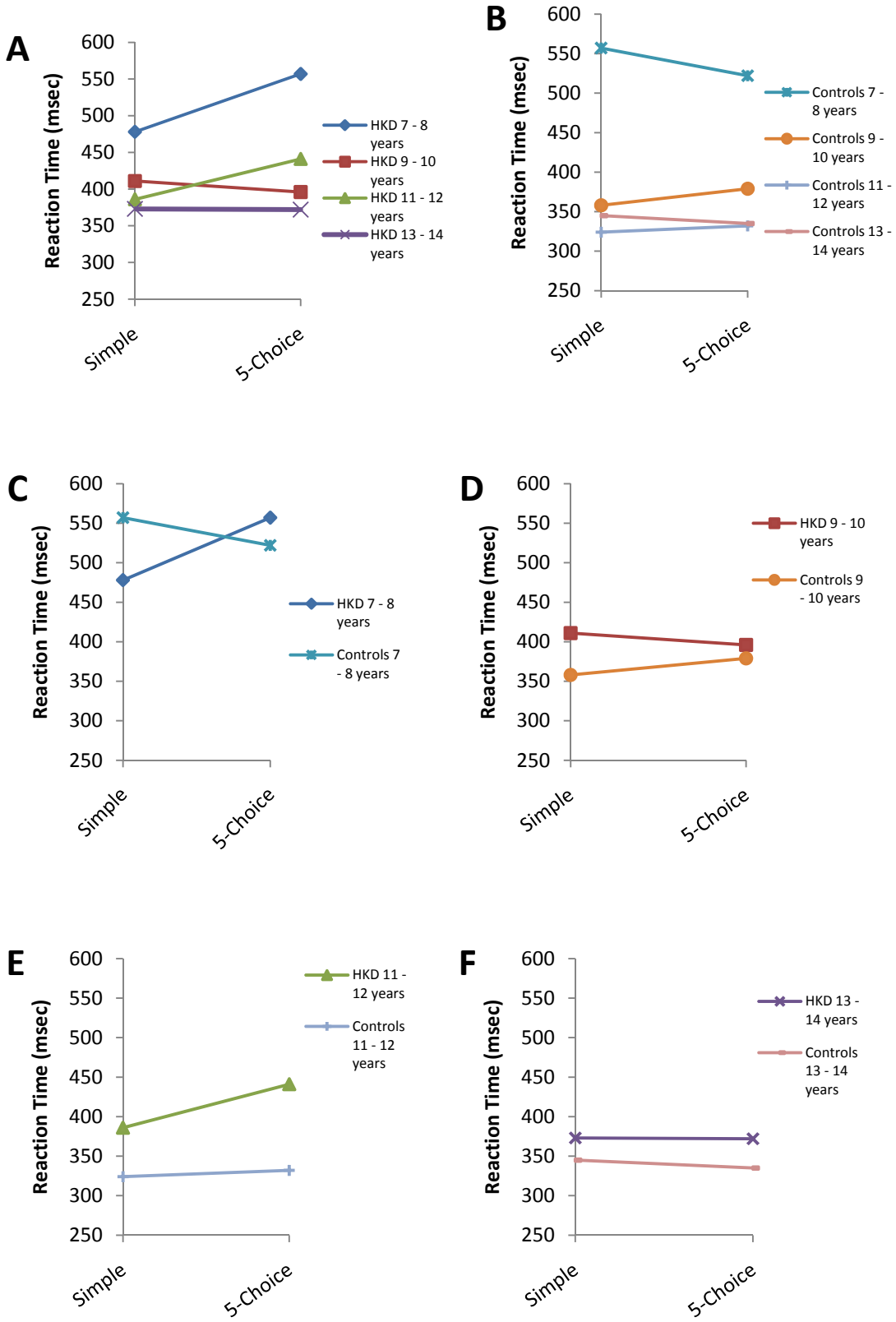


Figure 7.24: Interactions between difficulty and age in the development of Simple and 5-Choice Reaction time, in (A) Drug naïve boys with hyperkinetic disorder (n = 74) and (B) healthy Controls (n = 69) aged between 7 and 14 years, and interactions between difficulty and age and between difficulty and diagnostic status split by age for the same task in the same groups. (C) boys aged 7 – 8 years (D) boys aged 9 – 10 years (E) boys aged 11 – 12 years (F) boys aged 13 – 14 years.



Discussion

The Neuropsychological development of healthy children between the ages of 7 and 14 years.

The data presented here on the development of neuropsychological functioning in the healthy boys in the present study supports the hypothesis that the timing and rate of development differs between different aspects of neuropsychological functioning. It also provides partial support for non-executive memory developing earlier than executive functioning.

There was evidence that performance continues to develop between the ages of 7 and 14 years across many, but not all, of the neuropsychological tasks included in this study. No developmental effects were found for performance on two memory tasks with low executive demands, Spatial and Pattern Recognition. Clear developmental effects of age were, however, found for several of the other low executive demand tasks; Spatial Span, Delayed Matching to Sample, Paired Associates Learning and reaction times on both the Reaction Time task and the Go/NoGo task. Developmental effects were also found for high executive demand tasks across several domains of functioning; inhibition (Go/NoGo), working memory (Spatial Working Memory), planning and strategy (Stockings of Cambridge, Spatial Working Memory) and attentional set-shifting (Intradimensional/Extradimensional Set-shifting). On two of these tasks that have both a high executive demand and increasing levels of difficulty (Spatial Working Memory and Stockings of Cambridge) the developmental trends in improvement were only demonstrated at the more difficult levels with even the youngest children performing as well as the older children on the easier levels. Interestingly, for two other tasks (Delayed Matching to Sample, Reaction Time) there was no interaction between age and difficulty with younger children performing less well than older children even at the simpler levels.

These findings are in broad agreement with those published by Luciana & Nelson (Luciana & Nelson 1998), Luciana et al (2005) and De Luca et al (2003) and extend these findings by including the performance of both children and adolescents across a broader set of tasks. The only notable difference from these studies was the present finding of improved performance with increasing age on the Intradimensional/Extradimensional Set-shifting task, which does not replicate the finding of De Luca et al (2003) who reported no changes in task performance between the ages of 8 – 14 years (or between 8 and 64 years). Visual inspection of the graphs of several tasks and the results of the pairwise comparisons of the performance of children from different age bands suggests the possibility that performance on some tasks may reach mature levels before age 14 years. For example, reaction time to targets on the Go/NoGo task and Spatial Span do not improve further beyond the 11 – 12 year old group. Unfortunately this study was insufficiently powered to specifically address these issues and it is therefore possible that, had a larger sample been studied, further improvements could have been seen on some tasks.

As noted above, the performance of the healthy children on the Spatial and Pattern Recognition tasks did not improve as the boys got older. Although the boys' performance on these tasks was reasonably good, on both tasks it remained somewhat below the levels for healthy young adults that are reported by the makers of the CANTAB battery (mean performance [% correct] of 7 – 8 yr olds on Spatial Recognition was 64.2 (SD 13.6) compared with a mean score of 85.3 (SD 9.3) for adults aged 24 – 39 and for Pattern Recognition mean performance of the 7 – 8 yr olds was 79.9 (SD 15.6) compared with a mean score of 89.4 (SD 10.8) for adults aged 24 – 39 – normative data; personal communication Cambridge Cognition Ltd.). These findings mirror those reported by Luciana et al (2005). It is therefore not clear whether recognition memory improves at some point between 14 and 24 years or whether there are important but unknown differences

between the population included in this study and those used by Cambridge Cognition to calculate their normative data. For example, it may be the case that the performance of the children in our sample has already reached adult levels for the population from which they were drawn (urban with relatively high levels of deprivation), with this population having poorer performance than the sample used to generate the norms.

Comparison of neuropsychological development between children and adolescents with and without HKD

These data also provide general support for the hypothesis that children with HKD demonstrate similar patterns of neuropsychological development to that seen in healthy children but that their development is generally delayed. One of the most important findings of this analysis is that there was no statistical support for there being any GROUP x AGE-BAND interactions for any of the tasks studied. Whilst the study was neither specifically designed nor statistically powered to detect such differences, a visual inspection of the data suggests that for almost all tasks, the neuropsychological development of those with HKD runs parallel to that of healthy children and adolescents. The one task for which inspection of the data suggest a potential interaction is Paired Associates Learning (total trials and total errors) on which there appears to be a separation between the HKD and Control boys at age 7 – 8 years with HKD boys performing less well at this age, followed by a convergence by the age of 11 – 12 years. This is not supported statistically (GROUP x AGE-BAND; total trials [$F(3,134) = 1.4$, $p=.24$], total errors [$F(3,134) = 1.7$, $p<.18$] but cannot be completely excluded due to the aforementioned issues of statistical power.

Although the developmental trends for boys with HKD mirror those seen in healthy children, there is support for a developmental delay in HKD boys on several tasks (Spatial Span, Spatial Working Memory – between-search errors and strategy score, Delayed

Matching to Sample and Reaction time). On these tasks, the performance of boys with HKD continually lagged behind that of the healthy boys. On two further tasks, (Spatial Recognition, Pattern Recognition) the boys with HKD also performed less well than the healthy boys, but as there was no evidence of a developmental trend for these tasks across the age-bands included in these studies, it would be inaccurate to label this as a developmental delay. For the other tasks (Go/NoGo – reaction time to targets and errors to distracters, Stockings of Cambridge, Paired Associates Learning and Intradimensional/Extradimensional Set-shifting) there were no statistically significant differences between the two groups on this analysis (although see above for discussion of Paired Associates Learning data).

Taken together, these results suggest that across those tasks on which the boys with HKD performed less well than healthy boys, performance deficits remain stable between the ages of 7 and 14 years and that within this age range there is *no evidence* that the boys with HKD "catch up" with their healthy counterparts. Paired Associates Learning may be an exception but further study with larger groups is required. Further, on those tasks where there is no deficit, the development of neuropsychological functioning progresses at the same rate in both HKD and healthy boys.

These results therefore suggest that it is unlikely that differential patterns of neuropsychological development are responsible for the heterogeneity found within this group of boys with HKD. As there are no other published datasets to compare these findings with, it is currently not possible to comment on their generalisability, and replication in larger and independent samples is essential.

With respect to the generalisability of these data several issues relating to study design need to be considered. First, the study was cross sectional in design and it is therefore only possible to comment on the development of neuropsychological functioning across, but

not within, individuals. Whilst many children with AD-HKD continue to have problems in adolescence and into adulthood, a proportion seem to "grow out" of their AD-HKD as they mature. All of the HKD boys in this study met criteria for HKD at the time of testing and the data for the older boys is therefore relevant to those whose HKD has persisted into adolescence. It is possible that, if we followed up the younger boys over time and directly measured their neuropsychological development, we would find that some of these boys would "grow out" of their problem behaviours and / or catch up with the healthy children with respect to their neuropsychological performance. Indeed, this was the situation reported in the longitudinal study of the clinical and neuropsychological of a group of "hard to manage" children conducted by Brophy, Taylor and Hughes (2002). On the other hand, as all of the HKD boys included in the present study presented with continuing symptoms and impairment that was sufficient to warrant a diagnosis of HKD, it may be safe to conclude that age differences do not seem to be sufficient to account for the neuropsychological heterogeneity reported within samples of children who currently meet diagnostic criteria. Longitudinal studies of neuropsychological development in healthy and ADHKD children are required to fully answer this question.

Second, as only boys were included it is not possible to say whether or not these results would generalise to girls.

Finally, all of the AD-HKD boys included in this study met criteria for the more restrictive diagnosis of ICD-10 defined HKD and it is not possible to say whether these results will generalise to those with the broader DSM-IV diagnosis of ADHD. For other aspects of the data analysis the inclusion of only those boys with HKD can be regarded as a relative strength – if similar patterns of heterogeneity are found in this potentially more homogeneous group as have been previously reported in those with the broader ADHD phenotype, then heterogeneity can be assumed to be a core component of the AD-HKD

phenotype. However, for this analysis the opposite is true and the finding of similarities in the trajectories of neuropsychological development between healthy boys and those with HKD does not imply that the same is likely to be true for those with the broader ADHD phenotype. However, as the patterns of neuropsychological heterogeneity appear to be very similar in both HKD and ADHD, it would seem relatively unlikely that in one case this heterogeneity would be due to developmental differences whilst in the other it would not.

Summary and Conclusions

These data suggest that different aspects of neuropsychological performance develop at different rates and times. However, the neuropsychological performance of boys with ongoing HKD follows a similar pattern to that of healthy boys but with delayed development on certain tasks. Whilst it is possible that some boys with HKD will, if followed up over time, "grow out" of their HKD and/or the associated neuropsychological deficits, the evidence presented here suggests that, for many tasks where boys with HKD have deficits compared with healthy boys, boys with HKD and ongoing symptoms and impairment will not "catch up" with healthy boys. These findings therefore suggest that differential patterns of development are unlikely to account for either within or between group heterogeneity in neuropsychological functioning.

Chapter 8

Does Comorbidity with Either Oppositional Defiant Disorder or Conduct Disorder Impact on the Neuropsychological Heterogeneity of Hyperkinetic Disorder?

Background

Comorbidity with other types of psychiatric and non-psychiatric problems represents an important potential source of clinical and neuropsychological heterogeneity in AD-HKD. Uncomplicated AD-HKD is rarely seen in a clinical setting, with over half of all children diagnosed with AD-HKD also meeting criteria for a comorbid psychiatric diagnosis and many children who would otherwise meet criteria for hyperkinetic disorder are only excluded from this diagnosis by virtue of meeting the criteria for hyperkinetic conduct disorder or for another psychiatric disorder (Biederman, Faraone, & Lapey 1992; Biederman, Newcorn, & Sprich 1991; Gillberg, Gillberg, Rasmussen, Kadesjo, Soderstrom, Rastam, Johnson, Rothenberger, & Niklasson 2004; Jensen, Martin, & Cantwell 1997; Sprich-Buckminster, Biederman, Milberger, Faraone, & Lehman 1993; Taylor, Dopfner, Sergeant, Asherson, Banaschewski, Buitelaar, Coghill, Danckaerts, Rothenberger, Sonuga-Barke, Steinhausen, & Zuddas 2004). Whilst these findings may in part be a consequence of Berkson's bias, increased rates of comorbidity have also been found in community samples (Anderson, Williams, McGee, & Silva 1987; Bird, Canino, Rubio-Stipec, Gould, Ribera, Sesman, Woodbury, Huertas-Goldman, Pagan, & Sanchez-Lacay 1988; Bird, Gould, & Staghezza 1993; Kadesjo & Gillberg 2001; Meltzer, Goodman, & Ford 2000).

The two most commonly diagnosed comorbid conditions are Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD), both of which co-occur with AD-HKD at a frequency

greater than would be predicted to occur by chance (Waschbusch 2002). The reported rates of ODD in all children with DSM-IV ADHD are between 50 and 60% with even higher rates being reported for those with combined type ADHD (Gillberg, Gillberg, Rasmussen, Kadesjo, Soderstrom, Rastam, Johnson, Rothenberger, & Niklasson 2004). The rates of coexisting CD are less well studied but appear to be around 14% (MTA Cooperative Group 1999). The essential features of ODD are *a recurrent pattern of negativistic, defiant, disobedient, and hostile behaviour towards authority figures, which leads to impairment* and those of CD are *a repetitive and persistent pattern of behaviour in which the basic rights of others and major age-appropriate societal norms or rules are violated* (American Psychiatric Association 1994). The symptom definitions for CD and ODD are identical for ICD-10 and DSM-IV and, whilst each system combines them in slightly different ways, the two diagnostic systems are very similar. This makes it easier to compare research data on CD and ODD than is the case for ADHD and HKD. The data presented in this chapter was collected using the ICD-10 criteria for ODD and CD, which are described in detail in figure 8.1.

Table 8.1: ICD-10 Diagnostic Criteria for Conduct Disorder and Oppositional Defiant Disorder (World Health Organisation 1993)

Symptoms

(1) Unusually frequent or severe temper tantrums for the child's developmental level.
(2) Often argues with adults.
(3) Often actively defies or refuses adults' requests or rules.
(4) Often, apparently deliberately, does things that annoy other people.
(5) Often blames others for one's own mistakes or misbehaviour.
(6) Often touchy or easily annoyed by others.
(7) Often angry or resentful.
(8) Often spiteful or vindictive.
(9) Frequent and marked lying (except to avoid abusive treatment).
(10) Excessive fighting with other children, with frequent initiation of fights (not including fights with siblings).
(11) Uses a weapon that can cause serious physical harm to others (e.g. a bat, brick, broken bottle, knife, gun).
(12) Often stays out after dark without permission (beginning before 13 years of age).
(13) Physical cruelty to other people (e.g. ties up, cuts or burns a victim).
(14) Physical cruelty to animals.
(15) Deliberate destruction of others' property (other than by fire-setting).
(16) Deliberate fire-setting with a risk or intention of causing serious damage.
(17) At least two episodes of stealing of objects of value (e.g. money) from home (excluding taking of food).
(18) At least two episodes of stealing outside the home without confrontation with the victim (e.g. shoplifting, burglary or forgery).
(19) Frequent truancy from school beginning before 13 years of age.
(20) Running away from home (unless this was to avoid physical or sexual abuse).
(21) Any episode of crime involving confrontation with a victim (including purse snatching, extortion, mugging).
(22) Forcing another person into sexual activity against their wishes.
(23) Frequent bullying of others (i.e. deliberate infliction of pain or hurt including persistent intimidation, tormenting, or molestation).
(24) Breaks into someone else's house, building or car.

Conduct Disorder requires

The Presence of three or more symptoms from those listed above, of which at least three must be from items 9 – 24
At least one of the symptoms from items 9 - 24 must have been present for at least six months

Oppositional defiant disorder requires

The presence of four or more symptoms from those listed above, of which no more than two from items 9 – 24
These symptoms must be maladaptive and inconsistent with the developmental level
At least four of the symptoms must have been present for at least 6 months

Both CD and ODD are relatively common conditions within community settings. Prevalence rates vary between 1 and 16% depending on the age of the sample, methods of assessment and the diagnostic criteria used (Loeber et al. 2000). For 5 to 10 year olds approximately 4.8% of boys and 2.1% of girls meet criteria for ODD and 1.7% of boys and 0.6% of girls meet criteria for CD. Prevalence is higher in lower socioeconomic groups and the differences between urban and rural rates of ODD/CD disappear once the degree of socioeconomic deprivation has been taken into account. There is a high degree of overlap between ODD and CD in terms of epidemiology (Maughan et al. 2004a) and shared risk factors such as low socioeconomic status, parental antisocial personality disorder, harsh and critical parenting, low baseline levels of arousal, deficient social information processing, and AD-HKD (Dodge 1991; Faraone et al. 1991; Frick et al. 1992; Lahey et al. 1992; Lahey et al. 2000; Patterson 1982; Raine 2002; Schachar & Wachsmuth 1990; Whittinger et al. 2007), and it is proposed that these may, to a large degree, reflect a common genetic underpinning (Eaves et al. 2000).

Most children with CD also meet criteria for ODD and, indeed, ODD is regarded by some authors as a milder version of CD (Eaves, Rutter, Silberg, Shillady, Maes, & Pickles 2000; Schachar & Wachsmuth 1990) and often as the primary precursor of CD (Lahey, Schwab-Stone, Goodman, Waldman, Canino, Rathouz, Miller, Dennis, Bird, & Jensen 2000; Rowe et al. 2002). Many children with ODD will not, however, go on to develop CD and the majority of the research to date supports them continuing to be seen as distinct disorders (Lahey, Loeber, Quay, Frick, & Grimm 1992; Loeber, Burke, Lahey, Winters, & Zera 2000; Rowe, Maughan, Pickles, Costello, & Angold 2002). Although there are major shifts in the types of disruptive behaviours displayed at different stages in development, it is generally the case that there is a degree of continuity with the most disruptive children at one age also being the most disruptive at a later age (Farrington 1997).

Moffitt (1993) proposed a dual taxonomy, which describes two types of CD: a less common type, which appears early in the pre-adolescent period and is associated with *life-course persistent* antisocial behaviours and the other more common *adolescent limited* type, which appears later and is associated with antisocial behaviours that both start and finish during adolescence. The validity of these two groups has been supported by a consensus of research findings (Tolan & Thomas 1995) and was confirmed by Lahey et al. (1998a) in two large studies, although there is evidence to suggest that the distinction is less clear for girls than it is for boys (Zoccolillo 1993).

As the heritability of adult criminality is much higher than that of juvenile delinquency, it has been proposed that it would be expected that child CD samples will have a higher heritability than those containing adolescents, as the child samples will contain a higher proportion of those who will go on to have life persistent subtype than the adolescent samples, in which the adolescent onset subtype should predominate (Pennington 2002). Consistent with this, Nadder et al (1998) found a heritability for the combined diagnoses of CD and ODD of 0.65 for boys and of 0.53 for girls. These are considerably higher than the heritabilites quoted for juvenile delinquency in the review of DiLalla and Gottesman (1989) where the differences between MZ (87%) and DZ (72%) twins were small and suggested a fairly large shared environment effect. Eley, Lichtenstein and Stevenson (1999) examined age and gender effects on the heritability of aggression and delinquency and found delinquency to be considerably less heritable (h^2; males .47, females .00) than aggression (h^2; males .69, females .70), and delinquency to be considerably more heritable in children (h^2 = .36) than adolescents (h^2 = .12). It therefore appears that although a few studies that have found the opposite pattern (Silberg et al. 1996), overall the data is broadly supportive of Moffit's (1993) theory.

The relationships between CD, ODD and AD-HKD are important not only because the comorbidity of both CD and ODD with AD-HKD is so common, but also because this co-occurrence has significant negative impact on severity, course and outcome. Evidence suggests that AD-HKD with comorbid CD is severe and persistent with more adverse outcomes than either disorder alone (Hinshaw, Lahey, & Hart 1993; Jensen, Martin, & Cantwell 1997; Kuhne, Schachar, & Tannock 1997). These negative effects have been reviewed on several occasions (e.g. Jensen, Martin, & Cantwell 1997; Loeber, Burke, Lahey, Winters, & Zera 2000; Satterfield & Schell 1997; Thapar et al. 2006; Whittinger, Langley, Fowler, Thomas, & Thapar 2007) and include; increased levels of aggression and more increased and serious delinquency (Kuhne, Schachar, & Tannock 1997; Loney et al. 1981; Waschbusch et al. 2002), worse academic achievement (Faraone, Biederman, Keenan, & Tsuang 1991), poor social adjustment (August, Stewart, & Holmes 1983; Barkley, Fischer, Edelbrock, & Smallish 1990a), low self esteem (Kuhne, Schachar, & Tannock 1997), increased rates of antisocial personality disorder (Fischer, Barkley, Smallish, & Fletcher 2002), substance abuse (Disney, Elkins, McGue, & Iacono 1999) and other psychiatric disorders (Fischer et al. 1990). Many studies have found that AD-HKD in childhood is predictive of later antisocial behaviours (Taylor, Chadwick, Heptinstall, & Danckaerts 1996). One of the most consistent findings is that boys with AD-HKD and comorbid CD have an earlier age of onset of disruptive behaviours than those with CD alone (Moffitt 1990), and there is a much stronger association between AD-HKD and early onset, and therefore *life-course persistent* CD than between AD-HKD and *adolescent limited* CD (Fergusson, Horwood, & Lynskey 1994; Lahey, Schwab-Stone, Goodman, Waldman, Canino, Rathouz, Miller, Dennis, Bird, & Jensen 2000; Lahey et al. 2005; Satterfield & Schell 1997).

Thapar et al. (2006) reviewed the predictors of antisocial behaviour in children with AD-HKD. Whilst they concluded that relatively little is known about which risk factors and

mechanisms contribute to the link between these disorders, they do list a number of clinical, genetic and environmental factors, which are supported by at least some evidence.

Clinical Predictors

- AD-HKD symptoms; there is a dose response relationship between AD-HKD symptoms and antisocial behaviour (Fergusson, Lynskey, & Horwood 1997) and evidence that AD-HKD symptom severity predicts future antisocial outcomes (Taylor, Chadwick, Heptinstall, & Danckaerts 1996).

- Hyperactive-impulsive symptoms are more predictive of oppositionality than inattentive symptoms (Burns & Walsh 2002).

- Pervasive AD-HKD (home and school) is more predictive of ODD than non-pervasive AD-HKD (Mannuzza, Klein, & Moulton, III 2002; McArdle, O'Brien, & Kolvin 1995).

- As noted above AD-HKD, is more strongly related with childhood than adolescent onset disruptive behaviour and AD-HKD is predictive of persistent difficulties (Farrington, Loeber, & Van Kammen 1990; Moffitt 1990).

- Similarly, the presence of cognitive deficits are more strongly associated with life-course persistent CD than the adolescent limited type (Caspi & Moffitt 1995; Raine et al. 2005) although it is less certain whether this relates to a lower general cognitive ability (Frazier, Demaree, & Youngstrom 2004) or specific deficits of either executive or non-executive neuropsychological functioning (Huang-Pollock & Nigg 2003; Moffitt 1990; Raine 2002; Raine, Moffitt, Caspi, Loeber, Stouthamer-Loeber, & Lynam 2005). The cognitive correlates of AD-HKD, ODD and CD will be discussed in more detail below.

- Anxiety and dysthymic disorder may have a protective effect on the development of CD in children with AD-HKD (Sanders et al. 2005)

- Both AD-HKD and CD have been associated with higher novelty seeking, and disinhibition and although specific evidence is scant, these factors could account for the increased association between the two disorders (Hirshfeld-Becker et al. 2002; Ruchkin, Eisemann, & Cloninger 1998; Tillman et al. 2003)

Genetic contributions

- Attention deficit that is associated with antisocial behaviour is more strongly familial (Faraone, Biederman, & Monuteaux 2000) and more heritable (Thapar, Harrington, & McGuffin 2001) than pure AD-HKD.

- Twin studies suggest that AD-HKD and antisocial behaviours are, at least in part, accounted for by common genetic factors (Nadder et al. 2002; Silberg, Rutter, Meyer, Maes, Hewitt, Simonoff, Pickles, Loeber, & Eaves 1996; Thapar, Harrington, & McGuffin 2001). One study also found shared environmental risk factors (Burt et al. 2003).

- One study has supported the notion that self reported executive functioning deficits also share common genetic factors with AD-HKD , CD and ODD (Coolidge, Thede, & Young 2000).

- Several genes have been implicated in these processes;

    - A combined analysis of samples from Eire and the UK found evidence to support the association of the DRD4 7 repeat allele and antisocial behaviour in children with AD-HKD (Holmes, Payton, Barrett, Harrington, McGuffin, Owen, Ollier, Worthington, Gill, Kirley, Hawi, Fitzgerald,

Asherson, Curran, Mill, Gould, Taylor, Kent, Craddock, & Thapar 2002), and a separate study also reported an association with this same allele in those with AD-HKD and ODD (Kirley, Lowe, Mullins, McCarron, Daly, Waldman, Fitzgerald, Gill, & Hawi 2004).

- Recent studies have supported genetic heterogeneity with respect to children with AD-HKD with and without antisocial behaviours and a link between early onset antisocial behaviours and the $Val^{158}Met$ polymorphism of the catechol 0-methyltransferase gene (COMT), which was specific to children with AD-HKD (Caspi et al. 2008; Thapar et al. 2005).

- Although these authors speculate that the COMT polymorphism may impact via effects on cognition and have suggested that this COMT polymorphism can impact on executive functioning (Barnett et al. 2007b; Barnett et al. 2007a), studies in children with AD-HKD (Mills et al. 2004; Taerk et al. 2004) and other populations (Barnett, Scoriels, & Munafo 2008) do not support such an association.

- There has been longstanding interest in the potential role of serotonergic neurotransmission as a potential causal factor for both impulsivity and aggression (Mitsis, Halperin, & Newcorn 2000). Although there is some evidence linking functional variants of the serotonin transporter gene with both AD-HKD and antisocial behaviour (Beitchman et al. 2003; Retz et al. 2004), the evidence linking serotonergic neurotransmission is inconsistent.

Environmental risk factors

- An increased risk of CD has been found for those AD-HKD children whose mothers smoked cigarettes during pregnancy (odds ratio= 3.14). This odds ratio was

increased > 5 for those children from a lower social class whose mothers smoked during pregnancy (Langley et al. 2007). It must be noted, however, that these associations do not necessarily reflect a causal pathway as it is also possible that they are mediated either by genetic or other environmental factors (Maughan et al. 2004b; Silberg, Parr, Neale, Rutter, Angold, & Eaves 2003).

- There is less consistent evidence to support an association between antenatal use of other substances (e.g. alcohol or illicit drugs) and the development of CD in those with AD-HKD (Linnet, Dalsgaard, Obel, Wisborg, Henriksen, Rodriguez, Kotimaa, Moilanen, Thomsen, Olsen, & Jarvelin 2003; Raine 2002).

- There is, however, some evidence to support an association between maternal anxiety and antisocial behaviour and AD-HKD in their children (O'Connor et al. 2003; Van den Bergh & Marcoen 2004).

- Family factors such as increased levels of family conflict (Biederman et al. 2001; Burt, Krueger, McGue, & Iacono 2003), decreased family cohesion (Biederman, Mick, Faraone, & Burback 2001) and poor quality of parenting (Barkley et al. 1991) also increase the risk of CD and ODD. In particular, hostile critical parenting is associated with persistence of ODD in AD-HKD (August et al. 1999).

- Peer rejection has also been suggested as a partial mediator of the relationship between early AD-HKD symptoms and antisocial behaviours (Miller-Johnson et al. 2002).

Gene-environment interplay

- Behaviour genetic studies of antisocial behaviour have suggested that gene-environment interplay may be an important factor (Simonoff 2001), with evidence that the effects of environmental factors are increased in those with increased

genetic risk (G x E interactions) (Cadoret et al. 1990; Cadoret et al. 1995) and that part of the effects of genes on antisocial behaviour is through (G)(E) correlations, with these genes resulting in negative environmental conditions (Ge et al. 1996; O'Connor et al. 1998).

- At a molecular genetics level, the effects of childhood maltreatment on the development of later antisocial behaviours have been demonstrated to vary depending on the presence or absence of an allelic variant of the MAO A gene (Caspi et al. 2002a).

- Only one study has reported the effects of gene-environment interplay between AD-HKD and antisocial behaviour. Thapar et al. (2005) reported an interaction between birth weight and a Val/Met variant of the COMT gene whereby in an AD-HKD sample the presence of the COMT variant increased the impact of low birth weight on antisocial behaviour.

The neuropsychology of AD-HKD, ODD and CD

Neuropsychological correlates have been consistently reported for psychopathy (Blair et al. 2006) and life-course-persistent CD (Moffitt & Lynam, Jr. 1994; Pennington & Ozonoff 1996; Willcutt, Sonuga-Barke, Nigg, & Sergeant 2008).

Psychopathy is a separate but overlapping concept to CD in children and adolescents and antisocial personality disorders in adults. About 25% of those with CD show psychopathic tendencies (Blair, Peschardt, Budhani, Mitchell, & Pine 2006). Several types of neuropsychological impairment have been described in psychopathic individuals. Whilst executive deficits linked to impulsivity have been described (Miller et al. 2003; Whiteside & Lynam 2001), the predicted difficulties with set-shifting have not (Mitchell et al. 2002).

According to Blair et al (2006) the two main forms of impairment to be associated with psychopathy are associated with amygdale functioning.

- Problems in forming stimulus-reinforcement associations. These are hypothesized to be linked to the specific forms of fear and empathy deficits seen in psychopaths and are thought to result in socialization problems.
- Impairments in altering stimulus-response associations as a function of contingency change. This is thought to act as a risk factor for frustration and to lead to increased reactive aggression.

Children with CD and adults with antisocial behaviours are also consistently found to score about 0.5 of a standard deviation lower than matched Controls on overall measures of intelligence (Caspi & Moffitt 1995; Heilbrun, Jr. & Heilbrun 1985). There appears to be some specificity to these deficits with verbal IQ usually being lower than performance IQ (Caspi & Moffitt 1995).

Both of these groups have also consistently been reported to have deficits in executive functioning (Caspi & Moffitt 1995; Morgan & Lilienfeld 2000; Pennington & Ozonoff 1996; Willcutt, Sonuga-Barke, Nigg, & Sergeant 2008). These deficits appear to be greater in children with early onset antisocial behaviour, who are on course for life course persistent difficulties, than they are for those with adolescent onset antisocial behaviours (Raine, Moffitt, Caspi, Loeber, Stouthamer-Loeber, & Lynam 2005). Hughes, Dunn and White (1998) found a group of hard-to-manage 4 year olds, selected for high levels of parental hyperactivity and/or conduct problems, to be impaired on measures of inhibitory control and working memory/planning (but not set-shifting) compared with a group of matched healthy Controls (Brophy, Taylor, & Hughes 2002). These same children showed continuing impairments in inhibitory control, but intact working memory/planning and set-shifting,

when retested , later aged 7 years. Extending these findings further down the age range, Hughes and Ensor (2006) found that for 2 year olds selected from a high risk population, harsh parenting and poor theory of mind skills and deficits in verbal ability, but not executive functioning measures, predicted variance of behaviour problems. By the ages of 3 and 4 years the pattern of these relationships had changed. Theory of mind and verbal abilities now showed non-specific associations with problematic behaviours whilst there was a strong and specific association between executive functioning difficulties and behaviour problems (Hughes & Ensor 2008). Executive functioning at age 3 years fully mediated the relationship between verbal ability at age 2 years and problem behaviours at 4 years even when problem behaviours at 2 years were controlled for (Hughes & Ensor 2008). Also, even though no relationship between early executive functioning and early problem behaviours had been demonstrated, early executive functioning deficits was significantly predictive of later problem behaviours, whilst early problem behaviours were only marginally predictive of later executive functioning deficits (Hughes & Ensor 2008). Unfortunately, as many of the children in these studies had significant impairments in both the hyperactivity and conduct, it is not possible to comment on the independent impact of these two problem domains.

Raine et al (2002) assessed the verbal and spatial abilities of a large group (n = 330) of children at both 3 and 11 years of age and also measured their antisocial behaviour at ages 8 and 17 years. Those children with persistent antisocial behaviour (n = 47) were found to have had spatial but not verbal deficits at age 3 years compared with a comparison group but both spatial and verbal deficits at age 11 years. The spatial deficits at age 3 years were independent of early hyperactivity, social adversity, poor test motivation, poor test comprehension, and social discomfort during testing, and were found in both females and males. These findings suggest that early spatial deficits may contribute to the development

of persistent antisocial behaviour whereas verbal deficits are more likely to be developmentally acquired. Raine et al. (2005) found that the group of children whose antisocial behaviour appeared to be limited to childhood and did not continue into adolescence demonstrated similar impairments to those seen in the life course persistent group on 3 of the 4 memory tasks (mean effect size; child limited 0.48, life course persistent 0.73), a dichotic listening task and several tasks measuring general intelligence.

In an early meta-analysis of six executive functioning tasks (Category Test of the Halstead-Reitan Neuropsychological Battery (HRNB), Q score on the Porteus Mazes Task, Stroop Interference Test, Part B of the Trail Making Test, perseverative error score on the Wisconsin Card Sorting Test (WCST) and Verbal Fluency Tests) Morgan and Lilienfield (2000) reported an overall effect size of 0.62 for children with CD and adults with antisocial behaviours compared with comparison groups. There was a significant variation between studies, which was dependent on the way that antisocial behaviour had been operationalised. The largest effect size was seen for the Porteus Mazes Q score, which was reported as being in the large (≥ 0.8) range. The effect sizes for the other tasks were in the small to medium range (between 0.2 and 0.8). The deficits were not restricted to executive functioning tasks with significant findings for several non executive functioning tests also being reported. Part A of the Trail Making Test had an effect size (0.39) virtually identical to that reported for Part B (0.4). Categories on the WCST also had a similar effect size (0.37) whilst the effect size for Porteus Trails A was negligible (0.08) (Morgan & Lilienfeld 2000).

Willcutt et al. (2008) recently updated previous reviews and conducted a comprehensive review of the neuropsychology of childhood disorders. They included a broad (but not fully comprehensive) range of tasks and banded results according to effect size versus healthy Controls. For ODD and CD no tasks had an effect size versus Controls greater than 1.0. A "large" effect size (0.7 – 0.9) was reported for response variability (e.g. Oosterlaan &

Sergeant 1996; Oosterlaan & Sergeant 1998b; Scheres, Oosterlaan, & Sergeant 2001). A "medium" effect size (0.4 – 0.6) was reported for response inhibition (e.g. Chee et al. 1989; Oosterlaan, Scheres, & Sergeant 2005; Scheres, Oosterlaan, & Sergeant 2001), working memory (e.g. Olvera et al. 2005; Raine, Moffitt, Caspi, Loeber, Stouthamer-Loeber, & Lynam 2005; Seguin et al. 1999; Van Goozen et al. 2004), set-shifting (e.g. Moffitt & Henry 1989; Seguin, Boulerice, Harden, Tremblay, & Pihl 1999; Toupin et al. 2000), planning (e.g. Moffitt & Henry 1989; Oosterlaan, Scheres, & Sergeant 2005; Toupin, Dery, Pauze, Mercier, & Fortin 2000), vigilance (e.g. Chee, Logan, Schachar, Lindsay, & Wachsmuth 1989; Olvera, Semrud-Clikeman, Pliszka, & O'Donnell 2005), interference control (Olvera, Semrud-Clikeman, Pliszka, & O'Donnell 2005; Toupin, Dery, Pauze, Mercier, & Fortin 2000) and processing speed (Moffitt & Henry 1989) and a "small" effect size (0.1 – 0.3) for fluency (e.g. Olvera, Semrud-Clikeman, Pliszka, & O'Donnell 2005; Toupin, Dery, Pauze, Mercier, & Fortin 2000).

Importantly, all of these neuropsychological deficits have been reported to be present in AD-HKD and with the exception of set-shifting and fluency, the same review found that for these tasks the effect size for AD-HKD subjects was either the same or greater than that for ODD/CD (Willcutt, Sonuga-Barke, Nigg, & Sergeant 2008).

Whilst none of the adult studies and few of the early child and adolescent studies controlled for comorbid AD-HKD, several more recent studies have done so. Most have reported that cognitive deficits remain after controlling for the presence of AD-HKD and are therefore at least partially independent of AD-HKD (Raine, Moffitt, Caspi, Loeber, Stouthamer-Loeber, & Lynam 2005; Seguin, Boulerice, Harden, Tremblay, & Pihl 1999; Sergeant, Geurts, & Oosterlaan 2002), however some authors have argued that antisocial boys without AD-HKD do not show neuropsychological impairment (e.g. Clark, Prior, & Kinsella 2000; Moffitt 1990; Speltz et al. 1999). In their recent review Willcutt et al (2008)

found that, for studies of children and young people with CD or ODD, after controlling for AD-HKD the deficits in response variability, vigilance and working memory remained (Scheres, Oosterlaan, & Sergeant 2001; Seguin, Boulerice, Harden, Tremblay, & Pihl 1999; Toupin, Dery, Pauze, Mercier, & Fortin 2000), whilst those for processing speed, and response inhibition were no longer significant (Chee, Logan, Schachar, Lindsay, & Wachsmuth 1989; Moffitt & Henry 1989). For some studies the group with CD/ODD without AD-HKD differed from Controls on measures of planning and set-shifting (Toupin, Dery, Pauze, Mercier, & Fortin 2000) whilst these effects were explained by AD-HKD in other studies (Moffitt & Henry 1989; Olvera, Semrud-Clikeman, Pliszka, & O'Donnell 2005; Van Goozen, Cohen-Kettenis, Snoek, Matthys, Swaab-Barneveld, & van Engeland 2004).

Approaching this question from another direction, it is also important to ask whether the neuropsychological deficits found in AD-HKD remain once comorbidity with CD and ODD is accounted for. Numerous studies have reported that significant AD-HKD effects remain when the effects of CD/ODD are either excluded or controlled for (Antrop et al. 2006; Chee, Logan, Schachar, Lindsay, & Wachsmuth 1989; Geurts et al. 2004; Johnson et al. 2007; Klorman et al. 1999; Nigg, Hinshaw, Carte, & Treuting 1998; Nigg 1999; Oosterlaan, Scheres, & Sergeant 2005). The review of Willcutt et al. (2008) also found the effect of AD-HKD to be independent of CD and ODD on all of their included measures. However it is still uncertain whether the presence of either CD or ODD has an impact on the degree of neuropsychological impairment seen in AD-HKD.

- Several studies have suggested that the presence of comorbid ODD or CD has no effect on cognitive performance in children with AD-HKD (Geurts, Verte, Oosterlaan, Roeyers, & Sergeant 2004; Oosterlaan, Logan, & Sergeant 1998).
- Other studies have reported that those with AD-HKD and comorbid CD or ODD are more impaired than those with AD-HKD alone on measures planning (Klorman,

Hazel-Fernandez, Shaywitz, Fletcher, Marchione, Holahan, Stuebing, & Shaywitz 1999).

- Others have reported that those with AD-HKD and CD/ODD are less impaired than those with AD-HKD alone on measures of response inhibition (Schachar, Mota, Logan, Tannock, & Klim 2000), planning (Oosterlaan, Scheres, & Sergeant 2005), and vigilance (Chee, Logan, Schachar, Lindsay, & Wachsmuth 1989).

Taken together, the available data suggests that;

1. CD and ODD are associated with deficits in neuropsychological functioning that are similar to those seen in AD-HKD;

2. That these deficits are present even when AD-HKD is controlled for;

3. Whilst they may contribute towards the deficits seen in AD-HKD, they do not completely account for them.

It is not yet clear whether these comorbidities could account for some of the heterogeneity in neuropsychological functioning reported both within and between samples of children and young people with AD-HKD. Finally, no studies have reported on whether there is an interaction between comorbidity between AD-HKD, ODD and CD, and the neuropsychological response to methylphenidate (MPH).

The aim of this chapter, therefore, is to describe the neuropsychological profiles of boys with “pure” HKD, HKD + ODD and HKD + CD and to compare their performance on a battery of neuropsychological tasks with each other and with that of healthy boys.

The specific research questions are;

- Compared with healthy boys, do boys with "pure" HKD, HKD + ODD and HKD + CD all demonstrate neuropsychological deficits?

- Are the patterns of neuropsychological deficit the same for HKD, HKD + ODD and HKD + CD?

- Does the presence or absence of comorbid ODD or CD influence the degree of neuropsychological deficit seen in boys with HKD when compared with healthy boys?

The hypotheses to be tested are:

- Boys with "pure" HKD, HKD + ODD and HKD + CD will all demonstrate neuropsychological deficits compared with healthy boys.

- The presence or absence of comorbid ODD or CD will not impact on the patterns or degree of neuropsychological deficits seen in HKD boys.

Methods

Sample selection

The HKD, HKD + ODD and HKD + CD samples were drawn from the overall participant group. All diagnoses were based on the KIDDIE-SADS-PL (Kaufman et al. 2000) interview data and made using ICD-10 research diagnostic criteria (World Health Organisation 1993). The potential numbers of boys with each pattern of comorbidity are described in table 8.2. Three boys with ODD and three boys with CD had an additional comorbid condition (anxiety, depression or tics) and were excluded.

The remaining 18 boys with “pure” HKD and the 18 boys with HKD + CD were included in the analysis. Eighteen boys with HKD + ODD and eighteen Control boys, matched for age with both the “pure” HKD group and the HKD + ODD groups, were also included in the analysis. The characteristics of these groups are described in table 8.3. Whilst there were overall no differences between the groups with respect to age, contrasts revealed that the HKD + CD group were older than the “pure” HKD group. There were group differences with respect the British Picture Vocabulary Scale (BPVS) percentile rank scores with HKD + CD boys having lower scores than boys in the other three groups. There were no differences in BPVS scores between the other three groups.

Table 8.2: Distribution of cases of "pure" non-comorbid hyperkinetic disorder (Pure HKD), and HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) within the study sample of drug naïve boys with HKD at baseline.

	n	*% of sample*
Pure HKD	18	24
HKD + ODD (no CD)	31	41.3
HKD + CD	21	28

Table 8.3: Comparisons of the Age and BPVS profiles at baseline of the "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) within the study sample of drug naïve boys with HKD and the healthy Control groups.

	Pure HKD (SD)	HKD + ODD (SD)	HKD + CD (SD)	Healthy Boys (SD)	Group comparison
Age	10.7 (2.6)	11.3 (2.5)	12.5 (2.2)	11.6 (2.6)	(F (3,68) = 1.7, p >.05) pure < CD
BPVS	40.1 (25.1)	43.0 (28.7)	27.1 (28.5)	59.2 (28.0)	(F (3,68) = 4.1, p =.01) CD < pure, ODD, cont

Statistical Considerations

Analyses were conducted on the raw baseline performance data. The neuropsychological performance of boys in the four diagnostic groups was compared. Descriptive data for task performance by group is presented. Data were then analyzed using univariate or repeated-measures ANCOVA with a between subject factor of GROUP (pure HKD vs. HKD + ODD vs. HKD + CD vs. Controls). Repeated-measures ANCOVA was conducted on the following measures with difficulty level included as a within subject factor: Go/NoGo (Blocks 1 and 2), Spatial Working Memory Between-search Errors (3, 4, 6, 8 boxes), Stockings of Cambridge Average Moves, Initial Thinking Time, Subsequent Thinking Time (2-5 moves), Delayed Matching to Sample delay conditions (0, 4, 12 seconds delay). Age and BPVS Percentile Rank were used as covariates in all analyses. Following ANCOVA, further exploration of the data was conducted using planned pairwise comparisons. Effect sizes are reported as Cohen's d (SE) and were calculated using the method of Cohen (Cohen 1992) and corrected for bias using the method of Hedges and Olkin (1985) with an effect size (*d*) of 0.2 – 0.49 considered small, of 0.5 – 0.79 medium ,and ≥ 0.8 large.

Results

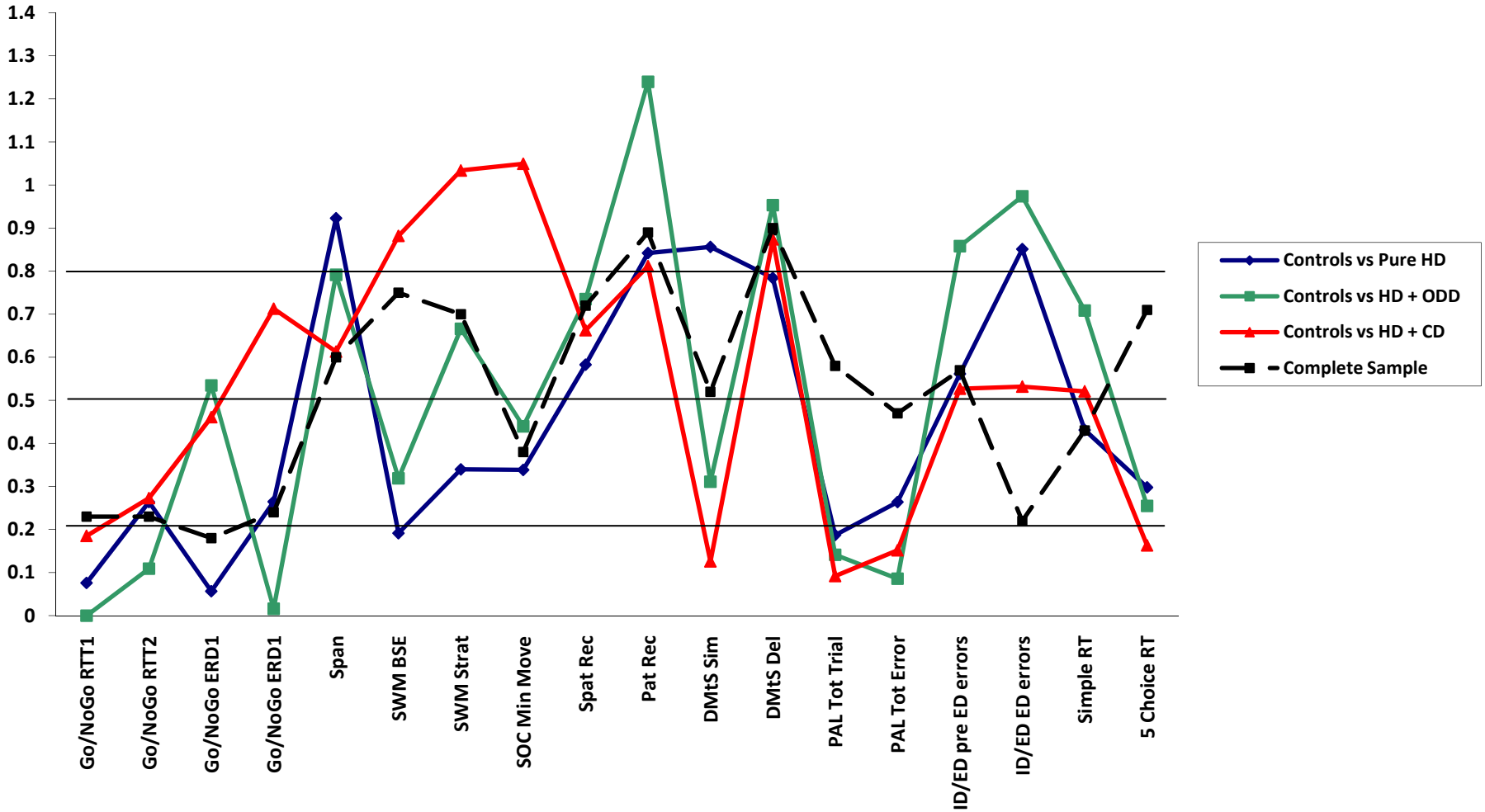
The age and BPVS adjusted means for neuropsychological performance across the pure HKD, HKD + ODD, HKD + CD and Control groups are presented in table 8.4. The effect sizes by group are presented in Figures 8.1 and 8.2 to which the effect sizes for the whole HKD vs. the whole Control group have been added for comparison.

Table 8.4: Summary of age and BPVS adjusted means for baseline neuropsychological performance of boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls.

Measure	Pure HKD (N = 18) Age and BPVS Adjusted Mean (SD)	HKD-ODD (N = 18) Age and BPVS Adjusted Mean (SD)	HKD-CD (N = 18) Age and BPVS Adjusted Mean (SD)	Controls (N = 18) Age, and BPVS Adjusted Mean (SD)
Go/NoGo				
RTT (block type 1, msec)	468 (110)	460 (78)	443 (84)	460 (95)
RTT (block type 2, msec)	490 (113)	454 (76)	442 (64)	463 (85)
ERD (block type 1)	2.01(1.52)	2.79 (1.86)	2.48 (1.11)	1.93 (1.22)
ERD (block type 2)	1.96 (1.56)	2.54 (2.05)	2.51 (1.21)	1.56 (1.39)
Spatial Span	5.07 (1.19)	4.96 (1.78)	5.41 (1.28)	6.17 (1.14)
Spatial working Memory				
Total BSE Strategy Score	44.00 (19.88) 34.79 (3.77)	47.54 (24.77) 36.74 (5.62)	58.08 (18.04) 37.70 (4.20)	39.88 (22.11) 33.48 (3.77)
Stockings of Cambridge				
Solved in Minimum Moves	7.66 (2.00)	7.34 (2.51)	6.68 (1.37)	8.29 (1.62)
Spatial Recognition				
% Correct	68.85 (15.31)	66.99 (14.25)	67.37 (16.11)	77.55 (13.84)
Pattern Recognition				
% correct	82.77 (10.76)	79.86 (9.47)	82.63 (11.66)	90.87 (7.82)
Delayed Matching to Sample				
% Correct (Sim)	82.46 (19.33)	92.50 (10.03)	96.51 (10.29)	95.34 (7.67)
% Correct (Tot Delay)	61.10 (18.37)	56.71 (21.22)	61.73 (14.14)	73.84 (12.93)
Paired Associates Learning				
Total Trials	11.63 (3.87)	12.95 (3.40)	12.84 (5.13)	12.4 (4.17)
Total Errors	9.04 (13.53)	11.38 (9.19)	10.90 (10.24)	12.89 (14.96)
ID/ED				
Pre ED errors	7.40 (3.20)	11.48 (8.75)	8.44 (6.30)	5.98 (1.41)
Errors at ED shift	21.25 (8.05)	22.63 (8.52)	18.87 (10.70)	13.10 (10.51)
Reaction Time				
Simple	405 (180)	422 (134)	435 (229)	345 (68)
5 Choice	462 (289)	427 (130)	411 (72)	395 (115)

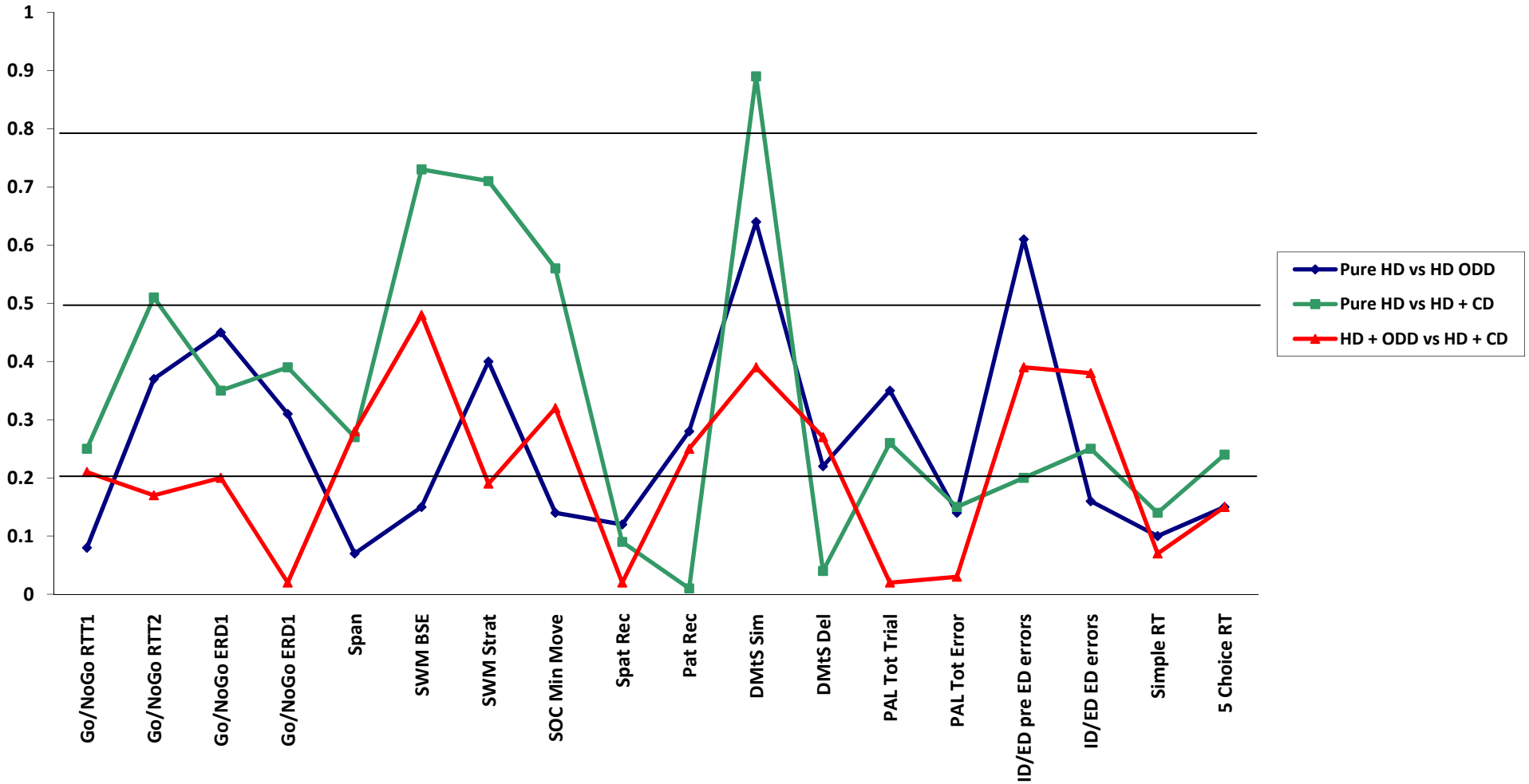
RTT, reaction time to targets; ERD errors to distracters; BSE, between-search errors; ID/ED, Intradimensional/Extradimensional Set-shifting

Figure 8.1: Effect sizes vs. controls for baseline neuropsychological performance of boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy controls.



RTT, reation time to target; ERD errors to distracters; SWM, Spatial Working Memory; BSE, between-search errors; Strat, strategy; SOC, Stockings of Cambridge; Spat Rec, Spatial Recognition; Pat Rec, Pattrn ecognition; DMtS, Delayed Matching to Sample; PAL, paired Associates Learning; ID/ED, Intradimensional/Extradimensional Set-shifting; RT, reaction time.
Horizontal lines indicate boundaries of effect size; 0.2 – 0.49 = small, 0.5 – 0.79 = medium, ≥ 0.8 = large.

Figure 8.2: Comparative effect sizes for baseline neuropsychological performance of boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD)



RTT, reation time to target; ERD errors to distracters; SWM, Spatial Working Memory; BSE, between-search errors; Strat, strategy; SOC, Stockings of Cambridge; Spat Rec, Spatial Recognition; Pat Rec, Patetrn recognition; DMtS, Delayed Matching to Sample; PAL, paired Associates Learning; ID/ED, Intradimensional/Extradimensional Set-shifting; RT, reaction time.
Horizontal lines indicate boundaries of effect size; 0.2 – 0.49 = small, 0.5 – 0.79 = medium, ≥ 0.8 = large.

Go/NoGo

There was no effect of GROUP for either block type with respect to reaction times to targets or errors to distracters. All $p > .1$. The effect sizes for reaction time to targets and errors to distracters are shown in tables 8.5 to 8.8.

Table 8.5: Effect sizes fro Go/NoGo reaction times to targets (block type 1) for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls

Pure HKD	HKD + ODD	HKD + CD	Effect size *d (se)*
0.08 (0.33)	0.00 (0.33)	0.19 (0.33)	Control
	0.08 (0.33)	0.25 (0.33)	Pure HKD
		0.21 (0.33)	HKD + ODD

Table 8.6: Effect sizes fro Go/NoGo reaction times to targets (block type 2) for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls

Pure HKD	HKD + ODD	HKD + CD	Effect size *d (se)*
0.26 (0.33)	0.11 (0.33)	0.27 (0.33)	Control
	0.37 (0.34)	0.51 (0.34)	Pure HKD
		0.17 (0.33)	HKD + ODD

Table 8.7: Effect sizes for Go/NoGo errors to distractors (block type 1) for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls

Pure HKD	HKD + ODD	HKD + CD	Effect size *d (se)*
0.06 (0.33)	0.53 (0.34)	0.46 (0.34)	Control
	0.45 (0.34)	0.35 (0.34)	Pure HKD
		0.20 (0.33)	HKD + ODD

Table 8.8: Effect sizes fro Go/NoGo errors to distractors (block type 2) for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls

Pure HKD	HKD + ODD	HKD + CD	Effect size *d (se)*
0.27 (0.33)	0.55 (0.34)	0.71 (0.34)	Control
	0.31 (0.34)	0.39 (0.34)	Pure HKD
		0.02 (0.33)	HKD + ODD

Spatial Span

There was an effect of GROUP with respect to Spatial Span [F(3,68)=3.05, p=.035]. Paired contrasts revealed that the HKD-ODD had a shorter span than the Control group (p = .04) and that there was a trend towards the pure HKD having a shorter span than the Control group (p = .1). There were no differences between the other groups. The effect sizes for spatial span are shown in table 8.9.

Table 8.9: Effect sizes for Spatial Span for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls

Pure HKD	HKD + ODD	HKD + CD	Effect size *d (se)*
0.92 (0.35)	0.79 (0.35)	0.61 (0.34)	Control
	0.07 (0.33)	0.27 (0.33)	Pure HKD
		0.28 (0.34)	HKD + ODD

Spatial Working Memory

There was an effect of GROUP with respect to Between-search Errors [F(3,68)=3.50, p=.020]. Paired contrasts revealed that the Control group had less errors than the HKD + CD group (p = .003). There were no differences between the other groups. The effect sizes for Between-search Errors are shown in table 8.10.

In the repeated-measures analysis there was an effect of DIFFICULTY [F(1,65)=93.9, p<.001], AGE [F(1,65)=48.4, p<.001] and GROUP [F(3,65)=3.17, p=.03], Paired contrasts revealed that the Control group and the pure HKD group had less errors than the HKD + CD group (p = .004 and p= .026 respectively).There was an interaction between DIFFICULTY and AGE [F(1,65)=35.6, p<.001] with the younger subjects having more problems with the more difficult levels. There was also an interaction between DIFFICULTY and GROUP [F(1,65)=2.77, p=.048] with the HKD + CD group having more problems with the more difficult levels . The relationship between the groups and task difficulty is illustrated in figure 8.3.

There was an effect of GROUP with respect to Strategy Score [F(3,68)=3.20, p=.029]. Paired contrasts revealed that the Control group made a better use of strategy than the HKD + CD group (p = .045). There were no differences between the other groups. The effect sizes for Strategy Score are shown in table 8.11.

Table 8.10: Effect sizes for Spatial Working Memory - Between-search Errors for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls

Pure HKD	HKD + ODD	HKD + CD	Effect size *d (se)*
0.19 (.33)	0.32 (0.34)	0.88 (0.35)	Control
	0.15 (0.33)	0.73 (0.34)	Pure HKD
		0.48 (0.34)	HKD + ODD

Figure 8.3: Spatial Working Memory - Between-search Errors by clinical group and level of task difficulty for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls

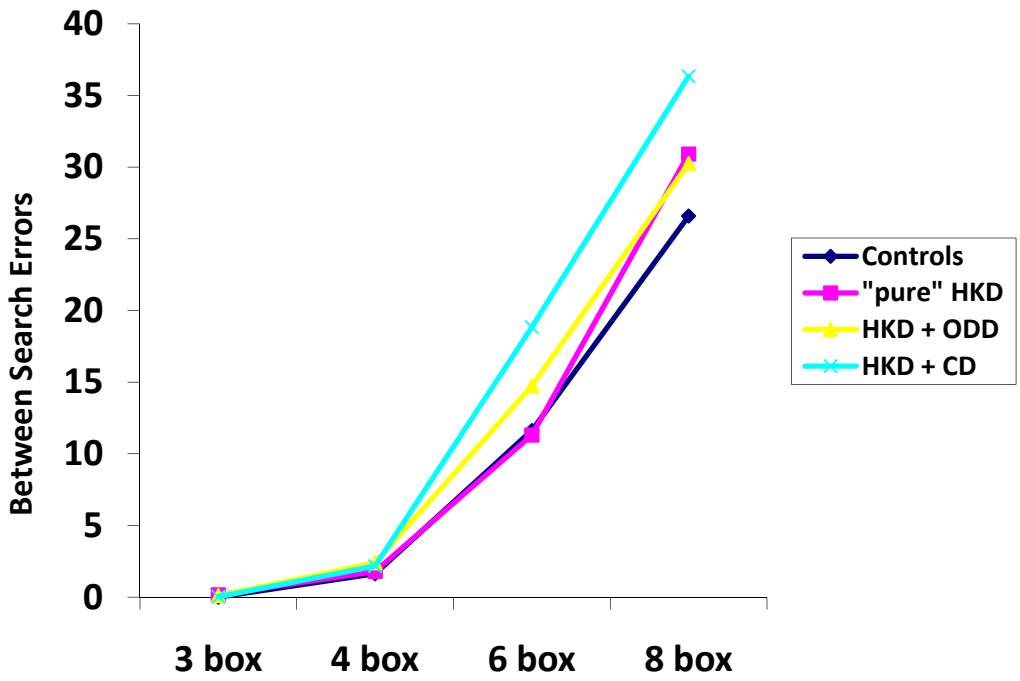


Table 8.11: Effect sizes for Spatial Working Memory – Strategy Score for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls

Pure HKD	HKD + ODD	HKD + CD	Effect size *d (se)*
0.34 (0.34)	0.67 (0.34)	1.03 (0.35)	Control
	0.40 (0.34)	0.71 (0.34)	Pure HKD
		0.19 (0.33)	HKD + ODD

Stockings of Cambridge

There was a trend towards a GROUP difference with respect to Problems solved in minimum moves [F(3,68)=2.29, p=.087]. Paired contrasts revealed that there was also a trend for the Control group to score better than the HKD + CD group (p = .077). There were no differences between the other groups. The effect sizes for Between-search Errors are shown in table 8.12.

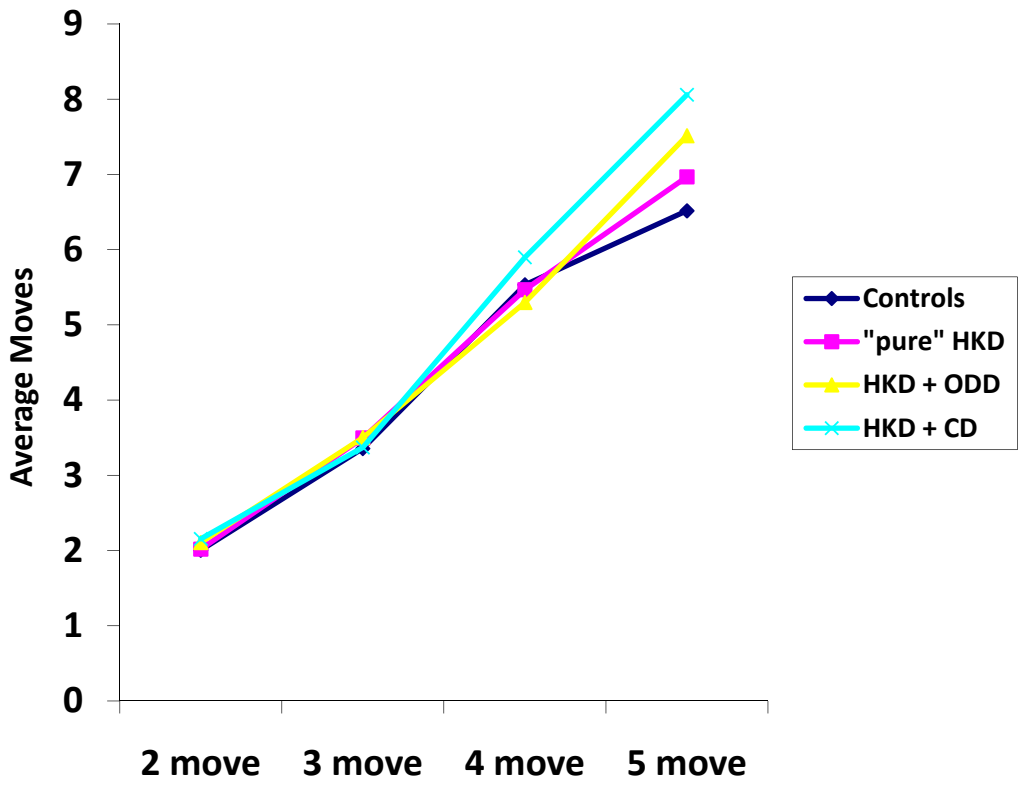
On the repeated-measures analysis of average moves to solution there was an effect of DIFFICULTY [F(1,65)=76.8, p<.001], AGE [F(1,65)=16.3, p<.001] and GROUP [F(3,65)=3.04, p=.035], Paired contrasts revealed that the Control group and the pure HKD group had less errors than the HKD + CD group (p = .005 and p= .033 respectively).There was an interaction between DIFFICULTY and AGE [F(1,65)=8.60, p=.005] with the younger subjects having more problems with the more difficult levels. There was also an interaction between DIFFICULTY and GROUP [F(1,65)=3.56, p=.019] with the HKD + CD group having more problems with the more difficult levels . The relationship between the groups and task difficulty is illustrated in figure 8.4.

Repeated-measures ANCOVAs of initial and subsequent thinking found no main effect of DIFFICULTY or GROUP and no DIFFICULTY x GROUP interactions.

Table 8.12: Effect sizes for Stockings of Cambridge – Problems Solved in Minimum Moves for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls

Pure HKD	HKD + ODD	HKD + CD	Effect size *d (se)*
0.34 (0.34)	0.44 (0.34)	1.05 (0.36)	Control
	0.14 (0.33)	0.56 (0.34)	Pure HKD
		0.32 (0.34)	HKD + ODD

Figure 8.4: Stockings of Cambridge - Average Moves to Solution by clinical group and level of task difficulty for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls



Spatial Recognition

There was no effect of GROUP with respect to % correct on the Spatial Recognition task p > .1. The effect sizes for Between-search Errors are shown in table 8.13.

Pattern Recognition

There was an effect of GROUP with respect to Pattern Recognition [F(3,68)=3.56, p=.019]. Paired contrasts revealed that the Control group made fewer errors than all of the clinical groups (vs. pure HKD p = .03, vs. HKD + ODD p = .002, vs. HKD + CD p = .04). There were no differences between the clinical groups. The effect sizes for spatial span are shown in table 8.14.

Table 8.13: Effect sizes for Spatial Recognition for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls

Pure HKD	HKD + ODD	HKD + CD	Effect size *d (se)*
0.58 (0.35)	0.74 (0.34)	0.66 (0.34)	Control
	0.12 (0.33)	0.09 (0.33)	Pure HKD
		0.02 (0.33)	HKD + ODD

Table 8.14: Effect sizes for Pattern Recognition for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls

Pure HKD	HKD + ODD	HKD + CD	Effect size *d (se)*
0.84 (0.35)	1.24 (0.36)	0.81 (0.35)	Control
	0.28 (0.33)	0.01 (0.33)	Pure HKD
		0.25 (0.33)	HKD + ODD

Delayed Matching to Sample

There was an effect of GROUP with respect to % correct in the simultaneous condition [F(3,68)=4.43, p=.007]. Paired contrasts revealed that the Control group scored better than the pure HKD group (p = .026). There were no differences between the other groups. The effect sizes for % correct in the simultaneous condition are shown in table 8.15.

There was an effect of GROUP with respect to % correct in the total delays [F(3,68)=3.84, p=.014]. Paired contrasts revealed that the Control group scored better than all three clinical groups (pure HKD p = .021, HKD + CD p = .002, HKD + CD p = .031). There were no differences between the clinical groups. The effect sizes for % correct in the total delays condition are shown in table 8.16.

On the repeated-measures analysis of average moves to solution there was no effect of DIFFICULTY [F< 1] but there was an effect of AGE [F(1,65)=17.4, p<.001] and of GROUP [F(3,65)=4.07, p=.010], Paired contrasts revealed that the Control group had less errors than all three clinical groups (pure HKD p = .015, HKD + ODD p = 0.001, HKD + CD p = .033).There were no interactions between DIFFICULTY and AGE [F< 1] or DIFFICULTY and GROUP [p > 1] although graphically the pattern of results looks similar to the delay dependent deficit described for the whole sample . The relationship between the groups and task difficulty is illustrated in figure 8.5.

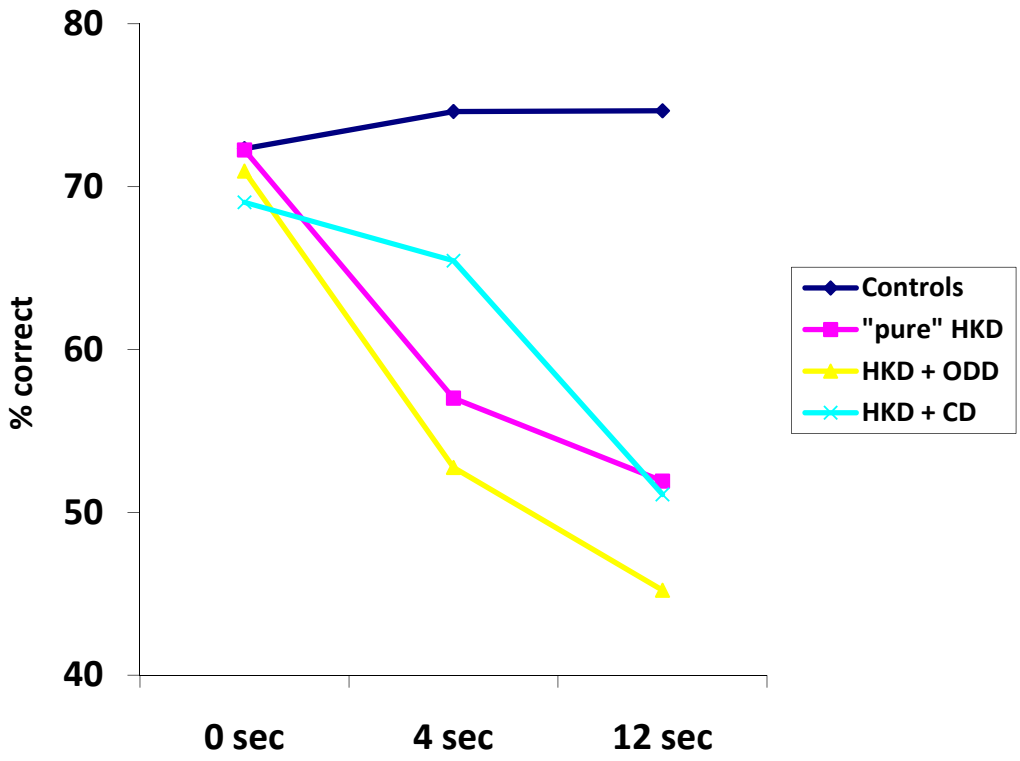
Table 8.15: Effect sizes for Delayed Matching to Sample - % correct in the simultaneous condition for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls

Pure HKD	HKD + ODD	HKD + CD	Effect size *d (se)*
0.86 (0.35)	0.31 (0.34)	0.13 (0.33)	Control
	0.64 (0.34)	0.89 (0.35)	Pure HKD
		0.39 (0.34)	HKD + ODD

Table 8.16: Effect sizes for Delayed Matching to Sample - % correct in the total delays condition for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls

Pure HKD	HKD + ODD	HKD + CD	Effect size *d (se)*
0.78 (0.35)	0.95 (0.35)	0.87 (0.35)	Control
	0.22 (0.33)	0.04 (0.33)	Pure HKD
		0.27 (0.33)	HKD + ODD

Figure 8.5: Delayed Matching to Sample - % correct by clinical group and level of task difficulty for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls



Paired Associates Learning

There was no effect of GROUP with respect to either total trials [F< 1] or total errors [F<1]. The effect sizes for total trials and total errors are shown in tables 8.17 and 8.18.

Intradimensional/Extradimensional Set-shifting

There was an effect of GROUP with respect to pre ED errors [F(3,68)=2.90, p=.041]. Paired contrasts revealed that the Control group scored better than the HKD + ODD group (p = .007). There were no differences between the other groups. The effect sizes for pre ED errors are shown in table 8.19.

There was an effect of GROUP with respect to errors at the ED shift [F(3,68)=3.84, p=.014]. Paired contrasts revealed that the Control group scored better than the pure HKD group (p = .018), and the HKD + ODD group (p = .005). There were no differences between the other groups. The effect sizes for errors at the ED shift are shown in table 8.20.

Table 8.17: Effect sizes for Paired Associates Learning – total trials for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls

Pure HKD	HKD + ODD	HKD + CD	Effect size *d (se)*
0.19 (0.33)	0.14 (0.33)	0.09 (0.33)	Control
	0.35 (0.34)	0.26 (0.33)	Pure HKD
		0.02 (0.33)	HKD + ODD

Table 8.18: Effect sizes for Paired Associates Learning – total errors for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls

Pure HKD	HKD + ODD	HKD + CD	Effect size *d (se)*
0.26 (0.33)	0.09 (0.33)	0.15 (0.33)	Control
	0.14 (0.33)	0.15 (0.33)	Pure HKD
		0.03 (0.33)	HKD + ODD

Table 8.19: Effect sizes for Intradimensional/Extradimensional Set-shifting – pre ED errors for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls

Pure HKD	HKD + ODD	HKD + CD	Effect size *d (se)*
0.56(0.34)	0.86 (0.35)	0.53 (0.34)	Control
	0.61 (0.34)	0.20 (0.33)	Pure HKD
		0.39 (0.34)	HKD + ODD

Table 8.20: Effect sizes for Intradimensional/Extradimensional Set-shifting – errors at the ED shift for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls

Pure HKD	HKD + ODD	HKD + CD	Effect size *d (se)*
0.85 (0.35)	0.97 (0.35)	0.53 (0.34)	Control
	0.16 (0.33)	0.25 (0.33)	Pure HKD
		0.8 (0.34)	HKD + ODD

Reaction Time

There was no effect of GROUP with respect to either Simple or 5-choice reaction time [F<1]. On repeated-measures ANCOVA there was an effect of AGE [F(1,65)=17.6, p=.001] but no effect of either DIFFICULTY or GROUP nor an interaction between DIFFICULTY and GROUP [all F < 1]. The effect sizes for Simple and 5-choice are shown in tables 8.21 and 8.22.

Table 8.21: Effect sizes for Simple reaction time for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls

Pure HKD	HKD + ODD	HKD + CD	Effect size *d (se)*
0.43 (0.34)	0.71 (0.34)	0.52 (0.34)	Control
	0.10 (0.33)	0.14 (0.33)	Pure HKD
		0.07 (0.33)	HKD + ODD

Table 8.22: Effect sizes for 5-choice reaction time for boys with "pure" non-comorbid hyperkinetic disorder (Pure HKD), HKD comorbid with oppositional defiant disorder (HKD + ODD) and HKD comorbid with conduct disorder (HKD + CD) and healthy Controls

Pure HKD	HKD + ODD	HKD + CD	Effect size *d (se)*
0.30 (0.34)	0.25 (0.33)	0.16 (0.33)	Control
	0.15 (0.33)	0.24 (0.33)	Pure HKD
		0.15 (0.33)	HKD + ODD

Discussion

Do boys with pure HKD, HKD + ODD and HKD + CD all demonstrate neuropsychological deficits?

These data support the hypothesis that "compared with healthy boys, boys with pure HKD, HKD + ODD and HKD + CD all demonstrate neuropsychological deficits". The ANCOVAs identified overall group differences for 6 of the 10 tasks (Spatial Span, Spatial Working Memory, Stockings of Cambridge, Pattern Recognition, Delayed Matching to Sample, Intradimensional/Extradimensional Set-shifting). Relative to healthy Controls, boys in each of the three clinical groups had deficits on some, but not all, of the tasks.

An important finding was that boys with pure HKD had deficits relative to Controls on 4 measures from 3 tasks (Pattern Recognition, Delayed Matching to Sample – simultaneous and total delays, and Intradimensional/ Extradimensional Set-shifting errors at the ED shift), and a trend towards a deficit on the Spatial Span task. The effect sizes for these deficits were in the medium to large range (0.78 – 0.92). These findings support those reported in the meta-analysis of Willcutt et al (2008). They indicate that pure HKD is independently associated with neuropsychological deficits, which are not accounted for by comorbid conditions.

Neuropsychological deficits were also found for the other two clinical groups, indicating that if ODD and CD offer a degree of protection for boys with HKD from neuropsychological deficits - as has been suggested by several authors (Chee, Logan, Schachar, Lindsay, & Wachsmuth 1989; Oosterlaan, Scheres, & Sergeant 2005; Schachar, Mota, Logan, Tannock, & Klim 2000) - this protection is not absolute and does not extend across all areas of neuropsychological functioning. Boys in both the HKD + ODD and HKD + CD groups demonstrated deficits relative to healthy Controls in Pattern Recognition and Delayed Matching to Sample total delays. The boys in the HKD + ODD group also demonstrated

deficits in Spatial Span and Intradimensional/Extradimensional Set-shifting pre-ED errors and ED errors. The boys in the HKD + CD group also demonstrated deficits in Spatial Working Memory between-search errors and strategy and Stockings of Cambridge problems solved in minimum moves and average moves to solution.

No differences between the four groups were found on six measures from four of the tasks (Go/NoGo, Spatial Recognition, Paired Associates Learning – Total Trials and Total Errors, and Simple and 5 choice Reaction Time). The lack of a difference between the groups on the Go/NoGo measures and the simple reaction time mirrors the results of the analyses conducted on the whole sample (see Chapter 5 for details). As these measures did not distinguish between the whole of the HKD group (n=75) and the Control group (n = 70) it would have been surprising, but not impossible, to have found differences between these smaller, but more clinically homogeneous groups (n = 18 in each group). The lack of a group difference in this analysis between healthy Controls and any of the clinical groups on the Spatial Recognition, Paired Associates Learning and 5 choice Reaction time measures is different from the results of the whole group analysis where, relative to Controls, the boys with HKD had significant deficits on all three tasks (Spatial Recognition effect size d = 0.72; Paired Associates Learning - total trials d = 0.58, total errors d = 0.47; 5-choice Reaction Time d = 0.71). The lack of effect found for these tasks in this analysis may be due to a lack of power in these analyses and, indeed, this seems the most likely explanation for the Spatial Recognition results where although the p value was > 0.05, the F ratio for the overall ANCOVA was 1.8, and the effect sizes for the groups vs. Controls were similar to those for the whole HKD group vs. the Control group; pure HKD d =0. 58, HKD + ODD d = 0.74 and HKD + CD d = 0.66. However, the F ratio for the Paired Associates Learning measures and 5-choice Reaction Time measure for each of the ANCOVAs was ≤ 1 and the effect sizes vs. Controls for each group were ≤ 0.3. Thus, for all three measures these effect

sizes were considerably lower than those for the whole sample. It is possible that either having pure HKD or HKD with either ODD or CD protects against deficits on these three tasks or protects against, or is incompatible with, another factor that results in the deficit. Alternatively, these deficits may be independently related to another unobserved factor, which happens not to be present in the children included in these samples

Does the presence or absence of comorbid ODD or CD influence the pattern or degree of neuropsychological deficit seen in boys with HKD when compared with healthy boys?

These data do not support the hypothesis that "the presence or absence of comorbid ODD or CD will not impact on the patterns or degree of neuropsychological deficits seen in HKD boys". Each of the three clinical groups was associated with at least one unique deficit when compared with the Control boys.

The boys with pure HKD were the only group with a deficit on the simultaneous condition in the Delayed Matching to Sample task relative to Controls. They also demonstrated a moderate deficit on this measure compared with boys with HKD + ODD (d = 0.64) and large deficit relative to boys with HKD + CD (d = 0.89). The reasons behind these group differences are unclear. This is a simple task where the subject only needs to pick out and match the stimulus pattern with one of four similar patterns on the screen. All five patterns remain on the screen and so, unlike the delay conditions, there is no memory component to this aspect of the task. A subject can perform poorly if they try to rush the task and don't take time to look at the differences between the patterns but if this were the case, one would expect there to be a reduced latency for incorrect responses. This was not found for this analysis as there was no effect of GROUP on incorrect latency ($F < 1$). Alternatively, it is possible that the boys with pure HKD had difficulties in distinguishing patterns. This also seems unlikely as the pure group were not more impaired on the pattern recognition task.

This explanation would seem to imply that ODD and CD protect or compensate for this problem, which also seems unlikely. However, it is possible that pure HKD and HKD with either ODD or CD are different conditions with different causes, and that the causes of pure HKD also result in problems with identifying complex patterns like those used in the Delayed Matching to Sample task, but not the more simple patterns that are used in the Pattern Recognition task.

The boys with HKD + ODD were the only group to demonstrate impairment on the pre-ED errors measure, which is the simpler of the 2 Intradimensional/Extradimensional Set-shifting measures. The stages covered by this measure are considerably easier than the ED shift stages, and notwithstanding the group differences with respect to the number of errors, these stages were successfully negotiated by the boys in all four groups. Relative to the Controls, the boys with HKD + ODD and boys with Pure HKD, but not those with HKD + CD, also had deficits at the ED shift stage of this task with the HKD + ODD group having the greatest difficulties. These results suggest that a proportion of the difficulties in set-shifting may be related to the presence of ODD. ODD is often characterised by stubbornness and it is possible that, at least in part, this stubbornness related to quite basic difficulties in switching between tasks. This finding could account for some of the inconsistencies that have been reported across different studies with respect to attentional set-shifting and AD-HKD (Willcutt, Doyle, Nigg, Faraone, & Pennington 2005; Willcutt, Sonuga-Barke, Nigg, & Sergeant 2008). The HKD + ODD group were also the only group to demonstrate a statistically significant difference vs. Controls on the spatial span task. A closer inspection of the patterns of response on this measure reveals a trend towards a difference for the pure HKD group and whilst the HKD + CD group were not statistically different from Controls, there was a moderate effect size for the difference between the two groups. A lack of

power with respect to this task would seem to be the most likely cause of this pattern of results.

Perhaps the most striking group differences are between the boys with HKD + CD and the other two HKD groups. The boys with HKD + CD had deficits on both measures of the Spatial Working Memory task and the Stockings of Cambridge task, which indexes planning, but also has a working memory component. The effect sizes for the HKD + CD groups vs. Controls for these tasks were all large. The effect sizes for the HKD + CD boys vs. the boys with pure HKD were in the moderate range and were similar to those reported for the whole HKD group vs. Controls. Interestingly, the effect sizes vs. Controls on both of the Spatial Working Memory measures for the pure HKD group and on between-search errors for the HKD + ODD group were much lower than those previously reported for the whole HKD group vs. Controls. These results suggest that CD may play an important role in mediating the effects of HKD on these measures of executive functioning and may account for some of the between group differences previously reported in the literature (Martinussen, Hayden, Hogg-Johnson, & Tannock 2004).

There are, however, certain aspects of neuropsychological functioning, which appear to be independent of these comorbidities. Relative to Controls all three of the patient groups had deficits on the Pattern Recognition task and Delayed Matching to Sample delay measures. These were the two measures for which the largest effect sizes were found in the analysis of the whole sample. The clear suggestion from this analysis is that these deficits are *specifically* related to HKD, as they are seen in pure HKD and are not mediated or moderated by the presence of either ODD or CD. The clinical and pathophysiological implications of these findings for causal models of AD-HKD, which were discussed in previous chapters (e.g. potentially implicating the temporal lobe and/or the amygdale/hippocampal complex), would be strengthened if these deficits were indeed

found to be specific to AD-HKD (i.e. are not present in other psychiatric disorders) and, when present in AD-HKD, are not affected by the presence or absence of other comorbidities not tested for within this analysis.

Although, as has been discussed previously, it is not possible to specifically link any one particular neuropsychological deficit with a specific brain region or pathophysiology, there is considerable evidence to support a certain degree of neuroanatomical and pathophysiological specificity with several of the CANTAB tasks. The ED shift learning in the ID/ED Shift task, here found to be associated with the presence of ODD, has been demonstrated to be associated with increased activation in the left anterior prefrontal cortex and the right dorsolateral prefrontal cortex and decreased activation in the occipito-temporal cortex (Rogers, Andrews, Grasby, Brooks, & Robbins 2000). Optimal performance on the Spatial Working Memory task, associated here with CD, involves activation of the dorsal and ventral prefrontal cortical regions (Mehta, Owen, Sahakian, Mavaddat, Pickard, & Robbins 2000; Owen, Morris, Sahakian, Polkey, & Robbins 1996b; Robbins, James, Owen, Sahakian, Lawrence, McInnes, & Rabbitt 1998). For the Stockings of Cambridge task, also associated with CD, the parietal lobe bilaterally and the left dorsolateral prefrontal cortex and left caudate nucleus in the dorsal striatum (Baker, Rogers, Owen, Frith, Dolan, Frackowiak, & Robbins 1996; Morris, Ahmed, Syed, & Toone 1993; Owen, Doyon, Petrides, & Evans 1996a) are essential. The Delayed Matching to Sample and Pattern Recognition tasks, deficits on which were found in all groups, and neither of which were affected by the presence or absence of either ODD or CD, are both sensitive to damage of either the temporal lobes, the amygdale or the hippocampus (Owen, Sahakian, Semple, Polkey, & Robbins 1995). It is therefore possible that the different pattern of performance across the three clinical groups is a consequence of each of the three disorders (HKD, ODD and CD) being associated with different underlying neuroanatomical and pathophysiological

substrates. Future studies that include functional imaging would help to identify whether or not this is the case.

An important caveat to these findings is that the results are based on relatively small samples. Although, by definition the statistically significant findings reported here are unlikely to have arisen by chance, non-significant differences between groups may reflect a combination of sample size and the neuropsychological heterogeneity demonstrated in Chapter 6. On the other hand, the CANTAB tasks have been shown to be sensitive measures of group differences, and group sizes of 18 are typical for CANTAB studies.

Summary and Conclusions

Although the data presented in this chapter is, to a degree, limited by a lack of statistical power, these analyses suggest that whilst boys with "pure" HKD, HKD + ODD and HKD + CD all demonstrate neuropsychological deficits when compared with healthy boys, the presence of comorbid ODD and CD does impact both on the pattern and degree of neuropsychological deficits. In particular, boys with HKD + ODD have more difficulties with aspects of attentional set-shifting and boys with HKD + CD have greater problems with respect to working memory and planning. It therefore seems reasonable to conclude that whilst these two common comorbidities are not responsible for the neuropsychological deficits associated with AD-HKD, they make a contribution to the neuropsychological, as well as clinical heterogeneity seen both within and between boys with AD-HKD.

Chapters 6, 7 and 8 have explored the neuropsychological heterogeneity within a group of stimulant medication naïve boys with HKD and the potential contributions of developmental processes and common comorbidities on this heterogeneity. In Chapter 9 I will shift focus to look at the heterogeneity with respect to clinical and neuropsychological

response to MPH in this same group of boys. I will investigate the relationships between clinical response to MPH and both baseline neuropsychological performance and neuropsychological response to MPH.

Chapter 9

Heterogeneity and Predictors of Clinical Response to Methylphenidate (MPH)

Background

Predicting Response to MPH

Despite over 50 years experience in clinical use, good evidence for clinical efficacy and effectiveness (National Institute for Health and Clinical Excellence 2005; Scottish Intercollegiate Guidelines Network 2001) and a strong safety profile (Graham & Coghill 2008), there is still much public (e.g. Panorama 2007) and (at times) professional (Marcovitch 2004; Timimi & Taylor 2004) scepticism surrounding the use of methylphenidate (MPH) in the treatment of AD-HKD.

The efficacy of MPH in reducing clinical symptoms has been demonstrated in a large number of trials and is supported by several systematic reviews and meta-analyses (e.g. Faraone et al. 2004; Faraone et al. 2006; Jadad et al. 1999; Lord & Paisley 2000). With a pooled effect size of approximately 0.9 MPH is one of the most effective treatments within psychiatric practice. As discussed in chapter 5, there is also a general agreement that MPH enhances aspects of cognitive functioning, although there is ongoing debate regarding which aspects are improved and in which circumstances (Coghill, Rhodes, & Matthews 2007).

As most clinical trials have only been analysed at the group level they only inform about the impact of medication on groups of children. Clinicians, however, are faced with making treatment decisions for individuals, and notwithstanding the general efficacy and effectiveness of MPH at a group level, it is accepted that not everyone with AD-HKD will

responds to MPH. Data from clinical trials suggest that around 70% will respond to MPH (Barkley 1977; Efron, Jarman, & Barker 1997a) and that around 95% of those with AD-HKD will have a good clinical response to one or other of the two stimulant medications available in the UK – MPH and dexamfetamine (Efron, Jarman, & Barker 1997a; Elia, Borcherding, Rapoport, & Keysor 1991). In order that we can target the use of MPH appropriately and ensure that children and young people are not being unnecessarily exposed to medication, it would be helpful to know whether there are aspects of an individual or their clinical presentation that predict whether or not they will respond to MPH.

The aim would be to use pre-treatment baseline measures to distinguish those who improve as a consequence of MPH treatment from those whose condition remains unchanged, or even deteriorates. Barkley reviewed the early literature and assessed the predictive value of eight predictor types; psychophysiological measures, neurological variables, family characteristics, demographic/social factors, diagnostic categories, rating scales scores, psychological test performance and profile types (Barkley 1976). He concluded that a group of measures, which could be broadly classified as measures of attention span were the most effective predictors. These included reaction time (Porges et al. 1975) and the Matching Familiar Figures Test (Rapoport et al. 1974). These and other tasks, including the number of toy changes in free play and the Porteus Mazes, were also shown to predict response to dexamfetamine (Barkley 1976).

More recent studies, which have attempted to address these questions have tended to report contradictory findings. For example, whilst both Taylor et al. (1987) and Buitelaar et al. (1995) found younger age to be a positive predictor of clinical response to MPH, the study of Taylor observed greater pre-treatment attentional impairment and hyperactivity, poor performance on attentional tests, lower IQ scores and clumsiness in ‘responders’.

Buitelaar et al., however, found the opposite pattern of effects with respect to attentional impairment, hyperactivity and I.Q. and found that responders were more likely than non-responders to have anxiety related difficulties.

Although there are relatively few good quality studies, Solanto (1999) reviewed the more recent evidence pertaining to inter-individual differences in both cognitive and behavioural responses to MPH and concluded that there is a great diversity in response to MPH, both between individuals and across domains of behaviour and learning. As most neuropsychopharmacological studies of MPH have relied either on single dose challenges or have withdrawn MPH for a brief period to allow testing off medication, there have been few opportunities to investigate the association between clinical and neuropsychological response and only one such study was identified. Aman and Turbott (1991) tested 26 children with AD-HKD who were initially drug naïve, before and after open label treatment with MPH. They used a battery of tasks that focused on attention constructs. The tasks used in the study included an automated Matching Familiar Figures Task (Kagan 1965). This task was similar in some respects to the Simultaneous Matching to Sample task used in the current study although it was used by Aman and Turbott to measure impulsivity. They also included a Memory Distraction Task (Aman, Mitchell, & Turbott 1987), which had some similarities to the 4 second delay condition of the Delayed Matching to Sample task used in the current study, however, the task used in the Aman and Turbott study included a distraction condition in addition to the delayed matching condition. There were was also a Continuous Performance Task (Rosvold et al. 1956), which had some similarities to the Go/NoGo task used here and several other tasks, which bore little relation to tasks used in this study. These included; Seat Movement, a measure of overactivity; Maze Task (Klove 1963), Graduated Holes Task (Klove 1963), Pursuit Rotor Task (Aman, Mitchell, & Turbott 1987) and Draw-A-Line-Slowly Task (Werry, Elkind, & Reeves 1987), all of which measure

attention and motor inhibition and require a fair degree of dexterity in addition to an ability to attend and inhibit; a Component Selection Task (Aman & Turbott 1986), which although designed as a measure of learning, was used by Aman and Turbott as a measure of selective attention; and a Cancellation Task (Aman & Turbott 1986) used as a measure of breadth of attention. Clinical response was measured using standardised parent and teacher rating scales. Improvement was noted on all clinical measures. Ten of the 22 variables showed significant improvement following medication (Matching Familiar Figure Task, accuracy and response time; Continuous Performance Task, omission errors and response time; Seat Activity; Component Selection Task, total components recalled; Cancellation Task, Correct Detections; Pursuit Rotor Task, contact time; Graduated Holes Task, error time and number of contacts). For most tasks baseline performance, prior to starting on medication, did not predict a positive response to medication. However, chronological age, accuracy on the non-distraction condition of the Memory Distraction Task, response time on distraction condition of this same task and number of contacts on the Graduated Holes Task were all moderately correlated with clinical outcome. Using stepwise multiple regression analyses to predict clinical outcome, age and the neuropsychological tasks predicted about 50% of outcome variance. Although these results are interpreted by the authors as at least partially supporting an association between baseline levels of attention and medication response, other interpretations are possible. For example, the Memory Distraction Task (particularly in the non-distraction condition) is also a measure of memory performance and the results could therefore be argued to support an association between memory functioning and clinical response to MPH. Performance on the Graduated Holes Task could also have been affected by motor coordination and it is therefore possible that the relationship between baseline performance on this task and clinical response to MPH is mediated by coordination problems, which are recognised as being commonly comorbid with AD-HKD.

If neuropsychological performance deficits play an important role in the causality of AD-HKD, one would expect a strong association between treatment mediated changes in symptoms and behaviour and a treatment mediated change in task performance. The Aman and Turbott (1991) study described above was the only previous study identified that addressed this question. Interestingly this predicted association was not generally supported, as a significant association between clinical and neuropsychological changes was detected only for the Maze Task. The authors comment that "there was virtually no relationship between clinical change and change on the performance tests" (Aman & Turbott 1991).

In routine clinical practice it is often noted that, amongst those who do respond to MPH, it is the case that children who outwardly appear similar to each other actually require very different doses for optimal treatment response. These clinical observations are supported by research findings, which suggest that, whilst there does appear to be a dose response curve for many of the clinical effects of MPH, with increased clinical response with increased dose at both group and individual levels (Rapport et al. 1988), there are also large inter-individual differences in optimum dosages, which cannot be easily explained by gender, age, weight or symptom severity (Rapport, Stoner, DuPaul, Kelly, Tucker, & Schoeler 1988; Rapport, DuPaul, & Kelly 1989).

In a highly influential paper, Sprague and Sleator (1977) reported a dose-related dissociation of cognitive and social responses to MPH. They found that the best performance on a paired associates learning task was reported at the lowest dose (0.3 mg/kg) with increased error rates at the higher dose (1.0 mg/kg). In contrast, the maximal clinical improvement ratings were found at the 1.0 mg/kg dose. They proposed a "window of response", which was best modelled as an inverted U curvilinear dose response curve. Sprague and Sleator's findings have not been replicated in subsequent studies, most of

which have reported linear dose response curves. Only 2 out of 11 studies reviewed by Rapport et al (1989) reported a decrease in cognitive abilities at higher doses, although in a separate analysis (Rapport & Kelly 1991) did find some evidence that dose response curves may vary depending on what type of task is being used. For example, whist vigilance tasks were very sensitive to medication effects there was no evidence to support improved performance with increased dose. On the other hand, tasks tapping into the impulsivity or learning domains were found to be highly sensitive to both overall medication effects and dose effects with better response at higher doses. They concluded that, at a group level, lower doses are required to optimize attention whilst higher doses are required for optimal performance on measures of impulsivity, more complex learning tasks such as paired associates learning and divergent thinking tasks. The current study found no evidence of impairment in cognitive performance at either the 0.3 or 0.6 mg/kg doses (See chapter 5 for details).

Taken together, these findings have led to the recommendation that, in clinical practice, once a decision to initiate treatment with MPH has been made, each child should be carefully titrated across a range of doses in order to ensure that they are exposed to, and maintained on, the most effective dose with the least adverse effects (Taylor, Dopfner, Sergeant, Asherson, Banaschewski, Buitelaar, Coghill, Danckaerts, Rothenberger, Sonuga-Barke, Steinhausen, & Zuddas 2004).

Defining Clinical Response

In psychiatric research, many different definitions of response have been proposed and one complicating factor in much of the research discussed above is a lack of standardization in defining “response”. Randomised controlled trials will often define response as a statistically superior change in scores on an outcome measure on the active treatment compared with that on the placebo or comparator treatment. By this definition, it is

possible to say that Treatment X is better either than placebo or than Treatment Y, but it is also possible that the improvement gained from this superior treatment is still not either clinically significant or meaningful. Even if a treatment does reliably result in clinically meaningful improvements in symptoms or reductions in impairments, “improved” individuals may still have a range of clinically impairing symptoms i.e. their condition has not been “normalized”.

Buitelaar et al. (1995) conducted their primary analyses using a relatively stringent definition of response and then repeated their analyses using more relaxed criteria. They found that levels of response could only be predicted by baseline characteristics when a fairly stringent and conservative definition of response was used and that these predictions did not generalise to the more liberally defined group.

It therefore appears that the definition of response is an important factor and raises the question as to whether different levels of response can be expected with different presentations. Such a situation could of course arise if, as suggested in chapters 5 and 6; different children with AD-HKD are presenting with heterogeneous neuropsychological profiles; different neuropsychological measures respond differently to MPH and; different aspects of neuropsychological performance are associated with different behavioural difficulties and impairments. For the analyses described in this Chapter, I will therefore use several complementary methods to describe clinical change. In addition to traditional methods of assessing response at the group level (ANOVAs and effect size [d]) I will adopt a similar strategy to that used by Buitelaar et al. (1995) and use the methods of Jacobson and Truax (1991) to calculate clinical change at an individual level. These methods allow response to be defined both in terms of a reliable change from baseline status and a clinically meaningful change.

The aims of this chapter are to describe the heterogeneity in clinical response to MPH in a group of previously drug naïve boys with hyperkinetic disorder, identify baseline sociodemographic, clinical and neuropsychological predictors of clinical response and assess the relationship between clinical change and change in neuropsychological task performance following treatment with MPH.

The specific research questions are;

- Does the definition of clinical response influence the pattern of clinical response?
- Is clinical response predicted by baseline sociodemographic, clinical or neuropsychological variables?
- Does the pattern of prediction vary depending on definition of response used?
- Is there an association between the clinical and neuropsychological responses to medication?

Specific hypotheses to be tested are that;

- The clinical response of HKD boys will be heterogeneous.
- Reliable and clinically significant change in clinical symptoms (as defined by Jacobson and Truax (1991)) will both be predicted by age and severity of symptoms at baseline.
- Based on the findings of Aman & Turbott (1991) both reliable and clinically significant change in clinical symptoms (as defined by Jacobson and Truax (1991)) will be predicted by baseline neuropsychological performance on the Recognition Memory Component (Component 4).

- Based on the findings of Aman & Turbott (1991) neither reliable nor clinically significant change in clinical symptoms (as defined by Jacobson and Truax (1991)) will be predicted by change in neuropsychological task performance.

Statistical Considerations

The analyses in this chapter were conducted using data from the baseline data (testing session 1) and the three chronic medication challenge testing sessions (testing sessions 3 – 5). Data from the chronic sessions were collapsed into the three treatment conditions; placebo, 0.3 mg/kg/dose and 0.6 mg/kg/dose. As the session order was counterbalanced using a Latin square design it was not necessary to use session order as a between subject variable. Baseline sociodemographic, clinical and neuropsychological data were investigated as potential predictors of response. Neuropsychological response to medication was defined as the difference on the main task measures between the active medication testing session and the placebo session.

Definitions of clinical response

As indicated above, in addition to traditional methods of assessing response at the group level (ANOVAs and effect size [d]), the methods of Jacobson and Truax (1991) were used to calculate clinical change. These methods allow for the consideration of both a reliable change from baseline status and a clinically significant change. The Jacobson and Truax method results in two measures - Clinically Significant Change and the Reliable Change Index.

- Clinically Significant Change is an index of “normalisation” that takes as its starting point the assumption that there is a relationship between making a Clinically Significant Change and a shift of symptoms from the abnormal/clinical range to the

normal/healthy range. The consequence of assessing Clinically Significant Change is a categorical decision that the observed change was or was not clinically significant.

- The Reliable Change Index provides a standardised method of calculating the amount of change that has occurred as a result of treatment and ensuring that this is reliably different from pre-treatment levels. The formula for calculating the Reliable Change Index results in a single score. This score can then easily be dichotomised to say whether Reliable Change was or was not achieved.

Both of these terms are described in more detail below.

Calculating Clinically Significant Change.

The total t-scores on Parent -rated 10-item Conners' Global Index rating scales (CGI-P, Conners 1997) were used to calculate Clinically Significant Change (3% missing data with complete data for 93% of cases) . It had been intended to use both parent and teacher ratings. However, teacher data could not be used as the response rate from teachers was too low (40% missing data with complete data for only 36% of cases).

To have made a clinically significant change a subject is required to have a level of functioning after treatment that is closer to the mean of a normal control population than to the mean of AD-HKD children not taking medication (Jacobson & Truax 1991). Whilst the CGI-P total score is considered to be the main measure of outcome, clinically significant change was also calculated separately for the restless/impulsive and emotional lability subscales of the CGI-P. The methods of Jacobson & Truax (1991) to calculate the appropriate cut off for these scales in this sample. In each case a t-score of ≤ 65 was indicative of Clinically Significant Change.

Calculating Reliable Change Index (RCI)

The total t-scores on Parent -rated 10-item Conners' Global Index rating scales (CGI-P, Conners 1997) were also used to calculate the Reliable Change Index (RCI). The RCI provides a standardised method of calculating the amount of change that has occurred as a result of treatment. It is calculated using the formula:

$$RCI = \frac{x_2 - x_1}{S_{diff}}$$

Where x_1 represents the subject's placebo score, x_2 represents that same subject's active treatment score and S_{diff} is the standard error of the difference between the two test scores.

S_{diff} is computed directly from the standard error of measurement according to the equation

$$S_{diff} = \sqrt{2(S_E)^2}$$

S_{diff} describes the spread of the distribution of change scores that would be expected if no actual change had occurred.

An RCI > 1.96 would be unlikely to occur ($p<0.05$) without actual change having taken place. Therefore an RCI of > 1.96 signifies a reliable change. In addition to categorising subjects as responders or non-responders the RCI can also be used as a continuous measure of change. CGI-P total score was again the main measure of outcome, however, the RCI was also calculated separately for the restless/ impulsive and emotional lability subscales of the CGI-P.

Defining Response using Clinically Significant Change and RCI

Taken together the measures of Clinically Significant Change and the RCI allow for 4 potential definitions of responder status for each clinical measure.

- "Full Response" – Clinically Significant Change and RCI > 1.96
- "Improved" - No Clinically Significant Change but RCI > 1.96
- "Normal but not improved" - Clinically Significant Change but RCI ≤ 1.96
- "Unimproved or worse" – No Clinically Significant Change and RCI ≤ 1.96

Clinically Significant Change and RCI were calculated for each subject separately for the two active doses of medication (0.3 mg/kg and 0.6 mg/kg) and for each of the subscales of the CGI-P (total, restless/impulsive, emotional lability).

Prediction of Clinical Response

A Principal Components Analysis (PCA), fully described in chapter 6, was conducted on the z scores (adjusted for age and BPVS) for the primary dependent measures derived from the neuropsychological tasks for which statistically significant baseline differences were found between the present sample of HKD boys and healthy matched Controls (Intradimensional Extradimensional Set-shifting, Spatial Span, Spatial Working Memory, Stockings of Cambridge, Pattern and Spatial Recognition, Delayed Matching to Sample, Paired Associates Learning and 5 Choice Reaction Time). From this PCA, 4 Components were identified with Eigen values >1. Separate linear and logistic regressions were used to investigate socio-demographic, clinical, neuropsychological predictors of clinical response for each of the two active dose levels (0.3 mg/kg/dose and 0.6 mg/kg/dose) and for each of the CGI-P subscales (total, restless/impulsive, emotional lability).

For the multiple regressions, the 4 component scores from the Principle Components Analysis ("Paired Associates Learning", "Mixed", "Working Memory and Planning" and "Recognition Memory"), age, BPVS percentile rank (a measure of verbal intelligence) and the baseline t-scores for the four subscales of the parent Conners' Rating Scales (CPRS;

hyperactivity, oppositional, cognitive and ADHD) were the predictors and the Reliable Change Index score was the outcome variable.

The components from the PCA were used as predictors in preference to the raw scores on each individual task measure as the components are designed to be independent of each other and are associated with less measurement error than individual task scores (see chapter 6 for a fuller discussion of this issue).

For the logistic regressions the same predictors were used. The outcome variable was defined as responder status.

Results

Clinical response to MPH

Chronic treatment with twice daily MPH at 0.3 and 0.6 mg/kg/dose improved functioning as measured by all subscales of the10 item Conners' Global Index (see Table 9.1). There were no statistically significant differences in degree of improvement between the two MPH doses, although there was a non-significant trend for increased response with the higher MPH dose on teacher-rated Conners' scores. Effect sizes on most scales were in the moderate to large range.

Table 9.1 Parent and teacher rated Connors' Global Index Scores and effect sizes for the differences between three treatment groups of previously drug naïve boys with HKD following a 3 x 1 month randomized placebo-controlled, double blind, crossover trial of MPH at three doses (placebo vs. 0.3 mg/kg/dose MPH vs. 0.6 mg/kg/dose MPH)

	Placebo Mean (s.d.)	MPH 0.3 mg/kg mean (s.d.)	MPH 0.6 mg/kg mean (s.d.)	F	P	Effect size	
						Pla vs. 0.3mg/kg	Pla vs. 0.6mg/kg
Parent Connors Global Index							
Total subscale (T score)	77.2 (11.1)	67.2 (13.5)	67.0 (14.8)	12.2	<0.001	0.81	0.78
Restless/impulsive subscale (T score)	77.1 (10.9)	68.4 (13.8)	65.5 (13.6)	14.2	<0.001	0.70	0.94
Emotional Lability subscale (T score)	71.6 (13.6)	65.2 (14.2)	65.6 (15.0)	4.0	0.02	0.46	0.42
Teachers Connors Global Index							
Total subscale (T score)	73.0 (11.3)	65.0 (14.1)	58.5 (12.8)	15.3	<0.001	0.63	1.20
Restless/impulsive subscale T score)	71.8 (9.9)	63.7 (13.6)	57.7 (11.4)	17.4	<0.001	0.68	1.32
Emotional lability subscale (T score)	69.0 (14.1)	62.6 (14.1)	57.8 (14.3)	7.5	0.001	0.45	0.79

The response rates as assessed by Clinically Significant Change and Reliable Change Index are summarised in table 9.2. As might be expected, the rates of response as measured by "Reliable Change" (symptomatic improvement) are generally greater than those for "Clinically Significant Change" (normalisation). Other than an increased rate of response with high dose medication as measured by "Reliable change" on the restless/impulsive subscale, the rates of response for each dose are very similar.

The rates for the 4 categories of change suggested by Jacobson and Truax (1991) are summarised in table 9.3. Rates are given for;

- "Full response" (Clinically Significant Change and RCI > 1.96)
- "Improved" (no Clinically Significant Change but RCI > 1.96)
- "Normal but not improved" (Clinically Significant Change but RCI ≤ 1.96)
- "Unimproved or worse" (no Clinically Significant Change and RCI > 1.96)

Rates for "full response" were considerably higher than those of either "improved" or "normal but not improved". Most subjects whose symptoms normalised (i.e. had a Clinically Significant Change) also had a robust reduction in symptoms (RCI > 1.96) (77 – 94% depending on measure and dose). Those subjects with robust improvement in symptoms (RCI > 1.96) also tended to have normalisation of their symptoms (Clinically Significant Change) (60 – 80% depending on measure and dose).

Table 9.2 Rates of "Reliable Change" and "Clinically Significant Change" as defined by Jacobson and Truax (1991) for response of boys with HKD to a chronic challenge with MPH administered via a 3 x 1 month randomized, placebo-controlled, double blind, crossover trial at three doses (placebo vs. 0.3 mg/kg/dose MPH vs. 0.6 mg/kg/dose MPH)

	Clinical Response	
	"Reliable Change" %	Clinically Significant Change %
Low dose (0.3 mg/kg)		
10 item Connors Parent Total	57.4	53.2
10 item Connors Parent Restless Impulsive scale	60.0	47.3
10 item Connors Parent Emotional Lability Scale	52.7	56.4
High dose (0.6 mg/kg)		
10 item Connors Parent Total	63.8	57.4
10 item Connors Parent Restless Impulsive scale	70.9	58.2
10 item Connors Parent Emotional Lability Scale	54.5	49.1

Table 9.3: Clinical response of boys with HKD to a chronic challenge with MPH administered via a 3 x 1 month randomized, placebo-controlled, double blind, crossover trial at three doses (placebo vs. 0.3 mg/kg/dose MPH vs. 0.6 mg/kg/dose MPH)

	Clinical Response			
	"Full Response" %	"Improved" %	"Normal but Not improved" %	"Unimproved or worse" %
Low dose (0.3 mg/kg)				
10 item Connors Parent Total	46.8	10.6	6.2	36.4
10 item Connors Parent Restless Impulsive scale	41.8	18.2	5.5	34.5
10 item Connors Parent Emotional Lability Scale	45.5	7.2	10.9	36.4
High dose (0.6 mg/kg)				
10 item Connors Parent Total	53.2	10.2	4.2	32.4
10 item Connors Parent Restless Impulsive scale	54.5	16.4	3.7	25.4
10 item Connors Parent Emotional Lability Scale	41.8	12.7	8.1	37.4

"Full response" = T score ≤ 65 and reliable change index > 1.96 on the various Connors' Global Impact scales (Parent), "Improved" = T score > 65 but reliable change index > 1.96 on the various Connors' Global Impact scales (Parent), "Normal but not improved" = T score ≤ 65 but reliable change index ≤ 1.96 on the various Connors' Global Impact scales (Parent), "Unimproved or worse" = T score > 65 and reliable change index > 1.96 on the various Connors' Global Impact scales (Parent).

Table 9.4 presents the response data in a slightly different way indicating the proportions who responded at neither dose, at one dose but not the other or at both doses. Although at a first glance the rates of “full response” appear somewhat low compared with the published rates of response (traditionally quoted as being around 70%), when one looks at the total number of responders (last column of table 9.4) it is clear that even using this rather conservative definition of “full response”, the overall response rates were similar to those from previous clinical trials.

Table 9.4 also demonstrates that whilst some children made a “Full Response” at both doses there were many whose response was considerably better at one dose than it was at the other. For example on the CGI-P total score 29.8% of boys made a full response at both doses, but 17% made a full response only at the 0.3 mg/kg dose and 23.4% only at the 0.6 mg/kg dose. The picture is different if one uses “Reliable Change” as an index of response as for this measure a greater proportion of responders responded at both doses (46.8 % - or for the CGI-P total score) than at either the 0.3 mg/kg (10.6) or 0.6 mg/kg (17.0%). This suggests that if you are going to have a robust symptomatic response at all it is quite likely that you will have some response at both 0.3 mg/kg and 0.6 mg/kg doses but that your optimal (and full) response may be to one particular dose level rather than the other.

Table 9.4: Response rates of previously drug naïve boys with HKD to different doses of MPH administered via a 3 x 1 month randomized, placebo-controlled, double blind, crossover trial at three doses (placebo vs. 0.3 mg/kg/dose MPH vs. 0.6 mg/kg/dose MPH)

Definition of response	Neither dose (%)	0.3 mg/kg dose only (%)	0.6 mg/kg dose only (%)	Both doses (%)	Total responders (%)
"Full Response" T score ≤ 65 <u>and</u> Reliable change index > 1.96 on 10 item Connors' Global Impact (Parent)					
Total Subscale	29.8	17.0	23.4	29.8	70.2
Restless Impulsive subscale	29.1	16.4	29.1	25.5	70.9
Emotional Lability Scale	38.2	20.0	16.4	25.5	61.8
Reliable Change Reliable change index > 1.96 on 10 item Connors' Global Impact (Parent)					
Total Subscale	25.5	10.6	17.0	46.8	74.5
Restless Impulsive subscale	21.8	7.3	18.2	52.7	78.2
Emotional Lability Scale	30.9	14.5	16.4	38.2	69.1
Clinically Significant Change T score ≤ 65 on 10 item Connors' Global Impact (Parent)					
Total Subscale	28.8	17.3	19.2	34.6	71.2
Restless Impulsive subscale	27.1	16.9	27.1	28.8	72.9
Emotional Lability Scale	25.4	27.1	16.9	30.5	74.6

Prediction of response to MPH

These results on clinical response to MPH and those previously described in chapter 5, which focused on neuropsychological response to MPH, clearly indicate that there is heterogeneity in both clinical and neuropsychological response to medication. It is therefore important to investigate whether any of the measured variables are helpful in identifying who will respond to MPH and at what does. This was investigated in a number of ways.

- Linear regressions were conducted using the Reliable Change Index as a continuous measure of outcome.

- ANOVAs and Logistic regressions were conducted with treatment outcome dichotomised into Responder / Non-Responder.

- In each case separate analyses were conducted on the three 10 item Conners' Global Index – Parent version (CGI-P) subscales (Total, Restless/Impulsive and Emotional Lability) in order to assess whether there were different predictors for each outcome.

- As the pattern of clinical responding suggested that different children respond differently at different doses, additional analyses were conducted separately for each dose level.

- In view of the small numbers of subjects in the "improved" and "normalised but not improved" groups, analyses were not conducted for these outcomes and these subjects were excluded from the analyses.

Linear Regressions

The predictors for the linear regressions were.

- Component scores from the four components that emerged from the PCA of neuropsychological performance at baseline of the HKD group subjects corresponding to Component 1 "*Paired Associates Learning*", Component 2 "*Mixed*" (Spatial Span, Reaction Time and Attentional Set-shifting), Component 3 "*Working Memory and Planning*" and Component 4 "*Recognition Memory*" (see chapter 6, figure 6.7 for details).
- Sociodemographic data (age, deprivation score and BPVS score).
- Baseline clinical measures (Parent Conners' Rating Scale- – Oppositional, Cognitive, Hyperactivity and ADHD subscale T-scores).

The outcome variable was the "Reliable Change Index" score on the 10 item Connor's Global Index – Parent version (CGI-P). The primary analyses were those for the CGI-P total score at both 0.3 mg/kg and 0.6 mg/kg MPH. Separate analyses were conducted, at each dose level, for the CGI-P restless/impulsive and emotional lability subscales. The results are summarised in table 9.5.

In each of the analyses at the lower dose, Component 4 ("Recognition Memory") was retained in the best fit equation. Poor baseline performance on Component 4 predicted a better response to medication. For the CGI-P total score only Component 4 was retained (r^2=.19, F(1,43)= 10.1, p=.003). For the restless/impulsive subscale, poor baseline performance on Component 4 and the lower (better) scores on the CPRS ADHD Subscale were both associated with a better response (r_2=.21, F (1,53)= 7.15, p=.002). For the emotional lability subscale, poor baseline performance on Component 4 and lower (better) scores on the CPRS cognitive subscale were retained (r_2=.27, F (1,53)= 9.80, p<.001).

There were no predictors of response from the linear regressions conducted on data from the higher dose challenges.

Table 9.5: Baseline Neuropsychological, sociodemographic and clinical predictors of MPH response (Linear Regression) measured by the "Reliable Change Index" of the parent rated Connors' Global Index" of boys with HKD following a 3 x 1 month randomized, placebo-controlled, double blind, crossover trial at three doses (placebo vs. 0.3 mg/kg/dose MPH vs. 0.6 mg/kg/dose MPH)

	Predictors of response (linear regression)	
"Reliable Change index" for Connors' Global Index – Parent	Low Dose (0.3 mg/kg)	High Dose (0.6 mg/kg)
Total Score	Component 4	None
Restless/Impulsive Subscale	Component 4 CPRS ADHD Subscale	None
Emotional Lability Subscale	Component 4 CPRS Cognitive Subscale	None
CPRS = Conners' Parent Rating Scale, Component 4 = component 4 "recognition memory" from the principle components analysis of baseline neuropsychological performance		

ANOVAs

These same predictor variables were entered into separate ANOVAs with responder status to either 0.3 or 0.6mg/kg as independent variables. These results are summarised in table 9.6.

For Connors' Global Index – Parent (CGI-P) total score MPH 0.3mg/kg, a significant difference was found only for the Component 4 "recognition memory" component [F (1,57) = 5.3, p = 0.025] with responders having worse baseline performance, and for 0.6mg/kg, only BPVS score differentiated between the groups [F (1,61) = 6.7, p = 0.012] with responders having higher BPVS scores than non-responders.

For CGI-P restless/impulsive subscale at MPH 0.3mg/kg, a significant difference was found for the Connors' Parent Rating Scale (CPRS) hyperactivity (F (1,53) = 5.1, p = 0.01) and ADHD subscales (F (1,53) = 4.1, p = 0.02) with responders having lower (better) CPRS scores than non-responders. For the 0.6 mg/kg MPH dose, there were no differences between responders and non-responders on any measure.

For CGI-P emotional lability subscale at MPH 0.3mg/kg, a significant difference was found for the Connors' Parent Rating Scale (CPRS) cognitive, (F (1,53) = 5.4, p = 0.07) hyperactivity (F (1,53) = 4.0, p = 0.02) and ADHD subscales (F (1,53) = 9.2, p <0.001) with '*responders*' having lower (better) CPRS cognitive subscale scores than non-responders. At the 0.6mg/kg dose, only BPVS score differentiated between the groups [F (1,59) = 3.8, p = 0.03] with '*responders*' having higher BPVS scores than non-responders.

Table 9.6: Neuropsychological, sociodemographic and clinical differences between "full responders" and non-responders (ANOVA) measured by "Full Response" of the parent rated Connors' Global Index" of boys with HKD following a 3 x 1 month randomized, placebo-controlled, double blind, crossover trial at three doses (placebo vs. 0.3 mg/kg/dose MPH vs. 0.6 mg/kg/dose MPH)

	Differences between full responders and non-responders at ANOVA	
"Full Response" for Connors' Global Index - Parent	Low Dose (0.3 mg/kg)	High Dose (0.6 mg/kg)
Total Score	Component 4	BPVS percentile rank
Restless/Impulsive Subscale	CPRS ADHD Subscale CPRS hyperactivity Subscale	None
Emotional Lability Subscale	CPRS ADHD Subscale CPRS hyperactivity Subscale CPRS Cognitive Subscale	None

"Full Response" = T score ≤ 65 and Reliable change index > 1.96 on 10 item Connors' Global Impact (Parent), CPRS = Conners' Parent Rating Scale, BPVS = British Picture Vocabulary Scale, Component 4 = component 4 "recognition memory" from the principle components analysis of baseline neuropsychological performance

Logistic Regressions

Several logistic regressions were conducted to expand on the findings of the ANOVAs. In each analysis the predictors were the same as those used previously;

- Component scores from the four components that emerged from the PCA of the baseline neuropsychological performance of the HKD group subjects corresponding to Component 1 "*Paired Associates Learning*", Component 2 "*Mixed*" (Spatial Span, Reaction Time and Attentional Set-shifting), Component 3 "*Working Memory and Planning*" and Component 4 "*Recognition Memory*" (see chapter 6, figure 6.7 for details).
- Sociodemographic data (age, deprivation score and BPVS score).
- Baseline clinical measures (Parent Conners' Rating Scale- – Oppositional, Cognitive, Hyperactivity and ADHD subscale T scores).

The primary outcome was "Full Response" (T score ≤ 65 and Reliable change index > 1.96) on the total scale of the 10 item Connors' Global Impact (Parent) (CGI-P) rating scale at each dose level. Additional analyses were conducted for each of the CGI-P subscales and each dose level and for two alternative definitions of response; "Reliable Change" (Reliable change index > 1.96) and "Clinically Significant Change" (T score ≤ 65). The significant findings are summarized in table 9.7.

Table 9.7: Neuropsychological, sociodemographic and clinical predictors of MPH response of boys with HKD (Logistic Regression) as defined by several different definitions of response following a 3 x 1 month randomized, placebo-controlled, double blind, crossover trial at three doses (placebo vs. 0.3 mg/kg/dose MPH vs. 0.6 mg/kg/dose MPH)

	Predictors of Clinical Response (Logistic Regression)		
	Low Dose (0.3 mg/kg)	High Dose (0.6 mg/kg)	Either or Both Doses (0.3 mg/kg or 0.6 mg/kg)
Connors' Global Index (Total Score)			
"Full Response"	Component 4	BPVS Percentile Rank CPRS Hyperactivity Subscale	None
"Reliable Change"	None	None	None
"Clinically Significant Change"	Component 4	CPRS Hyperactivity Subscale BPVS Percentile Rank	None
Connors' Global Index (Restless/Impulsive subscale)			
"Full Response"	None	None	None
"Reliable Change"	CPRS ADHD Subscale	None	None
"Clinically Significant Change"	None	None	None
Connors' Global Index (Emotional Lability subscale)			
"Full Response"	Component 3 CPRS Cognitive Subscale	Component 3 CPRS Hyperactivity Subscale BPVS Percentile Rank	Component 3 CPRS Cognitive Subscale
"Reliable Change"	Component 3 CPRS ADHD Subscale	Component 3	Component 3 CPRS ADHD Subscale
"Clinically Significant Change"	Component 3 CPRS Cognitive Subscale	Component 3 CPRS Hyperactivity Subscale BPVS Percentile Rank	Component 3 CPRS Cognitive Subscale

"Full Response" = T score ≤ 65 and Reliable change index > 1.96 on 10 item Connors' Global Impact (Parent), "Reliable Change" = Reliable change index > 1.96 on 10 item Connors' Global Impact (Parent), "Clinically Significant Change" = T score ≤ 65 on 10 item Connors' Global Impact (Parent), CPRS = Conners' Parent Rating Scale; BPVS = British Picture Vocabulary Scale; Component 3 = Component 3 "Working Memory and Planning" from the principle components analysis of baseline neuropsychological performance; Component 4 = component 4 "recognition memory" from the principle components analysis of baseline neuropsychological performance

Connors' Global Impact – Parent; Total Score

For 0.3 mg/kg dose MPH and CGI-P total score "Full Response", Component 4 ("Recognition Memory") was the only significant predictor (β(SE) = 1.43 (0.62) p = .016, r^2 = .20, Exp b = 4.41). Poor baseline performance on Component 4 predicted a good clinical response to MPH. The positive predictive power (responders correctly classified) was 47% and the negative predictive power (non-responders correctly classified) was 81%. For the 06 mg/kg MPH dose, there were no neuropsychological predictors of response. However, response was predicted by BPVS Percentile Rank (β(SE) = 0.028 (0.102) p = .015, Exp b = 1.03) and Connors' Parent Rating Scale (CPRS) Hyperactivity Subscale (β(SE) = 0.11 (0.046) p = .021, Exp b = 1.11) overall r^2 = .24. Responders had higher (worse) CPRS Hyperactivity subscale scores at baseline and higher BPVS scores, the positive predictive power was 48% and the negative predictive power was 79%. There were no predictors for "Full Response" at "either or both doses". The predictors for "Clinically Significant Change" for CGI-P total score were the same as those for "Full Response". There were no predictors for CGI-P total score "Reliable Change" at any dose.

In order to further investigate which components of the "Recognition Memory" Component predicted response, linear regression with CGI-P – total subscale T score for MPH 0.3 mg/kg change from placebo as the dependent variable, and Delayed Matching to Sample, Pattern and Spatial Recognition z-scores as predictors, revealed that only Delayed Matching to Sample was retained in the best fit equation (r^2 = 0.13, F(1,24) = 6., p = 0.01), with poorer baseline performance predicting a better response to medication.

Conners' Global Impact – Parent; Restless/Impulsive subscale

There were no predictors of "Full Response" or "Clinically Significant Change" on the CGI-P restless/impulsive subscale at 0.3 mg/kg, 0.6 mg/kg or at "either or both doses". The CPRS ADHD Subscale was the only predictor of "Reliable Change" on the CGI-P restless/impulsive

subscale, and then only at the 0.3 mg/kg dose (β(SE) = -0.18 (0.075) p = .014, r^2 = .18, Exp b = 0.83). Responders had lower (better) CPRS ADHD scores at baseline.

Connors' Global Impact – Parent; Emotional Lability subscale

Component 3 ("Working Memory and Planning") predicted response on the CGI-P emotional lability subscale at both doses and under all definitions of response. Poor baseline performance on Component 3 predicted a good clinical response to MPH. Response at several levels was also predicted by either the CPRS cognitive or CPRS hyperactivity subscales and by BPVS percent correct for the "Full Response" and "Clinically Significant Change" definitions at the high dose.

"Full response" at 0.3 mg/kg was predicted by Component 3 (β(SE) = 1.44 (0.69) p = .037, Exp b = 4.23) and CPRS cognitive subscale (β(SE) = -0.19 (0.065) p = .003, Exp b = 0.83) total r^2 = .32, poor baseline performance on Component 3 and lower (better) CPRS cognitive subscale scores predicted response. The positive predictive power was 55% and the negative predictive power was 81%.

"Full response" at high dose was predicted by Component 3 (β(SE) = 1.76 (0.82) p = .031, Exp b = 5.82), CPRS hyperactivity subscale (β(SE) = -0.16 (0.065) p = .013, Exp b = 1.17) and BPVS percentile rank (β(SE) = -0.037 (0.015) p = .011, Exp b = 1.04) total r^2 = .42, poor baseline performance on Component 3, lower (better) baseline CPRS hyperactivity subscale scores and higher BPVS scores predicted response. The positive predictive power was 41% and the negative predictive power was 87%.

Full Response at "either or both doses" was predicted by Component 3 (β(SE) = 1.48 (0.69) p = .039, Exp b = 4.38) and CPRS cognitive subscale (β(SE) = -0.18 (0.065) p = .007, Exp b = 0.84) total r^2 = .31, poor baseline performance on Component 3 and lower (better) CPRS

cognitive subscale scores predicted response. The positive predictive power was 67% and the negative predictive power was 77%.

For “Reliable Change”, in addition to poor baseline performance on Component 3 predicting response at both doses and at “either or both doses”, lower (better) scores on the CPRS ADHD subscale also predicted response. For “Clinically Significant Change” in addition to poor baseline performance on Component 3 predicting response at both doses and at “either or both doses”, lower (better) scores on the CPRS cognitive subscale also predicted response.

In order to further investigate which components of the “Working Memory and Planning” Component predicted response, further linear regressions were conducted at both dose levels with the CGI-P emotional lability subscale “Reliable Change Index” as the dependent variable, and Spatial Working Memory Between-search Errors and Strategy score and Stockings of Cambridge z-scores as predictors. None of these measures predicted response at either dose.

Summary of prediction of response to MPH

Taken together these results suggest that baseline clinical and neuropsychological factors have a role in the heterogeneity of clinical response to MPH. Whilst several factors predicted the degree of response to MPH in boys with HKD, the precise nature of these predictors was dependent on both the dose of MPH and the definition of response.

The main findings were;

- Age did not predict response.

- There were more positive predictive findings associated with response to the lower dose of MPH (0.3 mg/kg) than with the higher dose (0.6 mg/kg) or when response to "either or both doses" was the dependent measure.

- Where clinical response was predicted by baseline scores on the various CPRS subscales, it was generally true that better response was predicted by lower (better) scores at baseline (the exception was that both "Full Response" and "Reliable Change" were predicted in the logistic regressions by higher (worse) baseline scores on the CPRS Hyperactivity subscale).

- The most robust finding was that poor baseline performance on the recognition memory tasks that made up Component 4 (Delayed Matching to Sample, Pattern Recognition and Spatial Recognition) was predictive of a better response to the lower dose of MPH (0.3 mg/kg) as rated by the CGI-P Total Score.

- The logistic regressions (but not the other analyses) suggest that poor performance on the working memory and planning tasks that made up Component 3 (Spatial working Memory and Stockings of Cambridge) was predictive of response to MPH on the CGI-P Emotional Lability subscale at both of the doses tested.

- Of particular note is that although clinical response on the CGI-P Emotional Lability subscale was predicted by poor baseline working memory and planning it was also, at the lower 0.3 mg/kg dose of MPH and at "either or both doses", associated with lower levels of baseline problems on the parent rated CPRS Cognitive subscale.

Neuropsychopharmacological predictors of clinical response

Those measures for which there was a robust response to MPH on the CGI-P total score (see Chapter 5, Table 5.5) were investigated to assess whether neuropsychopharmacological change on these measures predicted clinical response.

For CGI-P total score at the 0.3mg/kg dose of MPH, the measures for which there was a response were Go/NoGo Block 2 Errors to Distractors (ERD) and Reaction Time to Targets (RTT); Spatial and Pattern Recognition (% correct), Delayed Matching to Sample (total % correct, plus 0,4 and 12s delays). Change scores (placebo vs. 0.3 mg/kg) were calculated for each of these variables and entered as predictors within a correlational regression analysis with the CGI-P total score "Reliable Change Index" as the dependent variable. Only Block 2 ERD (Block 2 was the simpler non-switch block) performance improvement was significantly correlated with clinical response ($p = 0.002$). This was also the only measure that was retained in the best fit equation ($r^2 = 0.17$, $F(1,44) = 8.9$, $p = 0.005$). A logistic regression was also conducted using the same measures as predictors and "Full Response" (robust change and normalisation) to 0.3 mg/kg MPH on the CGI-P total score as the dependent variable. Block 2 ERD was again the only significant predictor (β(SE) = -0.52 (0.27) $p = .05$, $r^2 = .10$, Exp b = 0.59) with a positive predictive power of 17% and a negative predictive power of 92%.

For CGI-P total score at the 0.6mg/kg dose of MPH, the measures for which there was a response were Go/NoGo Block 2 Errors to Distractors (ERD) and Block 1 ERD and RTT; Spatial and Pattern Recognition (% correct), Delayed Matching to Sample (total % correct, plus 0,4 and 12s delays). The same series of analyses were conducted as described for the 0.3 mg/kg dose above. There were no significant correlations between neuropsychological measures and clinical outcome at this dose and none of the neuropsychological measures predicted clinical response in either the correlational or logistic regressions.

Discussion

Heterogeneity of Clinical response

These results support the hypothesis that the clinical response of boys with HKD to MPH is heterogeneous and both provide some support for, and extend previous findings about, the prediction of response to MPH.

There are several important aspects of these results that require discussion.

The rates of clinical response and the effect sizes found for primary and secondary clinical outcome measures (the parent rated Conners' Global Index and its subscales) mirror those reported in the literature and support this as a "positive trial" (i.e. active medication clearly distinguished from placebo). This is important as it is a pre-requisite for the interpretation of all of the other results from the study.

Other than the study of Aman and Turbott (1991), most of the previous studies that investigated neuropsychological response to MPH were conducted with either acute medication challenges or after a brief withdrawal of medication and did not include measures of clinical outcome. It is, therefore, not possible to directly compare the present data directly with most of those already in the literature. The data presented here support a robust response to medication in around 75% of subjects with a "Full Response" (robust change and normalisation) in around 70% and effect sizes of around 0.8 on parent ratings at both dose levels and of 0.6 for low dose (0.3 mg/kg) and 1.2 for high dose (0.6 mg/kg) on teacher ratings. These data reveal one major limitation of the analysis presented here. Whilst the effect sizes based on parent report were similar for the two dose levels, for those on whom teacher data was available, the teachers consistently reported greater improvement at the higher dose. These data suggest that teachers and parents are may base their judgements about response to medication on different aspects of a child's

presentation. It would have been of considerable interest to have been able to look for differential predictors of response by dose level based on teacher reported outcome measures. However, this was not possible as due the large amount of missing teacher data (complete for only 36% of cases compared with 93% of parent data) it was not appropriate to conduct predictive analyses on the teacher reported outcomes.

From a clinical perspective it is interesting to note that with respect to the parent reported data, the majority of subjects who were scored as having made a “Reliable Change” in clinical presentation were also judged to have made a “Clinically Significant Change” (normalised) and, therefore, were judged to have made a “Full Response” as defined by Jacobson and Truax (1991). Similarly, almost all of those making a “Clinically Significant Change” were classified as “Full Responders”. From a clinical perspective this is important as it supports the notion that “normalisation” of AD-HKD symptoms is an achievable goal of treatment for the majority of subjects who make a response to MPH. This supports the findings of several large scale clinical trials including the influential Multimodal Treatment of ADHD Study (Greenhill et al. 2001). Notwithstanding these very positive findings, there is clearly a heterogeneous clinical response to MPH in this group of boys with HD. Clearly, not everyone will respond and for those that do, they will respond in different ways at different doses.

With respect to dose, there are different findings depending on the definition of response employed. If one is looking only for a reliable reduction in AD-HKD related symptoms and behaviours then many of those who are going to respond will have a reasonable response at both low and high dose MPH (63% for the CGI-P total score). However, only 42% of “full responders” will respond to both doses, with 24% making a full response only to the lower dose and 33% only to the higher dose. Therefore, from a clinical perspective there are two types of questions that can be asked about predicting response.

- Can we predict who will make a meaningful response to MPH at any dose?

- Can we predict who will respond best to either a high or low dose of MPH?

Can we predict who will make a meaningful response to MPH at any dose?

From these data there were few reliable predictors of overall response to MPH.

Unlike the findings from previous studies, clinical response, by any definition, was not predicted by age.

The relationship between baseline clinical characteristics and clinical response was complex. In many of the analyses none of the baseline clinical characteristics were predictive of clinical response. However, in those analyses where clinical response was predicted by baseline scores on the various CPRS subscales, it was generally true that better response was predicted by lower (better) scores at baseline (the exception was that both “Full Response” and “Reliable Change” were predicted in the logistic regressions by higher (worse) baseline scores on the CPRS Hyperactivity subscale).

No predictors of response (as defined by any of the three sets of criteria used – “Full Response”, “Reliable Change” and “Clinically Significant Change”), at “either or both doses”, were identified when CGI-P total score or the CGI-P restless/impulsive subscale, the two scales that would be expected to tap into the core AD-HKD symptoms, were used to define outcome.

Poor baseline performance on Component 3 (“Working Memory and Planning”), which indexes working memory and planning performance, two of the core executive functions, predicted response at “either or both doses” on the CGI-P emotional lability subscale. This brief 3 question subscale is concerned with symptoms of emotional lability and includes

questions that enquire about; temper outbursts, crying often and easily and mood changes quickly and drastically (the full questionnaire is in annex 5a). These symptoms are frequently associated with, but are not core to, AD-HKD. This association between Component 3 and clinical response was seen for all three definitions of response at “either or both doses” (and independently at each of the two dose levels).

“Full response” and “Clinically Significant Change” at “either or both doses” on the CGI-P emotional lability subscale were also predicted by the Connors’ Parent Rating Scale (CPRS) cognitive subscale, which includes items on; “difficulty doing or completing homework”, “fails to complete assignments”, “needs close supervision to get through assignments”, “avoids, expresses reluctance about, or has difficulties engaging in tasks that require sustained mental effort”, “has trouble concentration in class” and “does not follow through on instructions and fails to finish schoolwork, chores or duties in the workplace” (annex 2a). Interestingly however, for this measure, a better response was predicted by less baseline difficulty. It is also interesting that there was no association between response on this subscale and Component 4, which indexes non-executive aspects of recognition memory.

These findings are entirely novel as predictors of “emotional lability” response have not been previously studied. Taken together they raise the question as to whether the emotional lability frequently seen in AD-HKD is related to deficits in executive functioning, in particular difficulties with working memory and planning. These findings clearly warrant further investigation.

Can we predict who will respond best to either a high or low dose of MPH?

Different patterns of predictors were found for response to the lower (0.3 mg/kg) and higher (0.6 mg/kg) MPH doses and within each dose level these varied somewhat, depending on the definition of response and outcome scale used.

Baseline performance on Component 4 (Delayed Matching to Sample, Pattern Recognition and Spatial Recognition) predicted CGI-P total score "Full Response" and "Clinically significant Change" to 0.3 mg/kg MPH doses on both the linear and logistic regressions and for all three CGI-P scales in the linear regressions. In each case, poorer baseline neuropsychological performance predicted a better clinical response. This was the only neuropsychological Component to predict responder status rated by CGI-P total score at any dose. The additional analyses suggested that this effect is largely due to performance on the Delayed Matching to Sample task. These findings were limited to the 0.3 mg/kg dose condition.

The findings reported here show some intriguing similarities with those previously reported by Aman and Turbott (1991). Although these authors analysed and interpreted their findings from the perspective of attentional processes, one of the tasks that they found to be predictive of a clinical response to MPH had similarities to the Delayed Matching to Sample task used here. These findings clearly also warrant further investigation. They support the hypothesis that nonworking memory dysfunction and aspects of temporal lobe functioning may make an important contribution to AD-HKD pathophysiology (Castellanos, Sonuga-Barke, Milham, & Tannock 2006; Rhodes, Coghill, & Matthews 2004). The reasons for these findings being restricted to the low dose medication condition are unclear. However one might speculate that this non linear dose response curve is broadly supportive of the "non-executive memory" route to AD-HKD, being pathophysiologically

distinct from other routes and therefore, also supportive of the hypothesis that neuropsychological heterogeneity may be related to causal heterogeneity.

As was noted for the “either or both doses” condition, poor performance on “Component 3”, indexing working memory and planning, and better scores on the CPRS cognitive subscale scores were robust predictors of response to 0.3 mg/kg MPH. However, as they also predicted response at 0.6 mg/kg they were not useful in discriminating high and low dose responders.

No other neuropsychological predictors of clinical response were found for the 0.6 mg/kg dose MPH. Verbal intelligence (as measured by the BPVS) and CPRS hyperactivity subscale predicted both “Full Response “and “Clinically Significant Change” to 0.6 mg/kg on the CGI-P total score and emotional lability subscale. For both of these subscales, responder status was associated with higher levels of verbal intelligence, mirroring the findings of Buitelaar et al. (1995). However, whilst higher levels of symptoms on the CPRS hyperactivity scale predicted response on the CGI-P total score as was seen in Taylor et al (1987), lower levels were associated with response on the emotional lability subscale similar to the findings of Buitelaar et al (1995). BPVS score did not predict response to the lower dose of MPH. The CPRS hyperactivity subscale scores for low dose responders were generally lower than those of non-responders (table 9.6), but were not predictive of response in either the linear or logistic regressions.

In summary, the incomplete overlap between those responding to 0.3 and 0.6 mg/kg doses of MPH and the differential predictors for each dose level raises the possibility that MPH actions are mediated differently at different dose levels.

Does neuropsychological response to MPH predict clinical response?

Baseline neuropsychological performance on the non-executive memory tasks included in Component 4 (Delayed Matching to Sample, Pattern Recognition and Spatial Recognition) predicted response to MPH, and performance on these non-executive memory tasks was improved by the chronic administration of MPH. However, no association was found between improved task performance on these neuropsychological measures and improved clinical status. In fact, clinical response to MPH was only associated with neuropsychological response to MPH on a single measure from a single task (Go/NoGo Block 2 Errors to Distractors), a task that did not itself discriminate between HKD boys and healthy Controls at baseline (see chapter 5). These results mirror those reported by Aman and Turbott (1991) who also found little relationship between clinical change and change in task performance.

Thus, although there are measurable deficits on a range of neuropsychological tasks, and whilst some of these deficits are apparently ameliorated by MPH, we must consider the possibility that these deficits may not be related to the core functional impairments in AD-HKD in a meaningful way. It is also possible, and maybe even likely, that parents and teachers will tend to focus on different aspects of a child's functioning when they are rating that child's ADHD related difficulties and their response to medication. It could be that had it been possible to utilise teacher ratings of response, a greater number of predictors could have been identified. It also remains plausible that whilst improvements in neuropsychological functioning do mediate improvements in overall functioning and reduce overall impairment they do so in a manner, which is either more subtle, or less readily observed, than the improvements in core ADHD symptoms. Such improvements may not be captured by traditional, and brief, clinical rating scales like the 10 item Connors Global Impact scale that was used in this study. If true, this would suggest that it would be appropriate to consider the use of a broader range of outcome measures to assess

response to treatment in AD-HKD in addition to the traditional symptom rating scales. Whilst such measures could include a range of neuropsychological measures, the data from this study suggest that measures of recognition memory are likely to be particularly important.

Summary and Conclusions

The data presented in this Chapter support there being heterogeneity in boys with HKD with respect to their clinical response to MPH. Unlike previous studies, this heterogeneity of clinical response was not predicted by age. There was however some evidence to support the hypothesis that symptom levels at baseline are predictive of response and that these relationships were, to an extent, dose dependent and domain specific with very different patterns of predictors being associated with a good clinical response under different conditions. Lower levels of parent reported ADHD symptoms at baseline were associated with a positive response to MPH on the Restless/Impulsive subscale of the CGI-P but only at the lower 0.3 mg/kg dose of MPH, whilst lower levels of parent reported cognitive problems at baseline were predictive of positive response to MPH on the Emotional Lability subscale of the CGI-P. Again, this relationship was only seen at the lower MPH dose. Whilst higher levels of parent reported hyperactivity were associated with a better response to the higher 0.6 mg/kg dose MPH as measured by the CGI-P total score, lower levels were associated with a better response to the higher 0.6 mg/kg dose MPH as measured by the CGI-P Emotional Lability subscale.

Neuropsychological heterogeneity may contribute to the heterogeneity of response to MPH. Poor baseline performance on a Component comprising several recognition memory tasks was predictive of a better parent rated clinical response to MPH. This association was again limited to the 0.3 mg/kg condition. Poor performance on a component comprising working memory and planning tasks predicted a better response on the Emotional Lability

subscale of the CGI-P at both doses. Interestingly, neuropsychological response to MPH was not generally associated with clinical response except one single measure from a single task (Go/NoGo Block 2 Errors to Distractors), and this was the one task used in the study that failed to differentiate HKD boys from Controls.

Whilst much work remains to be done, these data suggest that the relationships between traditional symptom base clinical measures and neuropsychological measures are extremely complex and that it may be helpful to consider using broader measures of outcome in both clinical trials and clinical practice.

In the final Chapter I, will present an overall discussion of the findings from this study and comment on potential future avenues of research interest.

Chapter 10

Summary and general discussion, limitations and future directions

Summary and general discussion

The work presented in this thesis describes;

- The neuropsychological heterogeneity defined within a group of rigorously diagnosed, drug naïve boys with the relatively restrictive diagnosis of HKD
- The impact of two potential mediating factors, age and comorbidity, on this heterogeneity
- The relationship between neuropsychological functioning and clinical responses to methylphenidate.

Specific experimental findings were discussed in some detail at the end of each chapter. The purpose of this chapter, therefore, is to bring these findings together into a more general discussion, to consider the limitations of these studies and to suggest potential avenues for further investigation.

The data presented in Chapters 6 – 9 builds on previously published findings from this same study programme (Coghill, Rhodes, & Matthews 2007; Rhodes 2002; Rhodes, Coghill, & Matthews 2004; Rhodes, Coghill, & Matthews 2005; Rhodes, Coghill, & Matthews 2006). These papers established that this group of drug naïve boys with HKD were demonstrably significantly impaired across a broad range of neuropsychological tasks from the CANTAB battery and that, whilst methylphenidate (MPH) did not impact upon executive neuropsychological functioning , both acute and chronic methylphenidate exposure

significantly improved aspects of non-executive recognition memory. The main hypotheses and findings from each chapter are summarised in tables 10.1-10.4.

Table 70.1: Hypotheses and main findings from Chapter 6; Neuropsychological heterogeneity in drug naïve boys with hyperkinetic disorder

Chapter 6		
Hypothesis	Outcome	Comments
Drug naïve boys with ICD-10 defined HKD will demonstrate less neuropsychological heterogeneity than that previously found with DSM-IV defined ADHD samples.	Not supported	The pattern of neuropsychological heterogeneity for the boys with ICD-10 defined HKD was very similar to that previously reported for children with DSM-IV defined ADHD (Nigg, Willcutt, Doyle, & Sonuga-Barke 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington 2005).
HKD will be more strongly associated with executive rather than non-executive deficits in neuropsychological functioning.	Not supported	Whilst there were significant associations between HKD and deficits on a range of tasks with high executive demands, the strongest associations were with more simple recognition memory tasks with a low executive demand.
Both executive and non-executive neuropsychological tasks will independently discriminate between HKD and Controls but discrimination by executive tasks will be more effective than by the non-executive tasks.	Partially supported	Whilst the ability of the tasks to discriminate between the HKD and Control groups was only moderate, it was the case that some, but not all, of the executive and some but not all of the non-executive neuropsychological tasks independently discriminated between HKD and Controls. Several non-executive tasks (Spatial Recognition, Pattern Recognition, Delayed Matching to Sample and Spatial Span) were as effective as the most effective executive task (Spatial Working Memory).

Table 10.2: Hypotheses and main findings from Chapter 7; Development of Neuropsychological Functioning In Hyperkinetic Disorder

Chapter 7		
Hypothesis	Outcome	Comments
In healthy children the trajectory of development will differ between the different aspects of neuropsychological functioning, with non-executive aspects of memory developing earlier than executive functioning.	Partially supported	Two of the non-executive tasks studied (Pattern and Spatial Recognition) appeared to develop earlier than the other tasks. For the other tasks (both executive and non-executive) performance continues to develop between the ages of 7 and 14 years.
Children with HKD will show similar patterns of neuropsychological development to those seen in healthy children, with non-executive processes developing earlier than executive processes, but their overall development will be significantly delayed compared with these healthy Controls.	Supported	Whilst there was evidence that boys with HKD lagged behind the healthy boys with respect to the development of their neuropsychological performance, the pattern of development was similar with the performance of the HKD boys paralleling that of the healthy boys. This suggests that developmental issues do not account for the neuropsychological heterogeneity in the HKD boys.

Table 10.3: Hypotheses and main findings from Chapter 8; Does comorbidity with either oppositional defiant disorder or conduct disorder impact on the neuropsychological heterogeneity of hyperkinetic disorder?

Chapter 8		
Hypothesis	Outcome	Comments
Boys with "pure" HKD, HKD + ODD and HKD + CD will all demonstrate neuropsychological deficits compared with healthy boys.	Supported	All three clinical groups demonstrated deficits on several tasks compared with the healthy boys.
The presence or absence of comorbid ODD or CD will not impact on the patterns or degree of neuropsychological deficits seen in HKD boys.	Not supported	Compared with healthy boys each of the three clinical groups ("pure" HKD, HKD + ODD and HKD + CD) was associated with at least one unique neuropsychological deficit. This suggests that comorbidity between HKD and both ODD and CD may contribute to the neuropsychological heterogeneity in the HKD boys.

Table 10.4: Hypotheses and main findings from Chapter 9; Heterogeneity and Predictors of Clinical Response to MPH

Chapter 9		
Hypothesis	Outcome	Comments
The clinical response of HKD boys to MPH will be heterogeneous.	Supported	Depending on which scale and which definition of response was used, between 62 and 78% of boys with HKD responded to MPH treatment at either one or both of the doses. Whilst some boys showed a preferential response to the low dose (0.3 mg/kg) and some to the high dose (0.6 mg/kg), more boys responded to both doses than to either dose alone. The proportion responding to the different doses was dependent on the scale and definition of response used.
Reliable and clinically significant change in clinical symptoms will both be predicted by a.) Age and b.) Severity of symptoms at baseline.	a.) Not supported b.) Partially Supported	a.) Age did not predict clinical response to MPH. b.) Whilst there was some association between clinical response to MPH and baseline severity of symptoms this relationship was complex. Where clinical response was predicted by baseline scores on the various Conners' rating scale subscales, it was generally true that a better response was predicted by lower (better) scores at baseline (although in the logistic regressions "Full Response" and "Reliable Change" were predicted by higher (worse) baseline scores on the CPRS Hyperactivity subscale).
Based on the findings of Aman & Turbott (1991) both reliable and clinically significant change in clinical symptoms (as defined by Jacobson and Truax (1991)) will be predicted by baseline neuropsychological performance on Component 4 (Recognition Memory)	Supported	Baseline performance on Component 4 predicted CGI-P total score "Full Response" and "Clinically significant Change" at 0.3, but not 0.6, mg/kg MPH on both the linear and logistic regressions and for all three CGI-P scales in the linear regressions. In each case, poorer baseline neuropsychological performance predicted a better clinical response.
Following treatment with MPH neither reliable nor clinically significant change in clinical symptoms will be predicted by change in neuropsychological task performance.	Partially Supported	Clinical response to MPH was only associated with neuropsychological response to MPH on a single measure from a single task (Go/NoGo Block 2 Errors to Distractors), a task that did not itself discriminate between HKD boys and healthy Controls at baseline.

The primary finding is a rejection of the hypothesis that boys with ICD-10 defined HKD would demonstrate less neuropsychological heterogeneity than that previously reported in DSM-IV defined ADHD samples. It was predicted that, compared with those meeting the broader diagnostic criteria defined by DSM-IV ADHD, boys with the more restricted and clinically homogeneous ICD-10 defined diagnosis of HKD, all of whom will present with severe, pervasive and impairing hyperactive, impulsive and inattentive symptoms, and who also have a more consistent response to MPH than the ADHD group (Santosh, Taylor, Swanson, Wigal, Chuang, Davies, Greenhill, Newcorn, Arnold, Jensen, Vitiello, Elliott, Hinshaw, Hechtman, Abikoff, Pelham, Hoza, Molina, Wells, Epstein, & Posner 2005), would also be more homogeneous with respect to their neuropsychological presentation and, by extension, would have a higher degree of causal homogeneity. However, comparing these current data with those of previous studies (Nigg, Willcutt, Doyle, & Sonuga-Barke 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington 2005), which included boys with the broader ADHD phenotype - the pattern of neuropsychological heterogeneity appears to be very similar across the two groups. This could suggest that neuropsychological heterogeneity is *inherent* to the AD-HKD phenotype and not simply a product of the relatively broad spectrum of phenotypic expression allowed by DSM-IV. These data also indicate that, on their own, none of the observed neuropsychological deficits are either necessary, or sufficient, to cause AD-HKD. These important findings suggest that, irrespective of the definition used to define the disorder, if we are to develop a full understanding of AD-HKD we must embrace the notion that the clinical phenotype can arise as a consequence of several, probably independent, causal pathways (Castellanos & Tannock 2002; Coghill, Nigg, Rothenberger, Sonuga-Barke, & Tannock 2005; Sonuga-Barke 2002).

The principal components analysis (PCA) (described in Chapter 6) supported the contribution of independent executive and non-executive neuropsychological components

to the causality of AD-HKD and highlighted the important contribution made by non-executive neuropsychological deficits to AD-HKD and, in particular, the key role that deficits in recognition memory play in AD-HKD. The discriminant analysis further highlighted the importance of memory in AD-HKD and suggested that both executive (Spatial Working Memory) and non-executive (Delayed Matching to Sample) memory deficits make significant, but independent, contributions to the discrimination between HKD boys and Controls.

Taken together, these findings suggest that the current multi-pathway causal models (e.g. Castellanos & Tannock 2002; Solanto, Abikoff, Sonuga-Barke, Schachar, Logan, Wigal, Hechtman, Hinshaw, & Turkel 2001; Sonuga-Barke 2002) will need to be further expanded at the neuropsychological level of analysis to give greater prominence to both non-executive deficits in recognition memory and deficits in executive aspects of working memory.

These data also suggest that our conceptualisation of ADHD as a disorder of fronto/striatal (and possibly cerebellar) functioning needs to be reconsidered. Although it is not possible to simply map deficits in neuropsychological performance onto specific neuroanatomical and pathophysiological processes, there is a considerable body of evidence available, which describes the various structural and functional correlates of many of the CANTAB tasks (e.g. Baker, Rogers, Owen, Frith, Dolan, Frackowiak, & Robbins 1996; Mehta, Owen, Sahakian, Mavaddat, Pickard, & Robbins 2000; Morris, Ahmed, Syed, & Toone 1993; Owen, Sahakian, Semple, Polkey, & Robbins 1995; Owen, Morris, Sahakian, Polkey, & Robbins 1996b; Owen, Doyon, Petrides, & Evans 1996a; Robbins, James, Owen, Sahakian, Lawrence, McInnes, & Rabbitt 1998; Rogers, Andrews, Grasby, Brooks, & Robbins 2000). Whilst many of these tasks are reliant upon intact frontal lobe functioning, performance on two of the tasks most strongly associated with HKD in this sample, Delayed Matching to Sample and

Pattern Recognition, were *not* impaired in subjects who had undergone a frontal lobe resection but were impaired in those with either temporal lobe or amygdala/hippocampal damage (Owen, Sahakian, Semple, Polkey, & Robbins 1995). As the deficits on these tasks were independent of those on other tasks it suggests that, at least in a proportion of cases, HKD may be associated with sub-optimal functioning of the temporal lobe and/or the amygdala/hippocampus complex.

It is, of course, possible that the neuropsychological heterogeneity found in children with AD-HKD is mediated by some independent factor rather than being inherent to the AD-HKD. Two potential mediating factors, development and comorbidity, were investigated here.

Whilst it is clear that the different neuropsychological functions studied here do have different developmental profiles to each other, the current data suggests that the neuropsychological heterogeneity observed in the sample is not a consequence of differential patterns of neuropsychological development in boys with HKD. Indeed, whilst on several tasks (Spatial Span, Spatial Working Memory – between-search errors and strategy score, Delayed Matching to Sample and Reaction time) neuropsychological development appears delayed by several years in boys with HKD, the data provide general support for the hypothesis that boys with HKD demonstrate a very similar pattern of neuropsychological development to that seen in healthy boys. Taken together the data on neuropsychological development suggest that across those tasks on which the boys with HKD performed less well than healthy boys, the degree performance deficit remained relatively stable between the ages of 7 and 14 years with *no evidence* that the boys with HKD either “catch up” with their healthy counterparts or fall further behind them. Further, on those tasks where no deficit was observed, the development of neuropsychological functioning in the HKD progresses at the same rate as that of the healthy boys.

There is, however, some evidence to suggest that the neuropsychological heterogeneity seen in HKD may, at least in part, be a consequence of comorbidity between HKD, ODD and CD. Compared with healthy boys, each of the three clinical groups ("pure" HKD, HKD + ODD and HKD + CD) was found to be associated with a different pattern of neuropsychological deficits and each was also found to be associated with at least one unique deficit. Importantly, boys with 'pure' HKD had deficits relative to Controls on 3 tasks (Pattern Recognition, Delayed Matching to Sample – simultaneous and total delays, and Intradimensional/ Extradimensional Set-shifting errors at the ED shift) and a trend towards a deficit on the Spatial Span task. These findings support those reported in the meta-analysis of Willcutt et al (2008) and suggest that pure HKD is independently associated with neuropsychological deficits, which are not accounted for by comorbid conditions.

- Compared with the other two groups the boys with pure HKD were the only group with a deficit on the simultaneous condition in the Delayed Matching to Sample task relative to Controls. They also demonstrated a large deficit relative to boys with HKD + CD and a moderate deficit on this measure compared with boys with HKD + ODD.

- The boys with HKD + ODD were the only group to demonstrate impairment on the pre-ED errors measure, the more simple of the 2 Intradimensional/ Extradimensional Set-shifting measures.

- Relative to the Controls the boys with HKD + ODD and boys with Pure HKD but not those with HKD + CD also had deficits at the ED shift stage of this task, with the HKD + ODD group having the greatest difficulties.

- The most striking differences between the groups were between the boys with HKD + CD and the other two HKD groups. The boys with HKD + CD, but not the

other two groups, had deficits on both measures of the Spatial Working Memory task and the Stockings of Cambridge task. The effect sizes for the HKD + CD vs. the boys with pure HKD were in the moderate range and were similar to those reported for the whole HKD group vs. Controls. It is therefore possible that CD may play an important role in mediating the effects of HKD on these measures of executive functioning and may account for some of the between group differences previously reported in the literature.

Of equal importance was the finding that certain aspects of poor neuropsychological functioning appear to cut across all three clinical groups, and is independent of these comorbidities. In particular, when compared with Controls, all three clinical groups had similar performance difficulties on the Pattern Recognition task and the Delayed Matching to Sample delay measures. As these were the two measures for which the largest effect sizes were found in the analysis of the whole sample, these findings could suggest that, in this sample at least, these deficits are specifically associated with HKD as they are seen in pure HKD and are neither mediated nor moderated by the presence of either ODD or CD.

These different patterns of performance across the three clinical groups may indicate that each of the three disorders (HKD, ODD and CD) is associated with different underlying neuroanatomical and pathophysiological substrates and further studies utilising functional imaging and or electrophysiological techniques are warranted.

The final set of questions addressed concerned the potential impact of neuropsychological heterogeneity on clinical response to methylphenidate (MPH). The data on clinical response were broadly in line with expectations from the literature and demonstrated that most but not all of those with HKD had a good clinical response to MPH at one or both doses. There were, however, surprisingly few predictors of clinical response. Age did not predict response and the relationship between baseline clinical characteristics and clinical

response was complex. In many of the analyses, none of the baseline clinical characteristics were predictive of clinical response. In those analyses where clinical response was predicted by baseline scores on the various Conners' Parent Rating Scale (CPRS) subscale scores, it was generally the case that superior response was predicted by lower symptoms at baseline (although the in the logistic regressions both "Full Response" and "Reliable Change" were predicted by higher levels of symptoms CPRS Hyperactivity subscale).

With respect to neuropsychological predictors of response, baseline performance on Component 4 from the PCA (Delayed Matching to Sample, Pattern Recognition and Spatial Recognition) predicted response to 0.3 but not to 0.6 mg/kg on the total score of the parent rated Conners' Global Index (CGI-P) with poorer baseline neuropsychological performance predicting a better clinical response. This was the only neuropsychological Component to predict responder status rated by CGI-P total score. Additional analyses suggested that this effect was largely due to baseline performance on the Delayed Matching to Sample task. These findings add weight to the suggestion made above that the contribution made by non-executive recognition memory deficits to our understanding of the causes of ADHD needs to be taken seriously.

Another interesting finding was that poor baseline performance on Component 3 of the PCA, which indexed two of the core executive functions, working memory and planning - predicted response on the CGI-P emotional lability subscale. This is a brief 3 question subscale that is concerned with symptoms of emotional lability; e.g. temper outbursts, crying often and easily and mood changes quickly and drastically. These symptoms are frequently associated with, but are not considered core to, AD-HKD. This association was seen for all three definitions of response at "either or both doses" and independently at each of the two dose levels. Interestingly, response on the CGI-P emotional lability subscale was also predicted by having fewer baseline problems on the cognitive subscale of the

CPRS, which includes items indexing ability to initiate, to adhere to and to complete cognitively demanding tasks. These findings are entirely novel as predictors of "emotional lability" response have not been previously studied. Taken together they raise the question as to whether the emotional lability frequently seen in AD-HKD is in some way related to deficits in executive functioning, in particular difficulties with working memory and planning.

Unfortunately, although the baseline neuropsychological performance on the non-executive recognition memory tasks predicted response to MPH and although performance on these non-executive memory tasks was significantly improved by the acute and chronic administration of MPH, no association was found between improved task performance on these neuropsychological measures and improved clinical status. On one level, this is somewhat disappointing as one would have hoped that the neuropsychological response would have underpinned at least part of the observed clinical response. There are several possible interpretations of these findings. It is, of course, possible that the deficits in non-executive recognition memory are not meaningfully related to the core functional impairments in AD-HKD. This seems unlikely as the observed memory deficits were of significant magnitude (for example the deficits on the Delayed Matching to Sample task were similar to those described in Alzheimer's disease sufferers by Sahakian et al (1988)). It is also possible that improvements in neuropsychological functioning do mediate improvements in overall functioning and reduce overall impairment but do so in a manner, which is either more subtle or less readily observed, than the improvements in core ADHD symptoms. Such improvements may not be captured by traditional parent completed brief clinical rating scales like the 10 item Connors Global Impact scale such as was used in this study. It could be that had it been possible to utilise teacher ratings of response, a greater number of predictors would have been identified. It may, therefore, be important for

clinicians to consider using multiple informants and a broad range of outcome measures to assess response to treatment in AD-HKD.

The only measure for which neuropsychological response to MPH was associated with improved clinical status was Block 2 Errors to Distractors on the Go/NoGo task, a task that did not discriminate between HKD boys and healthy Controls at baseline. These results mirror those reported in the only similar published study (Aman & Turbott 1991) who also found few indications that improved clinical status was associated with improved neuropsychological performance.

Limitations

Although this study was designed to avoid many of the limitations of previous work in this field, it is inevitable that there were still several significant limitations.

The study sample, although larger than that of comparable studies and rigorously defined, included only referred, stimulant naïve boys. While this sample was of adequate size for most of the statistical analyses, it is possible that several of the subgroup analyses, in particular those investigating the impact of comorbidity, were somewhat underpowered. This may have resulted in Type II errors whereby actual group differences were not recognised due to a lack of study power.

It is also to be regretted that a more comprehensive and generalisable measure of intellectual functioning such as the WISC-IV was not used. The decision to use the British Picture Vocabulary Scale (BPVS: Dunn, Dunn, Whetton, & Burley 1997), a standardised measure of verbal abilities with good reliability and validity, which in UK samples correlates highly with measures of general intelligence was a pragmatic one and unlikely to have impacted greatly on the findings. However, using this method, no measures of non-verbal

or full-scale IQ were available and therefore no comment can be made with respect to these aspects of functioning.

As the sample was all male the results may not generalise to girls. Also, of course, the recruitment of a clinically referred sample may have introduced a Berkson bias (Berkson 1946) and these results may not generalise to a community sample. Although the effects of development are described, it must be acknowledged that these would have been stronger had a longitudinal rather than cross sectional design been used.

The battery of neuropsychological tasks used was more extensive than used in previous studies and, by utilising the CANTAB tasks, it was possible to include a cohesive and comprehensive battery of tasks that are rooted in experimental and laboratory neuroscience and which include a range of built in Control tasks that are usually missing from clinical neuropsychological batteries. There are, however, several potentially important additional tasks, which tap into other aspects of cognitive functioning thought to be important in AD-HKD. These include tasks measuring delay aversion (Sonuga-Barke, Taylor, Sembi, & Smith 1992; Sonuga-Barke, Taylor, & Heptinstall 1992), timing tasks (Smith, Taylor, Rogers, Newman, & Rubia 2002; Toplak, Rucklidge, Hetherington, John, & Tannock 2003), the Stop task (Oosterlaan, Logan, & Sergeant 1998) and the so called gambling or decision making tasks (Malloy-Diniz et al. 2007). Further studies are required to assess the contributions of these tasks to both heterogeneity and clinical response in AD-HKD.

Although participants were randomised following baseline testing, it is possible that the present findings are a consequence of latent differences between the treatment groups in either clinical or neuropsychological characteristics. However, there were no statistically significant differences between the three treatment groups on a wide range of clinical

variables: age, BPVS Percentile Rank, the presence of comorbid conditions, or with respect to neuropsychological functioning at baseline.

With respect to the treatment phase of the study, interpretation of these data is hindered by the absence of reliable and valid measures of treatment adherence. Although assigned to a specific treatment for a defined period of time, it is not possible to be certain that the participant actually took their medication as prescribed, nor that other stimulant drugs were avoided. Consistent performance improvements were seen on many of the tasks throughout the study, including those with parallel versions. Although SESSION was used as a covariant when appropriate, it is possible that global improvements in performance with repeated testing may have diminished the ability to detect small, yet significant changes in task performance. The lack of teacher ratings of outcome, due to excessive missing data was unfortunate as it is likely that parents and teachers will focus on different aspects of functioning when rating response and it is therefore possible that a different pattern of associations and predictors of response would emerge in relation to teacher as opposed to parent rated measures of outcome.

Future Directions

Seven main avenues for future studies are presented below; the use of latent variable analysies; improved and alternative sampling techniques, the issue of specificity, the use of a broader range of neuropsychological tasks; measurement across the various levels of analysis; the use of other medications; the use of broader measures of clinical outcome.

The Use of Latent Variable Analyses

Latent variable analyses are designed to examine average effects and individual differences in tandem and are therefore ideal tools to investigate the impact of these differences on neuropsychological functioning. Because they account for measurement error the latent

variables generated by these techniques allow the researcher to compare groups using 'true',rather than the overall, scores (which include measurement error). Although still relatively complex such analyses have become much more accessible in recent years with the development of statistical packages such as Mplus and AMOS. The use of a latent variable approach with confirmatory factor analyses with the HKD and control baseline data from this study would allow one to test whether :

- the tasks presumed to have either high or low executive demands did indeed separate as predicted
- the confirmatory factor analyses for each group showed measurement invariance (i.e. did the various tasks used in the study tap the same underlying constructs for both the HKD and control groups?). If this is not true for all tasks used in the study can a subset of tasks be identified that does allow a meaningful comparison between the two groups?
- there are group differences when the true (as opposed to overall) scores are used
- there was substantial heterogeneity in neuropsychological function within the HKD group, even when true scores are used.
- age contributes to this heterogeneity

A second set of confirmatory factor analyses could then be used to assess the heterogeneity in MPH response when true scores are used.

Improved and alternative sampling techniques

In order to ensure that the results of studies are generalisable, it will be important for future studies to be conducted using community samples and across cultures. It will also be important to utilise both developmental and genetically sensitive designs and sampling

techniques. Whilst much more expensive to conduct, longitudinal studies clearly provide the strongest developmental design and should be implemented if at all possible. Genetically sensitive designs should also be considered and future studies should seek to include unaffected siblings and parents in samples.

Issues of specificity

Whilst the current analyses have taken into account the impact of coexisting ODD and CD, further studies are required to describe the impact of these and other disorders on neuropsychological performance both in the presence and absence of coexisting AD-HKD. Whilst many other disorders have been associated with various deficits in neuropsychological functioning, few studies have looked at the issue of specificity i.e. which aspects of neuropsychological functioning are specific to a particular disorder and which are more general markers of psychopathology or developmental delay? Particular disorders of relevance to the current discussion include, but are not limited to, ODD, CD, autism spectrum disorders, depression, schizophrenia and bipolar disorder. An alternative approach is to investigate neuropsychological functioning in an epidemiological sample and to then map poor neuropsychological function (e.g. the bottom 10%) forwards onto psychopathology and impairment.

The use of a broader range of neuropsychological tasks

Whilst the battery of tasks used in this study covered a broader range of neuropsychological functions than those used in most other similar studies, and also included both Control tasks and, in most cases, included more than one task to address each area of functioning, it is still the case that these did not cover all of the potential neuropsychological associations of AD-HKD. Future studies should assess these other areas of functioning and investigate their heterogeneity within AD-HKD samples, their relationships to each other, as well as to the tasks included here, and their response to

medication. Of particular interest would be measures of delay aversion (Sonuga-Barke, Taylor, Sembi, & Smith 1992; Sonuga-Barke, Taylor, & Heptinstall 1992), timing (Smith, Taylor, Rogers, Newman, & Rubia 2002; Toplak, Rucklidge, Hetherington, John, & Tannock 2003) and gambling/decision making (Malloy-Diniz, Fuentes, Leite, Correa, & Bechara 2007). The association between each of these areas of functioning and AD-HKD has been replicated in independent samples by independent groups although response to MPH has not yet been reported for any of them. Another task that should be included in future studies is the Stop Task a measure of behavioural inhibition that has been demonstrated to be sensitive to AD-HKD by meta-analysis (Oosterlaan, Logan, & Sergeant 1998). The inclusion of the Stop Task would have been of particular interest in the current study in view of the failure to demonstrate baseline group differences on the Go/NoGo task. Wherever possible studies should use tasks, like those in the CANTAB, that are rooted in laboratory neuroscience and for which aspects of the neuroanatomical and pathophysiological substrates are understood.

Measurement across the various levels of analysis

In addition to the use of genetically sensitive sampling techniques, future studies should also include measures across the various levels of analysis. Thus it will be important to integrate genetic, environmental, imaging and electrophysiological measures into neuropsychopharmacological study designs and vice versa. Such studies are essential if we are to directly test proposed causal models and develop new ones. The neuropsychological deficits described here are generally thought of as endophenotypes, intermediate factors that bridge the gaps between genetic and environmental causative agents and their effects on pathophysiology and brain structure and functioning on the one hand, and the behavioural phenotype on the other. Whilst indirect evidence can sometimes be used to hypothesise the bridges between these different levels of analysis, only direct evidence

from well designed studies can really provide an adequate level of proof. Clearly such studies will be costly and will require close collaboration between groups with complementary skills, however, the payoff from a comprehensive, well designed and well powered study would be immense (Coghill, Nigg, Rothenberger, Sonuga-Barke, & Tannock 2005).

The use of other medications

Whilst methylphenidate is both the best understood and most commonly used medication to treat AD-HKD, there are other treatments available. These include licensed medications such as dexamfetamine and atomoxetine, unlicensed but relatively well established medications such as clonidine, guanfacine and bupropion and newer drugs that are either under investigation or are, as yet, less well established such as modafanil, cholinergic agonists, H_2 receptor antagonists, ampakines and the serotonin 1A/1B receptor agonists. Each of these has different mechanisms of action and therefore may also impact differently on neuropsychological functioning. Further study is required to understand how each of these drugs impacts both on symptoms and on neuropsychology. Clearly the hope for the future is that we can move to a situation whereby once one understands an individual's neuropsychological profile, it will be possible to predict which medication or combination of medications will be the most likely to improve performance and symptoms and reduce impairment. It will also be informative to measure the associations between the clinical and neuropsychological impact of non-pharmacological treatments, including cognitive training, neurofeedback and parent training.

The use of broader measures of clinical outcome

Lastly, and in view of the difficulties identifying the clinical consequences of improved neuropsychological functioning, it will important that future treatment studies include a broad range of outcome measures that access multiple viewpoints (e.g. self, parent,

teacher, clinician), both subjective (e.g. rating scales) and objective (e.g. academic productivity, neuropsychological testing, actigraphy, electrophysiology and functional imaging), and measures of symptoms, impairment and quality of life. By doing so we may be able to develop a better understanding of the impact of the various treatments, which would not only help us not only to understand their mechanisms of action and potential benefits, but also their limitations and potential adverse effects in order that, in the future, treatments can be targeted more efficiently, effectively and safely and that new treatments can be developed to fill the gaps left by current approaches.

Such improved and extended future studies would have the potential to further improve our understanding of the causes and impact of AD-HKD and aid in the development of new targeted treatments to improve our management of this common disorder that currently blights the lives of many children, young people and adults as well as those of their families and communities.

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Appendix 1

Whither causal models in the neuroscience of ADHD?

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Whither causal models in the neuroscience of ADHD?

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Abstract

In this paper we examine the current status of the science of ADHD from a theoretical point of view. While the field has reached the point at which a number of causal models have been proposed, it remains some distance away from demonstrating the viability of such models empirically. We identify a number of existing barriers and make proposals as to the best way for these to be overcome in future studies. These include the need to work across multiple levels of analysis in multidisciplinary teams; the need to recognize the existence of, and then model, causal heterogeneity; the need to integrate environmental and social processes into models of genetic and neurobiological influence; and the need to model developmental processes in a dynamic fashion. Such a model of science, although difficult to achieve, has the potential to provide the sort of framework for programmatic model-based research required if the power and sophistication of new neuroscience technologies are to be effectively exploited.

Introduction

The clinical construct of Attention Deficit Hyperactivity Disorder (ADHD) remains controversial. Those who doubt its validity frequently cite statements such as that made by the National Institute for Mental Health (Kupfer *et al.*, 2000) that 'after years of clinical research and experience with ADHD, our knowledge about the cause or causes of ADHD remains largely speculative' (p. 3). In countering this position, clinical specialists and researchers in ADHD point out that these comments are being used out of context and cite the many genetic, neuroimaging, neurophysiological and neuropsychological studies that not only support the validity of the disorder, but also provide evidence for it having a biological basis (Barkley *et al.*, 2002). Thus while the field has reached a point at which relatively sophisticated causal theories are proposed (Barkley, 1998; Sonuga-Barke, 2002), we still remain some distance from demonstrating a full causal model of ADHD, or its component symptom dimensions, in a way that incorporates multiple levels of analysis. That this is the case should come as no surprise. The brain is the most complex of biochemical 'machines' and this, linked with the complex polygenic genetic underpinnings of ADHD (Stevenson *et al.*, this issue, 2005), would mean that a full causal model would need to 'predict a ballet choreographed interactively over time among genotype, environment, and epigenetic factors, which gives rise to a particular phenotype' (Gottesman & Gould, 2003).

This paper explores some of the important barriers that we believe must be overcome if we are to shift from positing causal theories to demonstrating formal causal effects. To aid clarity we will utilize the developmental causal modelling framework proposed by Morton and Frith (1995). This framework provides a useful notation with which to describe the interplay between the various levels of analysis required to fully describe conditions like ADHD or its component dimensions. Three within-person levels of analysis are defined – biological, cognitive and behavioural – with a separate domain for environmental influences, which can interact at any of the three levels. Causal models are built by linking elements within the same or different levels into causal chains (Figure 1). Morton and Frith have proposed several important ground rules for guiding the construction and use of causal models (see Figure 2; Morton & Frith, 1995). Such models embrace the concept of change over time

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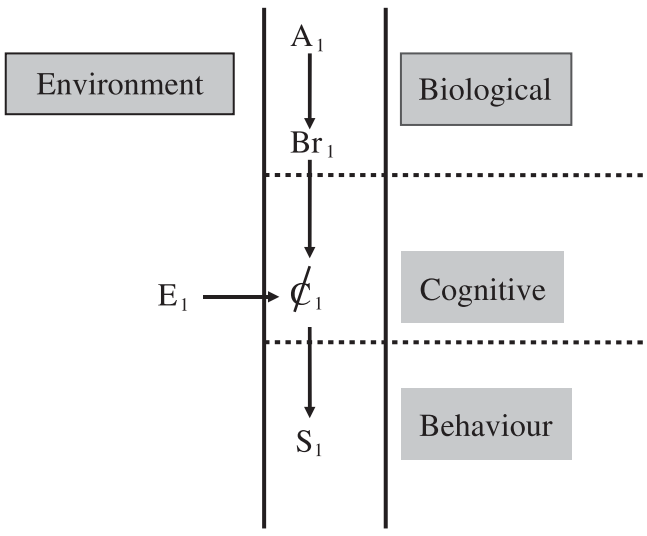

Figure 1 *A hypothetical simplified causal model. A_1 refers to genetic originating causes, E_1 refers to environmental originating causes, Br_1 to the abnormal brain conditions, the struck out C_1 to a cognitive process which is altered by virtue of the brain condition and S_1 to the signs and symptoms.*

and encourage integration across multiple levels of analysis, providing the structure for an explanation of the disorder that is as complete as possible.

The theoretical neutrality of this framework also allows for the comparison, and integration, of very different theoretical approaches. A similar causal modelling approach has been used successfully with several developmental disorders including autism (Frith, Morton & Leslie, 1991), dyslexia (Morton & Frith, 1993) and conduct disorder (Krol, Morton & De Bruyn, 2004). Several authors have utilized a causal modelling framework to structure discussions on the pathophysiology of ADHD (Sonuga-Barke, in press) and to propose possible endophenotypes for ADHD (Castellanos & Tannock, 2002). However, for our purposes, the framework suggests a number of considerations that can guide theoretical work on ADHD and help move towards the demonstration or evaluation of causal claims. We enumerate the most salient of these here.

The need to work across multiple levels of analysis

A complete causal model for ADHD or its symptom dimensions will require integration of genetic, neural, cognitive and behavioural mechanisms to describe complete causal chains occurring in development. The complexity inherent within each of these levels requires specialist knowledge and skills, and requires input from researchers with a wide range of scientific backgrounds. As a result, most researchers have, to date, worked at only one level. Thus, disparate evidence suggests the following causal pathway: genetic variations → functional abnormalities in both dopaminergic and noradrenergic neurotransmission within fronto-striatal pathways → deficits in executive and reward-related functioning → the behavioural manifestations of ADHD (Castellanos & Tannock, 2002). Yet few studies have accepted the challenge of working across these levels of analysis in order to define their interrelationships empirically in the same sample. Exceptions are beginning to emerge. For example, functional neuroimaging (e.g. Rubia *et al.*, 1999; Durston *et al.*, 2003) and electrophysiological studies (e.g. Rothenberger *et al.*, 2000; Brandeis *et al.*, 2002; Jonkman *et al.*, 2004) have started to describe the links between brain and cognitive function. Also a handful of pharmacogenomic (Seeger, Schloss & Schmidt, 2001; Roman, Rohde & Hutz, 2004) and family and genetic studies of neuropsychological functioning (e.g. Swanson *et al.*, 2000; Durston *et al.*, 2004; Nigg *et al.*, 2004) strive to make links between the genetic and neural and cognitive levels of analysis. However, much more emphasis will need to be placed on these bridging studies in order

1. ***Start with biology.*** The causal chain should start with the biological origins or a clear statement that there are no such factors.
2. ***Build causal chains.*** The causal chain should be specified, or at least sketched, from the origin to the behaviour.
3. ***Give full account.*** The causal model should account for, or at least mention, all signs and symptoms of the disorder.
4. ***Specific over general.*** A distinction between specific and general conditions must be made. Features that can be accounted for as part of a general condition need not be mentioned within the causal model of a specific condition.
5. ***Correlation is not causation.*** Do not confuse correlation with cause.

Figure 2 *Ground rules for causal modelling (Morton & Frith, 1995).*

that the causal chains linking the genetic and environmental causes of ADHD or its component symptom dimensions, through the subsequent biological and cognitive levels to the behavioural phenotype, can be understood.

It would, for example, be informative to integrate neuroimaging/electrophysiological, psychopharmacological and/or neuropsychological protocols within the large scale molecular and behavioural genetic studies into ADHD (e.g. Asherson & The IMAGE Consortium, 2004). The incorporation, for example, of a neuropsychological arm into such a study would assist in the building of causal chains by exploring the associations between candidate genes and neuropsychological endophenotypes and the mediating/moderating effects of these endophenotypes on genetic effects in ADHD. Another useful strategy might be to incorporate cognitive, neuroimaging and molecular genetic methods into existing prospective epidemiological studies of the impact of perinatal factors on developmental outcomes. For example, maternal smoking during pregnancy independently impacts on the expression of attention problems, other externalizing problems and academic problems (Batstra, Hadders-Algra & Neeleman, 2003). The inclusion of neuroimaging and genetics strategies would permit an assessment of causal chains between maternal psychopathology, genetic susceptibility to smoking, the prenatal and perinatal environment, and ADHD or attention problems in the offspring. Similar arguments could be made for a wide range of other important domains.

The need to recognize the existence of and then effectively model heterogeneity within ADHD samples

This need to embrace and address vertical integration across the different levels of analysis is mirrored by the need to recognize that the heterogeneity inherent within ADHD samples will also require there to be multiple pathways within a causal model and a need for horizontal integration between these pathways at each level, and probably diagonally across levels. Until recently, simple single-cause models dominated the ADHD literature. Such models carry an implicit suggestion that the behavioural symptoms of ADHD are a consequence of a single underlying factor such as deficient inhibitory control (Barkley, 1998), state regulation deficits (Sergeant, 2000), or reinforcement–response abnormalities and motivational deficits (Sagvolden *et al.*, in press). Whereas such theories have stimulated important findings (and indeed, note multiple processes that may be involved in ADHD), they have also tended to lead to a continuation of empirical designs that implicitly assume all children diagnosed with a given type of ADHD have the same causal aetiology. Such an assumption is unlikely to bear out, yet failure to model multiple pathways may ensure that between-group designs (ADHD versus control) will continue to find relatively small, mixed effects. In short, single-cause models have difficulty accounting for the heterogeneity which is being increasingly recognized as a key factor in the understanding of the causes of ADHD (Sonuga-Barke, 2002; Nigg, Willcutt, Doyle & Sonuga-Barke, in press). Data from several datasets provide convincing evidence to suggest considerable heterogeneity within samples of ADHD subjects (Solanto *et al.*, 2001; Nigg *et al.*, in press). While this within-sample heterogeneity is found across all levels of analysis, the complexities are well illustrated by focusing on the cognitive level. Heterogeneity may be manifest in several ways. First, cognitive dysfunctions may be differentially associated with the inattention and hyperactivity/impulsivity dimensions. A growing corpus of research suggests that inattention but not hyperactivity/impulsivity is associated with deficits in executive functioning and working memory, and poor academic achievement, even in non-clinical community samples (Rabiner & Coie, 2000; Chhabildas, Pennington & Willcutt, 2001; Martinussen & Tannock, in press; Martinussen *et al.*, in press). By contrast, hyperactivity/impulsivity appears to be more closely related to dysfunctions of reward mechanisms (Solanto *et al.*, 2001; Sonuga-Barke, Dalen & Remington, 2003; Toplak, Jain & Tannock, under review). Second, there is growing evidence that not all individuals with ADHD manifest cognitive deficits, suggesting heterogeneity in underlying neural mechanisms and/or marked heterogeneity in risk and protective factors (e.g. Nigg *et al.*, in press; Coghill, Rhodes & Matthews, unpublished data). Third, various cognitive deficits within individuals with ADHD may not be correlated, suggesting that ADHD may be the developmental outcome of a variety of anomalies in separable neural networks (Solanto *et al.*, 2001; Rhodes, Coghill & Matthews, under review; Toplak, Jain & Tannock, under review).

Thus causal models of ADHD will need to account not only for those both with and without cognitive deficits but also for the heterogeneity found within the cognitively affected group. Such data require us to consider the single-cause models not as separate entities, but as potentially complementary approaches which, when viewed together, can provide a fuller appreciation of a complex multi-dimensional scenario. More studies are needed in which researchers investigate these contrasting theoretical models within the same samples to further the development of multi-pathway models (Sonuga-Barke, 2003) and to identify specific causal claims more formally in ADHD. It is crucial to recognize that multiple pathways may not

simply represent alternative routes into ADHD. Rather, it may be the norm for most children to have contributions from several, but not necessarily all, pathways, in varying degrees. At least three general patterns of multi-pathway models could be generated. First, we could posit that ADHD is the common final behavioural consequence of any of several relatively independent pathways, such as 'cognitive deficit pathways' (e.g. a working memory pathway; Kempton *et al.*, 1999) and/or a non-working memory pathway (Rhodes, Coghill & Matthews, 2004)) and one or more non-cognitive pathways (for example, a motivational pathway, Sonuga-Barke, 2003) and/or an adaptation to stress pathway (Johnston & Mash, 2001). Each of these pathways on its own can result in the ADHD behavioural phenotype. Second, we could posit that ADHD is caused by a similar array of dysfunctions in each of these domains, with at least some dysfunction in all domains required before the phenotype is expressed. The extensive overlap in function demonstrated between ADHD and non-ADHD samples would require that ADHD arises due to the small but additive and interactive effects of each pathophysiological process with the phenotype only being expressed once a threshold has been reached. Third, it may be that the correct model is a combination of the two described above. Thus, while ADHD could arise as a consequence of one of several independent pathways, an interaction between several pathways might be more common, with the detail of the interactions dictating the precise presentation severity, and possibly response to treatment. The situation for ADHD with comorbidity will, of course, be even more complex.

This analysis points to the fact that it will be important to look beyond the frequently emphasized fronto-striatal/executive networks in the brain to account fully for ADHD, even at the cognitive level of analysis. Thus, structural and functional neuroimaging studies and electrophysiology, including transcranial magnetic stimulation, have shown various brain abnormalities in ADHD patients (e.g. Rubia *et al.*, 1999; Moll *et al.*, 2001; Yordanova *et al.*, 2001; Castellanos *et al.*, 2002; Brandeis *et al.*, 2002). These studies have mostly demonstrated the now well-recognized abnormalities in frontal cortical regions and basal ganglia. Yet, less often addressed are the morphological and functional differences that are revealed in the motor cortex, temporal and parietal lobes, cerebellum and corpus callosum (Castellanos *et al.*, 2002; Roessner *et al.*, 2004). Further, the alteration of the REM-sleep in ADHD (Kirov *et al.*, 2004) cannot be explained by the neuropsychological models described above.

Along the same lines, recent neuropsychological studies have utilized batteries of neuropsychological tasks measuring a range of abilities dependant on a broader range of neuronal substrates. Toplak *et al.* (2003, under review) reported deficits in ADHD children on several short duration timing tasks dependant on the cerebellum for accurate performance (Mangels, Ivry & Shimizu, 1998). Rhodes *et al.* (2004, under review) described performance deficits across a wide range of tasks from the CANTAB battery including a pattern of performance on two tasks, Delayed Matching to Sample and Pattern Recognition, which mirrored those seen in patients with temporal lobe, parietal lobe or amygdalo-hippocampal damage and Alzheimer's dementia more than patients with frontal lobe injury. Importantly, performance on both tasks was independent of behavioural inhibitory control and was improved following the administration of methylphenidate. These studies suggest that a conceptualization of ADHD largely restricted to fronto-striatal circuits may require broadening within a multi-pathway framework. However, further study is required to confirm the interrelationships between these and other cognitive deficits, to evaluate relative effect sizes, and to examine their relationships with genetic and environmental causal factors and associated neural mediating mechanisms.

The need to integrate environmental/social influences within genetic and neurobiological mechanisms

The causal modelling framework is neutral about the relative contribution of genetic and environmental factors as originating causes. The scientific belief that ADHD is best regarded as a biogenetic neuropsychiatric disorder receives support from the large and growing literature on the genetics and neurobiology of ADHD as cited earlier. Indeed, twin, family and adoption studies suggest a large genetic, but relatively small (mainly non-shared) environmental component (Rietveld *et al.*, 2003), which seems to remain relatively constant across levels of symptom severity (Willcutt *et al.*, 2001). Molecular genetic studies implicate a number of potentially (neurobiologically) functional susceptibility genes in the pathophysiology of the condition (especially those coding for the structure of dopamine receptors (e.g. DRD4) and transporters (e.g. DAT1; DiMaio, Grizenko & Joober, 2003)). While these different lines of evidence clearly support a role for genetic factors in ADHD, they do not suggest that this is to the exclusion of environmental factors. To point out one issue, genetic effects in the case of ADHD are necessarily expressed within, enabled by, and in some cases doubtless mediated and/or moderated by, particular biological and social environments that are at present not well mapped. Current designs are

sensitive to these effects. For example geno-environment correlations, in which the child's temperament elicits particular behavioural sequences in the social environment that in turn shape child development are expressed as genetic effects in twin study variance partitioning (see Ge, Conger, Cadoret & Neiderhiser, 1996). In short, viewing ADHD as essentially a genetically determined condition is an oversimplification at best.

The work of Kreppner and colleagues on the impact of the early severe deprivation experienced by children adopted out of the Romanian orphanages shows a raised incidence of ADHD (among other problems), increasing as a function of length of deprivation experienced (Kreppner, O'Connor & Rutter, 2001). This is highly suggestive of an environmental route into ADHD. The link between deprivation and ADHD is likely to be mediated by chronic changes in the neurobiology of the child, exemplifying the distinction between extrinsic causal mechanisms and intrinsic mediating factors in causal models. Similarly, neurobiological changes have been documented in animal models of environmentally induced stress (Matthews & Robbins, 2003). These studies highlight the importance of thinking clearly about the relationships between genetic and environmental influences and neurobiology: while genetic effects may well be mediated in part by neurobiological changes, they may also be mediated by psychosocial events due to genotype-environment correlations. Further, not all neurobiologically mediated effects will have a genetic origin.

The need to properly characterize endophenotypes

Endophenotypes are those mediating factors, the unseen components, which sit between the observed manifestations of a disease or disorder and its originating causes. With respect to neuropsychiatric conditions, they may be neuroanatomical, biochemical, neurophysiological or neuropsychological in nature (e.g. Gottesman & Gould, 2003). They are particularly useful in helping us to develop our understanding of conditions in which complex genetic and environmental factors must be linked to a behavioural phenotype, which is difficult to define precisely and consistently. The endophenotype concept fits comfortably within the causal modelling framework, with endophenotypes representing aspects of abnormal functioning at either the biological or cognitive levels. Accurate characterization of candidate endophenotypes for ADHD may suggest simpler clues to the originating causes of this disorder than the behavioural phenotype itself. Properly characterized endophenotypes could further aid genetic research by acting as measurable markers of genetic risk. Inherent to this argument is the suggestion that by deconstructing a disorder like ADHD into its underlying component processes we will not only simplify genetic analysis but also provide alternative ways of describing and classifying those with the disorder and hopefully reduce the heterogeneity associated with the current behavioural phenotypes.

Various criteria, which should be met by a valid endophenotype, have been described (Figure 3). Castellanos and Tannock (2002) suggest that an endophenotype should not be excluded solely on the basis that existing data suggests that they are not heritable/familial (i.e. 'genetic'); a criteria proposed by a number of authors. However, it is clearly of considerable importance to know whether or not an endophenotype relates to genetic causes of a disorder. In such cases, three further criteria apply: (1) the endophenotype should itself be heritable; (2) the endophenotype should co-segregate with illness within families; and (3) the endophenotypes found in affected family members should also be found in non-affected family members at a higher rate than in the general population (Gottesman & Gould, 2003).

Several potential neuropsychological endophenotypes for ADHD have been described, including a specific abnormality in reward-related circuitry that leads to shortened delay gradients and delay aversion (Sonuga-Barke, 2002), deficits in temporal processing that result

1. The endophenotype should be associated with illness in the population
2. Predict the disorder probalistically
3. Be closer to the site of the primary causative agent (whether genetic or environmental) than to diagnostic categories
4. Be rooted in biology and be biologically plausible
5. Be continuously quantifiable
6. Be state independent, i.e. manifest in an individual whether or not illness is active

Figure 3 *Criteria for an endophenotype.*

in high intra-subject inter-trial variability (Smith *et al.*, 2002; Toplak *et al.*, 2003), deficits in working memory (Rhodes, Coghill & Matthews, 2004; Bedard, Martinussen, Ickowicz & Tannock, 2004) and non-working visual memory (Rhodes, Coghill & Matthews, 2004), impaired stop-signal inhibition (Schachar *et al.*, 2000) and attentional set-shifting (Nigg *et al.*, in press). While each of these proposed neuropsychological endophenotypes meets several of the expected criteria, none meet them all. The heritability and co-segregation within families remains unexplored for most endophenotypes. Only attentional set shifting and stop signal inhibition have been demonstrated to be familial and more frequent in non-affected family members (Nigg *et al.*, in press).

While several of these endophenotypes have been demonstrated to be relatively sensitive markers for ADHD their specificity to ADHD is less clear (Banaschewski, Hollis, Oosterlaan, Roeyers, Rubia, Willcutt & Taylor, this issue, 2005). As previously suggested, it is unlikely that all endophenotypes will be present in all cases. It is, therefore, not surprising that cohort level analyses on such heterogeneous samples suggest high sensitivity but low specificity. This is one of the reasons for neuropsychological tests being relatively ineffective tools in the diagnosis of DSM or ICD defined ADHD. Additionally, several of the proposed endophenotypes appear to be common to several neurodevelopmental disorders. For example, working memory has also been proposed as an endophenotype for schizophrenia (Gottesman & Gould, 2003), and stop signal inhibition has been implicated in schizophrenia, language disorders, conduct disorder and autism. Indeed, the neuropsychological and neurophysiological similarities and dissimilarities between ADHD and other commonly comorbid conditions, such as conduct disorder (Schachar & Tannock, 1995; Oosterlaan & Sergeant, 1998; Banaschewski *et al.*, 2004) and specific learning difficulties (Tannock, Martinussen & Frijters, 2000), remain contentious and unresolved.

However, this does not imply that we should abandon our search for and description of endophenotypes. Rather, it may suggest that we should be investigating potential neuropsychological rather than behaviourally defined subtypes of ADHD (see Nigg, Blaskey, Stawicki & Sachek, 2004). The neuropsychological assessment of those with ADHD could then assist in more fully describing an individual's condition and aid clinicians to decide on the most appropriate pharmacological, psychological and educational treatment strategies. A more adventurous but potentially far more profitable strategy would be to concentrate on mapping out the causal pathways both to and from cognitive deficits in delay sensitivity, behavioural inhibition, working and non-working memory, and timing, rather than for ADHD *per se*.

The need to take developmental aspects seriously

Despite widespread recognition of ADHD as a developmental neuropsychiatric condition, very few causal explanations have seriously considered the two-way, interactions between pre-existing abnormal functioning and biological, cognitive, emotional, motor and social developmental processes, and their contribution to the expression of the behavioural phenotype (Olson, Bates, Sandy & Schilling, 2002; Nigg, Goldsmith & Sachek, 2004). Nigg *et al.* (2004) provide an outline of various temperament-based early precursors to ADHD that warrant consideration. Sonuga-Barke (in press) has discussed this issue with respect to the development of delay aversion and associated deficits in self-organizational skills, suggesting that at least three related developmental phenomenon are implicated. The first is characterized by *child* × *environment correlation*, whereby the developmentally antecedent impulsive response of the child shapes their social and family environment by eliciting a punitive or negative response from parents and siblings to a failure to engage effectively with the delay-rich environment. The second is *person* × *environment interactions*, whereby the punitive social environment, partially created by the behaviour of the child, moderates the links between underlying and early appearing impulsiveness and the emergence of a more generalized delay aversion. The final developmental process is characterized by *individual accommodation* to the child's underlying predisposition toward impulsiveness and the constraints this imposes on experience. It is likely that similar processes play a role in other causal pathways to ADHD.

Causal models must also take into account the ways in which a failure of development in one cognitive ability impacts on the development of successive cognitive abilities. The potential importance of this concept to causal modelling for ADHD can be illustrated by considering the role played by working memory deficits in the development of ADHD. Working memory deficits, although relatively understudied, have been considered by many to be core cognitive risk factors for ADHD requiring accommodation within a causal model of ADHD (Castellanos & Tannock, 2002). Deficits in timing (Toplak, Rucklidge, Hetherington, John & Tannock, 2003) and non-working visual memory (Rhodes, Coghill & Matthews, 2004), which, while not dependent on working memory performance, may themselves impact on the development of working memory, have been recently identified. Thus, if the usual development of accurate working memory performance is contingent upon the development of cerebellar timing functioning and spatial recognition memory, then impaired development of

either of these abilities may impact on the development of spatial working memory functioning. While such hypotheses are still speculative, they warrant further investigation and illustrate the potential importance of such considerations. Further, the possibility that very basic sensory and perceptual processes may be impaired in ADHD, which, over the course of development, may manifest subsequently as impaired performance on various tasks and interpreted as 'impairments in executive function', remains relatively unexplored (e.g. Jonkman *et al*., 2004).

Lastly, with regard to development, a causal model of ADHD must also account for changes in phenotypic expression over time. Future studies will need to differentiate between 'true' and 'apparent' changes in symptoms across the lifespan. For example, is the reduction in hyperactivity symptoms frequently noted in adolescence (Hart *et al.*, 1995) a true shift towards normality or simply an apparent change resulting as a consequence of normative development? That is, does that shift represent a change over time, mirroring normative development, from a more visible motoric hyperactivity to an inner restlessness and fidgetiness which, while less noticeable and impacting on others, is still both impairing to the individual and remains as far removed from the normal distribution of experience as the symptoms in earlier life (Barkley, 1998)? In each case, a causal modelling paradigm would make different, testable, predictions. If the shift is towards normalization, then this should be reflected by a similar shift in the underlying pathophysiology (e.g. Rothenberger, Woerner & Blanz, 1987), which would not be the case in the converse scenario. The accurate developmental description of each of these levels within causal chains would both aid the clarity of the resultant causal models and provide a more objective basis from which descriptions of ADHD across the lifespan, particularly in adolescence and adulthood, can be developed.

Concluding comments

The neuroscience of ADHD stands at a watershed. New brain study and genetic technologies provide us with the tools to examine the neurobiology of ADHD in an increasingly sophisticated and powerful way. If this is to be harnessed effectively, then research must be guided by equally sophisticated and powerful models of causes and causal processes. In this paper we have made a number of recommendations to overcome existing barriers to the development of empirically based causal models, and so facilitate model-guided research programmes in the neuroscience of ADHD. Such programmes should routinely use both the causal and developmental contingency modelling paradigms to promote research, which seeks to clarify the associations between both the different levels of analysis within a model and the interrelationships between various models and causal pathways. Such approaches will be particularly valuable because of their ability to model heterogeneity in ADHD at a number of different levels. For instance, a reduction of phenotypic heterogeneity is crucial for further progress in the identification of susceptibility genes for ADHD or its symptoms dimensions. On a more practical level, this sort of analysis may provide the basis for identifying different psychopathophysiological subtypes of ADHD associated with different causal pathways, which has the potential to provide the basis for a new classification system. Such studies will require a concerted effort to collaborate across a range of levels; between theorists with differing perspectives, between researchers with a wide range of experimental backgrounds, and between centres to enable the recruitment of the large samples that will be required to explore the types hypotheses generated from such an approach. Such a model of science, departing as it does from the discipline-specific and individual laboratory-based nature of current practice, will not be easy to achieve, but without it, it will not be possible to resolve the core issues in the neuroscience of ADHD.

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Appendix 2

Appendix 2a: Revised Conners' Parent Rating Scale short version, Conners, Sitarenios, Parker, & Epstein (1998a)

Appendix 2b: Revised Conners' Teacher Rating Scale short version, Conners, Sitarenios, Parker, & Epstein (1998b)

Conners' Parent Rating Scale - Revised (S)

by C. Keith Conners, Ph.D.

Child's Name:_____ **Gender: M F**

Birthdate:____/____/____ (Month / Day / Year) **Age:**_____ **School Grade:**_____

Parent's Name:_____ **Today's Date:**____/____/____ (Month / Day / Year)

Instructions: Below are a number of common problems that children have. Please rate each item according to your child's behavior in the last month. For each item, ask yourself, "How much of a problem has this been in the last month?", and circle the best answer for each one. If none, not at all, seldom, or very infrequently, you would circle 0. If very much true, or it occurs very often or frequently, you would circle 3. You would circle 1 or 2 for ratings in between. Please respond to each item.

	NOT TRUE AT ALL (Never, Seldom)	JUST A LITTLE TRUE (Occasionally)	PRETTY MUCH TRUE (Often, Quite a Bit)	VERY MUCH TRUE (Very Often, Very Frequent)
1. Inattentive, easily distracted	0	1	2	3
2. Angry and resentful	0	1	2	3
3. Difficulty doing or completing homework	0	1	2	3
4. Is always "on the go" or acts as if driven by a motor	0	1	2	3
5. Short attention span	0	1	2	3
6. Argues with adults	0	1	2	3
7. Fidgets with hands or feet or squirms in seat	0	1	2	3
8. Fails to complete assignments	0	1	2	3
9. Hard to control in malls or while grocery shopping	0	1	2	3
10. Messy or disorganized at home or school	0	1	2	3
11. Loses temper	0	1	2	3
12. Needs close supervision to get through assignments	0	1	2	3
13. Only attends if it is something he/she is very interested in	0	1	2	3
14. Runs about or climbs excessively in situations where it is inappropriate	0	1	2	3
15. Distractibility or attention span a problem	0	1	2	3
16. Irritable	0	1	2	3
17. Avoids, expresses reluctance about, or has difficulties engaging in tasks that require sustained mental effort (such as schoolwork or homework)	0	1	2	3
18. Restless in the "squirmy" sense	0	1	2	3
19. Gets distracted when given instructions to do something	0	1	2	3
20. Actively defies or refuses to comply with adults' requests	0	1	2	3
21. Has trouble concentrating in class	0	1	2	3
22. Has difficulty waiting in lines or awaiting turn in games or group situations	0	1	2	3
23. Leaves seat in classroom or in other situations in which remaining seated is expected	0	1	2	3
24. Deliberately does things that annoy other people	0	1	2	3
25. Does not follow through on instructions and fails to finish schoolwork, chores or duties in the workplace (not due to oppositional behavior or failure to understand instructions)	0	1	2	3
26. Has difficulty playing or engaging in leisure activities quietly	0	1	2	3
27. Easily frustrated in efforts	0	1	2	3

Conners' Teacher Rating Scale–Revised (S)

by C. Keith Conners, Ph.D.

Student's ID: _____ **Gender:** M F (Circle One)

Birthdate: ___/___/___ (Month Day Year) **Age:** _____ **School Grade:** _____

Teacher's ID: _____ **Today's Date:** ___/___/___ (Month Day Year)

Instructions: Below are a number of common problems that children have in school. Please rate each item according to how much of a problem it has been in the last month. For each item, ask yourself, "How much of a problem has this been in the last month?", and circle the best answer for each one. If none, not at all, seldom, or very infrequently, you would circle 0. If very much true, or it occurs very often or frequently, you would circle 3. You would circle 1 or 2 for ratings in between. Please respond to each item.

	NOT TRUE AT ALL (Never, Seldom)	JUST A LITTLE TRUE (Occasionally)	PRETTY MUCH TRUE (Often, Quite a Bit)	VERY MUCH TRUE (Very Often, Very Frequent)
1. Inattentive, easily distracted	0	1	2	3
2. Defiant	0	1	2	3
3. Restless in the "squirmy" sense	0	1	2	3
4. Forgets things he/she has already learned	0	1	2	3
5. Disturbs other children	0	1	2	3
6. Actively defies or refuses to comply with adults' requests	0	1	2	3
7. Is always "on the go" or acts as if driven by a motor	0	1	2	3
8. Poor in spelling	0	1	2	3
9. Cannot remain still	0	1	2	3
10. Spiteful or vindictive	0	1	2	3
11. Leaves seat in classroom or in other situations in which remaining seated is expected	0	1	2	3
12. Fidgets with hands or feet or squirms in seat	0	1	2	3
13. Not reading up to par	0	1	2	3
14. Short attention span	0	1	2	3
15. Argues with adults	0	1	2	3
16. Only pays attention to things he/she is really interested in	0	1	2	3
17. Has difficulty waiting his/her turn	0	1	2	3
18. Lacks interest in schoolwork	0	1	2	3
19. Distractibility or attention span a problem	0	1	2	3
20. Temper outbursts; explosive, unpredictable behavior	0	1	2	3
21. Runs about or climbs excessively in situations where it is inappropriate	0	1	2	3
22. Poor in arithmetic	0	1	2	3
23. Interrupts or intrudes on others (e.g., butts into others' conversations or games)	0	1	2	3
24. Has difficulty playing or engaging in leisure activities quietly	0	1	2	3
25. Fails to finish things he/she starts	0	1	2	3
26. Does not follow through on instructions and fails to finish schoolwork (not due to oppositional behavior or failure to understand instructions)	0	1	2	3
27. Excitable, impulsive	0	1	2	3
28. Restless, always up and on the go	0	1	2	3

Appendix 3

Kiddie Schedule for Affective Disorders and Schizophrenia – Present/Lifetime version (Kiddie SADS-PL) - ADHD Module, Kaufman, Birmaher, Brent, Rao, & Ryan (1996)

Kiddie SADS PL ADHD Module Symptom	CE		MSP

Difficulty sustaining attention on tasks or play activities *Has there ever been a time when you had trouble paying attention in school? Did it affect your schoolwork? Did you get into trouble because of this? When you were working on your homework did your mind wander? What about when you were playing games? Did you forget to go when it was your turn?*	0 1 2 3	No information Not present Subthreshold – occasional difficulty – minimal effect on functioning Threshold – often has difficulty – moderate to severe effect on functioning	0 1 2 3

Easily distracted *Was there ever a time when little distractions would make it very hard for you to keep your mind on what you were doing? Like if another kid in class asked the teacher a question while the class was working quietly was it ever hard for you to keep your mind on your work? When there was an interruption, like when the phone rang, was it hard to get back to what you were doing before the interruption? Were there times when you could keep your mind on what you were doing and little noises and things didn't bother you? How often were they a problem?*	0 1 2 3	No information Not present Subthreshold – occasionally distracted – minimal effect on functioning Threshold – attention often disrupted by minor distractions other kids would be able to ignore. Moderate to severe effect on functioning	0 1 2 3

Difficulty remaining seated *Was there ever a time when you got out of your seat a lot at school? Did you get into trouble for this? Was it hard to stay in you seat at school? What about dinner times?*	0 1 2 3	No information Not present Subthreshold: occasional difficulty staying seated when required – minimal effect on functioning Threshold: often has difficulty staying seated when required – moderate to severe effect on functioning	0 1 2 3

Makes a lot of careless mistakes *Do you make a lot of careless mistakes at school? Do you often get problems wrong on tests because you didn't read the instructions right? Do you often leave some questions blank by accident? Forget to do the problems on both sides of a handout? How often do these types of things happen? Has your teacher ever said you should pay more attention to detail?*	0 1 2 3	No information Not present Subthreshold: occasionally makes careless mistakes – minimal effect on function Threshold: often makes careless mistakes - moderate to severe effect on functioning	0 1 2 3

Doesn't listen *Is it hard for you to remember what your parents and teachers say? Do your parents or teachers complain that you don't listen to them when they talk to you? Do you "tune people out"? Do you get into trouble for not listening?*	0 1 2 3	No information Not present Subthreshold: occasionally doesn't listen – minimal effect on functioning Threshold: often doesn't listen. Moderate to severe effect on functioning.	0 1 2 3

Difficulty following instructions *Do your teachers complain that you don't follow instructions? When your parents or teacher tell you to do something, is it sometimes hard to remember what they said to do? Do you lose points on your assignments for not following directions?*	0 1 2 3	No information Not present Subthreshold: occasional difficulty following instructions – minimal effect on functioning Threshold: often difficulty following instructions. Moderate to severe effect on functioning.	0 1 2 3

Difficulty organising tasks *Is your desk or locker at school a mess? Does it make it hard for you to find things you need? Does your teacher complain that your work is messy or disorganised? When you do your worksheets, do you usually start at the beginning and do all the problems in order, or do you skip about? Do you often miss problems? Do you have a hard time getting ready for school in the morning?*	0 1 2 3	No information Not present Subthreshold: occasionally disorganised. Minimal effect on functioning Threshold: often disorganised. Moderate to severe effect on functioning	0 1 2 3

Dislikes/avoids tasks requiring attention *Are there some kinds of school work that you hate more than others? Which ones? Why? Dou you try to get out of doing your _____ assignments? Do you pretend to forget about your homework to get out of doing it? About how many times a week do you not do your homework?*	0 1 2 3	No information Not present Subthreshold: occasionally avoids tasks that need sustained attention and/or expresses mild dislike for these tasks. Minimal effect on functioning. Threshold: often avoids tasks that need sustained attention and/or expresses moderate dislike for these tasks. Moderate to severe effect on functioning.	0 1 2 3

Loses things *Do you lose things a lot? Your pencils at school? Homework assignments? Things around home? About how often does this happen?*	0 1 2 3	No information Not present Subthreshold; occasionally loses things. Minimal effect on functioning Threshold: often loses things (e.g. once a week or more). Moderate to severe effect on functioning	0 1 2 3

Forgetful in daily activities *Do you often leave your homework at home or your books or coat on the bus? Do you leave your things outside by accident? How often do these things happen? Has anyone ever said that you're too forgetful?*	0 1 2 3	No information Not present Subthreshold: occasionally forgetful. Minimal effect on functioning Threshold: often forgetful. Moderate to severe effect on functioning	0 1 2 3

Fidgets *Do people often tell you to sit still, to stop moving or stop squirming in your seat? Teachers? Parents? Do you sometimes get into trouble for squirming in your seat or playing with little things at your desk? Do you have a hard time keeping your arms and legs still?*	0 1 2 3	No information Not present Subthreshold: occasionally fidgets with hands or feet or squirms in seat. Minimal effect on functioning Threshold: Often fidgets with hands or feet or squirms in seat (e.g. at least 50% of time). Moderate to severe effect on functioning	0 1 2 3

Runs or climbs excessively *Do you get into trouble for running down the hall in school? Does your mum often have to remind you to walk instead of run when you're out together? Do your parents or teacher complain about you climbing things you shouldn't? What kinds of things? How often does this happen?* Adolescents: *Do you feel restless a lot? Feel like you have to move around, or that it is very hard to stay in one place?*	0 1 2 3	No information Not present Subthreshold: occasionally runs about or climbs excessively. Minimal effect on functioning Threshold: often runs about or climbs excessively. Moderate to severe effect on functioning. (In adolescents may be limited to a subjective feeling of restlessness).	0 1 2 3

On the go/acts like driven like a motor *Is it hard for you to slow down? Can you stay in one place for long, or are you always on the go? How long can you sit and watch TV and play a game? Do people tell you to slow down a lot?*	0 1 2 3	No information Not present Subthreshold: occasionally. Minimal effect on functioning Threshold: often acts as if driven by a motor. Moderate to severe effect on functioning	0 1 2 3

Difficulty playing quietly *Do your parents or teachers often tell you to quiet down when you're playing? Do you have a hard time playing quietly?*	0 1 2 3	No information Not present Subthreshold; occasionally has difficulty playing quietly. Minimal effect on functioning Threshold: often has difficulty playing quietly. Moderate to severe effect on functioning	0 1 2 3

Blurts out answers *At school, do you sometimes call out the answers before you're called on? Do you talk out of turn at home? Answer questions your parents ask your siblings? How often?*	0	No information	0
	1	Not present	1
	2	Subthreshold; talks out of turn. Minimal effect on functioning	2
	3	Threshold: often talks out of turn (e.g. daily or nearly daily). Moderate to severe effect on functioning	3

Difficulty waiting turn *Is it hard for you to wait your turn in games? What about in line in the cafeteria or at the water fountain?*	0	No information	0
	1	Not present	1
	2	Subthreshold; occasionally has difficulty waiting turn. Minimal effect on functioning	2
	3	Threshold: often has difficulty waiting turn. Moderate to severe effect on functioning	3

Interrupts or intrudes *Do you get into trouble for talking out of turn in school? Do your parents, teachers or any of the kids you know complain that you cut them off when they're talking? Do kids complain that you break in on games? Does this happen a lot?*	0	No information	0
	1	Not present	1
	2	Subthreshold; occasionally interrupts others.	2
	3	Threshold: often interrupts others.	3

Shifts activities *When you're playing or doing one thing, do you often stop what you're doing because you think of something else you'd rather do? Do you have trouble sticking with one activity? (Survey multiple items: e.g. setting the table, other chores, schoolwork, video games). Have other people said you do? Your teacher? Your mum?*	0	No information	0
	1	Not present	1
	2	Subthreshold: occasionally shifts tasks and doesn't complete activities.	2
	3	Threshold: shifts tasks and doesn't finish activities.	3

Talks excessively *Do people say you talk too much? Do you get into trouble at school for talking when you're not supposed to? Do people in your family say you talk too much?*	0	No information	0
	1	Not present	1
	2	Subthreshold; occasionally talks excessively	2
	3	Threshold: often talks out of turn (e.g. daily or nearly daily). Moderate to severe effect on functioning	3

ADHD Symptom count				Current episode	Most severe past
	CE	MSP	Symptom duration > 6 months	0 1 2	0 1 2
Inattention	……..	……	Age of onset under 7 (write in when: - _____ years)	0 1 2	0 1 2
Hyperactivity	……...	……	Impairment - with peers	0 1 2	0 1 2
Impulsivity	……	……	Impairment – with family	0 1 2	0 1 2
			Impairment – at school	0 1 2	0 1 2

Appendix 4

Child Behavior Checklist (CBCL)for ages 6 – 18 - Achenbach (1991)

ASEBA

Please print **CHILD BEHAVIOR CHECKLIST FOR AGES 6-18**

For office use only
ID #

CHILD'S FULL NAME First Middle Last

CHILD'S GENDER ☐ Boy ☐ Girl

CHILD'S AGE

CHILD'S ETHNIC GROUP OR RACE

TODAY'S DATE Mo._____ Date _____ Yr. _____

CHILD'S BIRTHDATE Mo._____ Date _____ Yr. _____

GRADE IN SCHOOL _____

NOT ATTENDING SCHOOL ☐

Please fill out this form to reflect *your* view of the child's behavior even if other people might not agree. Feel free to print additional comments beside each item and in the space provided on page 2. ***Be sure to answer all items.***

PARENTS' USUAL TYPE OF WORK, even if not working now. *(Please be specific — for example, auto mechanic, high school teacher, homemaker, laborer, lathe operator, shoe salesman, army sergeant.)*

FATHER'S TYPE OF WORK _____

MOTHER'S TYPE OF WORK _____

THIS FORM FILLED OUT BY: (print your full name)

Your gender: ☐ Male ☐ Female

Your relation to the child:

☐ Biological Parent ☐ Step Parent ☐ Grandparent
☐ Adoptive Parent ☐ Foster Parent ☐ Other (specify)_____

I. Please list the sports your child most likes to take part in. For example: swimming, baseball, skating, skate boarding, bike riding, fishing, etc.

☐ None

	Compared to others of the same age, about how much time does he/she spend in each?				Compared to others of the same age, how well does he/she do each one?			
	Less Than Average	Average	More Than Average	Don't Know	Below Average	Average	Above Average	Don't Know
a. _____	☐	☐	☐	☐	☐	☐	☐	☐
b. _____	☐	☐	☐	☐	☐	☐	☐	☐
c. _____	☐	☐	☐	☐	☐	☐	☐	☐

II. Please list your child's favorite hobbies, activities, and games, other than sports. For example: stamps, dolls, books, piano, crafts, cars, computers, singing, etc. (Do *not* include listening to radio or TV.)

☐ None

	Compared to others of the same age, about how much time does he/she spend in each?				Compared to others of the same age, how well does he/she do each one?			
	Less Than Average	Average	More Than Average	Don't Know	Below Average	Average	Above Average	Don't Know
a. _____	☐	☐	☐	☐	☐	☐	☐	☐
b. _____	☐	☐	☐	☐	☐	☐	☐	☐
c. _____	☐	☐	☐	☐	☐	☐	☐	☐

III. Please list any organizations, clubs, teams, or groups your child belongs to.

☐ None

	Compared to others of the same age, how active is he/she in each?			
	Less Active	Average	More Active	Don't Know
a. _____	☐	☐	☐	☐
b. _____	☐	☐	☐	☐
c. _____	☐	☐	☐	☐

IV. Please list any jobs or chores your child has. For example: paper route, babysitting, making bed, working in store, etc. (Include both paid and unpaid jobs and chores.)

☐ None

	Compared to others of the same age, how well does he/she carry them out?			
	Below Average	Average	Above Average	Don't Know
a. _____	☐	☐	☐	☐
b. _____	☐	☐	☐	☐
c. _____	☐	☐	☐	☐

Be sure you answered all items. Then see other side.

Please print. Be sure to answer all items.

V. 1. About how many close friends does your child have? (Do *not* include brothers & sisters)

❒ None ❒ 1 ❒ 2 or 3 ❒ 4 or more

2. About how many times a week does your child do things with any friends outside of regular school hours? (Do *not* include brothers & sisters) ❒ Less than 1 ❒ 1 or 2 ❒ 3 or more

VI. Compared to others of his/her age, how well does your child:

	Worse	Average	Better	
a. Get along with his/her brothers & sisters?	❒	❒	❒	❒ Has no brothers or sisters
b. Get along with other kids?	❒	❒	❒	
c. Behave with his/her parents?	❒	❒	❒	
d. Play and work alone?	❒	❒	❒	

VII. 1. Performance in academic subjects. ❒ Does not attend school because _____

Check a box for each subject that child takes	Failing	Below Average	Average	Above Average
a. Reading, English, or Language Arts	❒	❒	❒	❒
b. History or Social Studies	❒	❒	❒	❒
c. Arithmetic or Math	❒	❒	❒	❒
d. Science	❒	❒	❒	❒
e. _____	❒	❒	❒	❒
f. _____	❒	❒	❒	❒
g. _____	❒	❒	❒	❒

Other academic subjects–for example: computer courses, foreign language, business. Do ***not*** include gym, shop, driver's ed., or other nonacademic subjects.

2. Does your child receive special education or remedial services or attend a special class or special school?

❒ No ❒ Yes—kind of services, class, or school:

3. Has your child repeated any grades? ❒ No ❒ Yes—grades and reasons:

4. Has your child had any academic or other problems in school? ❒ No ❒ Yes—please describe:

When did these problems start?_____

Have these problems ended? ❒ No ❒ Yes–when?

Does your child have any illness or disability (either physical or mental)? ❒ No ❒ Yes—please describe:

What concerns you most about your child?

Please describe the best things about your child.

Be sure you answered all items.

Please print. Be sure to answer all items.

Below is a list of items that describe children and youths. For each item that describes your child ***now or within the past 6 months***, please circle the ***2*** if the item is ***very true or often true*** of your child. Circle the ***1*** if the item is ***somewhat or sometimes true*** of your child. If the item is ***not true*** of your child, circle the ***0***. Please answer all items as well as you can, even if some do not seem to apply to your child.

0 = Not True (as far as you know) **1 = Somewhat or Sometimes True** **2 = Very True or Often True**

0 1 2 1. Acts too young for his/her age
0 1 2 2. Drinks alcohol without parents' approval (describe):_____
_____
0 1 2 3. Argues a lot
0 1 2 4. Fails to finish things he/she starts
0 1 2 5. There is very little he/she enjoys
0 1 2 6. Bowel movements outside toilet
0 1 2 7. Bragging, boasting
0 1 2 8. Can't concentrate, can't pay attention for long
0 1 2 9. Can't get his/her mind off certain thoughts; obsessions (describe): _____
_____
0 1 2 10. Can't sit still, restless, or hyperactive
0 1 2 11. Clings to adults or too dependent
0 1 2 12. Complains of loneliness
0 1 2 13. Confused or seems to be in a fog
0 1 2 14. Cries a lot
0 1 2 15. Cruel to animals
0 1 2 16. Cruelty, bullying, or meanness to others
0 1 2 17. Daydreams or gets lost in his/her thoughts
0 1 2 18. Deliberately harms self or attempts suicide
0 1 2 19. Demands a lot of attention
0 1 2 20. Destroys his/her own things
0 1 2 21. Destroys things belonging to his/her family or others
0 1 2 22. Disobedient at home
0 1 2 23. Disobedient at school
0 1 2 24. Doesn't eat well
0 1 2 25. Doesn't get along with other kids
0 1 2 26. Doesn't seem to feel guilty after misbehaving
0 1 2 27. Easily jealous
0 1 2 28. Breaks rules at home, school, or elsewhere
0 1 2 29. Fears certain animals, situations, or places, other than school (describe): _____
_____
0 1 2 30. Fears going to school
0 1 2 31. Fears he/she might think or do something bad
0 1 2 32. Feels he/she has to be perfect
0 1 2 33. Feels or complains that no one loves him/her
0 1 2 34. Feels others are out to get him/her
0 1 2 35. Feels worthless or inferior
0 1 2 36. Gets hurt a lot, accident-prone
0 1 2 37. Gets in many fights
0 1 2 38. Gets teased a lot
0 1 2 39. Hangs around with others who get in trouble
0 1 2 40. Hears sounds or voices that aren't there (describe): _____
_____
0 1 2 41. Impulsive or acts without thinking
0 1 2 42. Would rather be alone than with others
0 1 2 43. Lying or cheating
0 1 2 44. Bites fingernails
0 1 2 45. Nervous, highstrung, or tense
0 1 2 46. Nervous movements or twitching (describe): ____
_____
_____
0 1 2 47. Nightmares
0 1 2 48. Not liked by other kids
0 1 2 49. Constipated, doesn't move bowels
0 1 2 50. Too fearful or anxious
0 1 2 51. Feels dizzy or lightheaded
0 1 2 52. Feels too guilty
0 1 2 53. Overeating
0 1 2 54. Overtired without good reason
0 1 2 55. Overweight
56. Physical problems ***without known medical cause:***
0 1 2 a. Aches or pains (***not*** stomach or headaches)
0 1 2 b. Headaches
0 1 2 c. Nausea, feels sick
0 1 2 d. Problems with eyes (***not*** if corrected by glasses) (describe): _____
0 1 2 e. Rashes or other skin problems
0 1 2 f. Stomachaches
0 1 2 g. Vomiting, throwing up
0 1 2 h. Other (describe): _____
_____

 Be sure you answered all items. Then see other side.

Please print. Be sure to answer all items.

0 = Not True (as far as you know) 1 = Somewhat or Sometimes True 2 = Very True or Often True

0 1 2 57. Physically attacks people
0 1 2 58. Picks nose, skin, or other parts of body (describe): _____
_____
0 1 2 59. Plays with own sex parts in public
0 1 2 60. Plays with own sex parts too much
0 1 2 61. Poor school work
0 1 2 62. Poorly coordinated or clumsy
0 1 2 63. Prefers being with older kids
0 1 2 64. Prefers being with younger kids
0 1 2 65. Refuses to talk
0 1 2 66. Repeats certain acts over and over; compulsions (describe): _____
_____
0 1 2 67. Runs away from home
0 1 2 68. Screams a lot
0 1 2 69. Secretive, keeps things to self
0 1 2 70. Sees things that aren't there (describe): _____
_____
_____
0 1 2 71. Self-conscious or easily embarrassed
0 1 2 72. Sets fires
0 1 2 73. Sexual problems (describe): _____
_____
_____
0 1 2 74. Showing off or clowning
0 1 2 75. Too shy or timid
0 1 2 76. Sleeps less than most kids
0 1 2 77. Sleeps more than most kids during day and/or night (describe): _____
_____
0 1 2 78. Inattentive or easily distracted
0 1 2 79. Speech problem (describe): _____
_____
0 1 2 80. Stares blankly
0 1 2 81. Steals at home
0 1 2 82. Steals outside the home
0 1 2 83. Stores up too many things he/she doesn't need (describe): _____
_____
_____
0 1 2 84. Strange behavior (describe): _____
_____
0 1 2 85. Strange ideas (describe): _____
_____
0 1 2 86. Stubborn, sullen, or irritable
0 1 2 87. Sudden changes in mood or feelings
0 1 2 88. Sulks a lot
0 1 2 89. Suspicious
0 1 2 90. Swearing or obscene language
0 1 2 91. Talks about killing self
0 1 2 92. Talks or walks in sleep (describe): _____
_____
0 1 2 93. Talks too much
0 1 2 94. Teases a lot
0 1 2 95. Temper tantrums or hot temper
0 1 2 96. Thinks about sex too much
0 1 2 97. Threatens people
0 1 2 98. Thumb-sucking
0 1 2 99. Smokes, chews, or sniffs tobacco
0 1 2 100. Trouble sleeping (describe): _____
_____
0 1 2 101. Truancy, skips school
0 1 2 102. Underactive, slow moving, or lacks energy
0 1 2 103. Unhappy, sad, or depressed
0 1 2 104. Unusually loud
0 1 2 105. Uses drugs for nonmedical purposes (***don't*** include alcohol or tobacco) (describe): _____
_____
_____
0 1 2 106. Vandalism
0 1 2 107. Wets self during the day
0 1 2 108. Wets the bed
0 1 2 109. Whining
0 1 2 110. Wishes to be of opposite sex
0 1 2 111. Withdrawn, doesn't get involved with others
0 1 2 112. Worries
113. Please write in any problems your child has that were not listed above:
0 1 2 _____
0 1 2 _____
0 1 2 _____

Please be sure you answered all items.

Appendix 5

Appendix 5a: Conners' Global Index – Parent (Conners 1997)

Appendix 5b: Conners' Global Index – Teacher (Conners 1997)

CRS48G

CGI-P: Conners' Global Index - Parent Version

by C. Keith Conners, Ph.D.

Child ID: _____ **Gender:** M F (Circle One)

Birthdate: ____/____/____ (Month / Day / Year) **Age:** _____ **School Grade:** _____

Parent ID: _____ **Today's Date:** ____/____/____ (Month / Day / Year)

Instructions: Below are a number of common problems that children have. Please rate each item according to your child's behavior in the last month. For each item, ask yourself, "How much of a problem has this been in the last month?", and circle the best answer for each item. If none, not at all, seldom, or very infrequently, you would circle 0. If very much true, or it occurs very often or frequently, you would circle 3. You would circle 1 or 2 for ratings in between. Please respond to all the items.

		NOT TRUE AT ALL (Never, Seldom)	JUST A LITTLE TRUE (Occasionally)	PRETTY MUCH TRUE (Often, Quite a Bit)	VERY MUCH TRUE (Very Often, Very Frequent)
1.	Restless or overactive	0	1	2	3
2.	Excitable, impulsive	0	1	2	3
3.	Fails to finish things he/she starts	0	1	2	3
4.	Inattentive, easily distracted	0	1	2	3
5.	Temper outbursts	0	1	2	3
6.	Fidgeting	0	1	2	3
7.	Disturbs other children	0	1	2	3
8.	Demands must be met immediately—easily frustrated	0	1	2	3
9.	Cries often and easily	0	1	2	3
10.	Mood changes quickly and drastically	0	1	2	3

CGI-T: Conners' Global Index - Teacher

by C. Keith Conners, Ph.D.

Student's ID: _____ **Gender:** M F (Circle One)

Birthdate: ____/____/____ (Month Day Year) **Age:** _____ **School Grade:** _____

Teacher's Name: _____ **Today's Date:** ____/____/____ (Month Day Year)

Instructions: Below are a number of common problems that children have in school. Please rate each item according to how much of a problem it has been in the last month. For each item, ask yourself, "How much of a problem has this been in the last month?", and circle the best answer for each item. If none, not at all, seldom, or very infrequently, you would circle 0. If very much true, or it occurs very often or frequently, you would circle 3. You would circle 1 or 2 for ratings in between. Please respond to all the items.

		NOT TRUE AT ALL (Never, Seldom)	JUST A LITTLE TRUE (Occasionally)	PRETTY MUCH TRUE (Often, Quite a Bit)	VERY MUCH TRUE (Very Often, Very Frequent)
1.	Temper outbursts; explosive, unpredictable behavior	0	1	2	3
2.	Excitable, impulsive	0	1	2	3
3.	Restless or overactive	0	1	2	3
4.	Cries often and easily	0	1	2	3
5.	Inattentive, easily distracted	0	1	2	3
6.	Fidgeting	0	1	2	3
7.	Disturbs other children	0	1	2	3
8.	Demands must be met immediately—easily frustrated	0	1	2	3
9.	Fails to finish things he/she starts	0	1	2	3
10.	Mood changes quickly and drastically	0	1	2	3

Appendix 6

Methylphenidate restores visual memory, but not working memory function in attention deficit-hyperkinetic disorder

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ORIGINAL INVESTIGATION

Sinead M. Rhodes · David R. Coghill · Keith Matthews

Methylphenidate restores visual memory, but not working memory function in attention deficit-hyperkinetic disorder

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Abstract *Rationale:* Dysfunction of executive neuropsychological performance, mediated by the prefrontal cortex, has been the central focus of recent attention deficit/hyperkinetic disorder (AD-HKD) research. The role of other potential neuropsychological "risk factors", such as recognition memory, remains understudied. Further, the impact of methylphenidate (MPH) on key neuropsychological processes in AD-HKD remains poorly understood. *Objectives:* To compare the performance of boys with AD-HKD on a spatial working memory (SWM) task and on two non-working memory tasks [a simultaneous and delayed matching-to-sample task (DMtS) and a pattern-recognition task] with that of healthy boys, and to investigate the impact of acute and chronic MPH on performance of these tasks. *Methods:* Baseline performance of 75 stimulant-naive boys with AD-HKD was compared with that of 70 healthy boys. The AD-HKD boys were then re-tested following the administration of acute and chronic challenges with MPH (0.3 mg/kg and 0.6 mg/kg) under randomised double-blind placebo controlled conditions. *Results:* Compared with healthy boys, the AD-HKD boys demonstrated performance deficits on all neuropsychological tasks. A single dose of MPH restored performance on the DMtS task but had no impact on the SWM or pattern-recognition tasks. Chronic MPH administration did not alter performance on the SWM task but did improve performance on both the pattern-recognition and DMtS tasks. However, the acute restorative effect of MPH on DMtS diminished with repeated administration. *Conclusions:* Our results suggest that current conceptualisations of the neuropsychological basis of AD-HKD and the proposed therapeutic mechanisms of MPH require broadening.

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Keywords ADHD · Methylphenidate · CANTAB · Delayed matching to sample · Visual memory · Working memory · Tolerance

Introduction

Disorders of attention and hyperactivity are common, but controversial, clinical constructs which present a major public health challenge (NIMH 2000). In view of continuing debate surrounding the nosology of these conditions, we have chosen to adopt the convention described by Schachar and Tannock (2002). Hence, we will refer to specific diagnostic terms, such as hyperkinetic disorder (HD) or attention deficit hyperactivity disorder (ADHD) when addressing a particular diagnostic entity and set of criteria. We will use the acronym deficit/hyperkinetic disorder (AD-HKD) when referring to characteristics that are believed to be shared by ADHD and HD. It is implausible that AD-HKD represents the clinical presentation of a single neuropsychological or neurophysiological abnormality (Castellanos and Tannock 2002; Todd 2000; Sonuga-Barke 2002). Whilst much AD-HKD research has sought to explain this disorder within a single "grand theory", genetic (Nadder et al. 2002; Todd et al. 2001), neuropsychological (Solanto et al. 2001), pathophysiological (Rothenberger et al. 2000) and phenotypic (Biederman et al. 1992) studies have all identified a high degree of heterogeneity within the AD-HKD population, suggesting a multi-factorial aetiology, which is unlikely to be accounted for within any such model. More likely, AD-HKD is a constellation of behavioural features generated by several relatively independent pathophysiological risk factors. Putative risk factors, or "endophenotypes", of assumed major effect, with direct experimental support, include deficits in executive neuropsychological functions such as inhibitory control (Barkley 1997) and working memory (Kempton et al. 1999). Executive neuropsychological functions are dependent on intact functioning of the prefrontal cortices and their projections to subcortical targets such as the caudate nucleus and nucleus accum-

bens (Fuster 1989). Imaging studies have consistently implicated these brain regions in the pathophysiology of AD-HKD (Giedd et al. 2001). Accurate performance of these tasks is dependent on intact dopaminergic and noradrenergic neurotransmission and can be modified by even small manipulations in catecholamine release (Mehta et al. 2001). Hence, the therapeutic effects of stimulant drugs such as methylphenidate (MPH) and dexamphetamine in AD-HKD are thought to arise from actions on these circuits (Volkow et al. 2001b). Delay aversion is another potential "endophenotype" with observed impulsivity representing a strategy to reduce the subjective experience of delay (Sonuga-Barke 2002).

Working memory and AD-HKD

Definitions of working memory are contentious and, at times, confusing. Whilst some authors consider working memory simply as the process of actively maintaining relevant information in mind for brief periods of time (Gleitman et al. 1999), a more comprehensive and influential view emphasises the importance of computational processing and states that working memory is best considered as the capacity to simultaneously store and manipulate information (Baddeley 2003, 1986). Indeed, Baddeley (1996) endorses Daneman and Carpenter's definition of a working memory task as "one that simultaneously requires the storage and manipulation of information" (Daneman and Carpenter 1980), thus differentiating such tasks from those that require storage but no manipulation. Whilst deficits on "true" working memory tasks, with substantial executive demands, have been accepted as part of the pathophysiology of AD-HKD, relatively little attention has been paid to the possibility that these children, many of whom are, by definition, disorganised and forgetful, may also demonstrate specific performance deficits on non-working memory tasks which place much lower demands on executive functioning. Studies have reported that children with AD-HKD demonstrate deficits on free recall (Borcherding et al. 1988; Loge et al. 1990), paired associates learning (Conte et al. 1986; Chang et al. 1999), spatial recognition (Kempton et al. 1999) and delayed matching-to-sample (Chelonis et al. 2002; Kempton et al. 1999) tasks (DMtS); however, negative findings have also been reported particularly on memory tasks in which stimuli are clustered or recall strategies are presented (August 1987; Benezra and Douglas 1988; Voelker et al. 1989), and also on a pattern-recognition task (Kempton et al. 1999), suggesting that when executive demands are reduced, the tasks become manageable. Unfortunately, much of this work has been hampered by a range of methodological concerns, including the failure to use clearly defined, specific, sensitive measures, small sample sizes, the use of rating scales rather than clinical interviews in the assessment of subjects and the inclusion of children with AD-HKD who were either currently taking stimulant medication or who had been recently withdrawn from stimulant medication.

Thus, we compared the performance of 75 stimulant-naive boys meeting diagnostic criteria for ICD-10 HD and DSM-IV ADHD combined subtype, aged between 7 years and 15 years, with 70 age-matched healthy controls on three memory tasks selected from the Cambridge neuropsychological test automated battery (CANTAB) neuropsychological test battery (Fray and Robbins 1996). The CANTAB battery has been extensively validated in both child (Curtis et al. 2002; Luciana and Nelson 1998; Hughes et al. 1999; Williams et al. 2000) and adult (Robbins et al. 1994) populations. Tasks within the battery have been shown to be differentially sensitive to dysfunction in several brain regions, including frontal, temporal and amygdalo-hippocampal regions (Owen et al. 1995). Here, we report performance on three memory tasks selected from the battery—a spatial working memory (SWM) task and two "non-working" recognition memory tasks (pattern recognition and both simultaneous and delayed matching to sample). Performance on further tasks from the CANTAB battery, including stockings of Cambridge (Tower of London), intra-dimensional/extra-dimensional shift, spatial span, spatial recognition, paired associates learning and reaction time, will be reported separately. Successful performance on this SWM task has been shown to be associated with activations of the dorsolateral and ventrolateral PFC and posterior parietal cortex in functional neuroimaging studies in children (Nelson et al. 2000) and adults (Mehta et al. 2000b; Owen et al. 1996). Performance deficits on this SWM task have previously been reported in children (Kempton et al. 1999) and adults (Mehta et al. 2000a) with ADHD. Successful performance of the pattern recognition and DMtS "non-working" visual recognition memory tasks requires intact short-term visual memory processing, imposes minimal "executive" demands and is sensitive to both temporal lobe and amygdalo-hippocampal (but not frontal lobe) damage (Owen et al. 1995). Deficits on this DMtS task have been reported in children with ADHD (Kempton et al. 1999). Kempton and colleagues did not, however, find performance deficits on the pattern-recognition task.

In the present study, we wished to test subjects under drug-free baseline conditions and then to re-test the AD-HKD under randomised, double-blind, placebo-controlled conditions on the three tasks following acute and chronic challenges with MPH. The inclusion of a medication condition serves several purposes. From a clinical perspective, it provides an indication as to which aspects of neuropsychological performance may be enhanced or diminished by MPH. Knowledge of the effects of MPH, an indirect dopamine agonist, on neuropsychological performance also increases understanding of the complex pathophysiological processes that underpin AD-HKD. Improved performance following administration of MPH has been reported for the SWM task (Mehta et al. 2000a,b) and on a DMtS task (Chelonis et al. 2002).

On the basis of data published prior to our initiation of the present study, we made three predictions: (1) at baseline AD-HKD boys will display performance deficits

on SWM, DMtS and pattern-recognition tasks; (2) acute MPH will improve performance on the SWM task but have no effect on the DMtS and pattern-recognition tasks; (3) the effects of chronic MPH on these tasks will be the same as those seen with acute MPH.

Materials and methods

This study was approved by the Tayside Committee on Medical Ethics. All volunteers provided written informed consent.

Subjects

Subjects in the AD-HKD group were recruited from a group of boys aged between 7 years and 15 years old who had been referred to the Tayside Child and Adolescent Psychiatry Service. We used a two-stage screening procedure. Eligible and consenting subjects scoring >1.5 standard deviations from the mean on both the Conners' parent rating scale short version (CPRS-26) and the Conners' teacher rating scale short version (CTRS-28) were interviewed by an experienced child and adolescent psychiatrist using the Kiddie-SADS present and lifetime (K-SADS-PL) (Kaufman et al. 1996) semi-structured diagnostic interview. Those meeting the diagnostic criteria for HD (F90)—as defined in the international classification of diseases version 10 (ICD 10 1992)—and ADHD combined subtype—as defined in the diagnostic and statistical manual version IV (DSM IV 1994)—and not meeting exclusion criteria, were invited to participate in the study. Exclusion criteria for subjects included a history of neurological impairment, previously determined learning disability (IQ<80), chronic physical illness, sensory or motor impairment, current or previous exposure to stimulant medication, and abuse of any illegal drugs. The presence of a range of commonly occurring co-morbid conditions, including oppositional defiant disorder, conduct disorder and anxiety disorder, did not result in exclusion from the study (Table 1). The intention was to ensure recruitment of a group of children representative of those seen in typical clinical practice within the National Health Service in the UK. All co-morbid diagnoses were considered secondary to the primary diagnosis of AD-HKD. Five children met criteria for multiple co-morbid diagnoses.

Subjects for the age-matched healthy control group were selected from local schools following a similar two-stage screen. Consenting pupils scoring <1 standard deviation from the mean on the CPRS-26 and the CTRS-28 and all subscales of the CBCL, with no current or past psychiatric diagnosis on the K-SADS-PL interview and not meeting exclusion criteria, were invited to participate in the study. Exclusion criteria were identical to that of the AD-HKD group

The British picture vocabulary scale (BPVS) (Dunn et al. 1997) [2nd edn] was used to estimate general intellectual ability for both the AD-HKD and control subjects. The BPVS assesses verbal intelligence and was chosen for its ease of administration and ability to be used with children aged between 3 years and 15 years. It is an individually administered, norm-referenced, wide-range test of receptive vocabulary for Standard English.

Table 1 Co-morbid diagnoses in the AD-HKD group

	N	% of sample
No co-morbid diagnosis	18	24
Co-morbid diagnoses		
Oppositional defiant disorder	31	41.3
Conduct disorder (CD)	21	28
Depressive disorder	3	4
Generalised anxiety disorder	2	2.7
Separation anxiety disorder	3	4
Tic disorder	2	2.7
Social phobia	1	1.3

Neuropsychological testing

Delayed matching to sample. The DMtS task was selected from the CANTAB (Owen et al. 1995; Robbins et al. 1997). This task assesses a subject's ability to remember the visual features of a complex, abstract, target stimulus. At the beginning of each trial, a pattern consisting of four quadrants, each differing in colour and form, appears in the centre of a touch-sensitive screen in a white box for a presentation period of 4.5 s. Subjects are asked to remember the pattern. In the "simultaneous condition", four choice patterns then appear in red boxes located under the target pattern. The subject is required to respond by touching the choice pattern that corresponds exactly (in both colour and form) to the target pattern above. Only one of the choice patterns is identical to the target. Correct and incorrect responses are signalled by differing auditory tones and visual feedback in the form of green ticks or red crosses. If subjects' make an incorrect response, they are required to continue to choose until the target stimulus has been chosen. The conditions for the delayed portion of the task are identical to those of the simultaneous condition with the exception that, after the initial presentation period, the target pattern disappears from the screen. The four choice patterns are then presented following one of three delays; 0, 4, and 12 s. Following three practice trials (one each of the simultaneous presentation, 0-s and 12-s delay), a total of 20 test trials are presented with each of the four conditions presented in a pseudorandom order. Data were analysed separately for the simultaneous and delay conditions.

Spatial working memory. This is a self-ordered searching task (Petrides and Milner 1982) that assesses working memory for spatial stimuli and requires a subject to use mnemonic information to work towards a goal. Subjects are required to "search through" a spatial array of coloured boxes presented on a screen to collect "blue tokens" hidden inside the boxes. Returning to a box where a token has already been found constitutes a "between search" error (BSE) and returning to a box already opened and shown to be empty earlier in the same search sequence constitutes a "within search" error (WSE). A strategy score is calculated based on how often a searching sequence was initiated from the same box during a trial (Fray and Robbins 1996).

Pattern recognition. This test measures a subject's ability to recognise a previously presented abstract pattern from two adjacent stimuli. The primary measure in this task is the number of correct patterns chosen across two trials of 12 patterns in each set.

Procedure

The study was conducted in three stages: baseline, acute challenge and chronic challenge.

We first compared the baseline performance of the drug-naive AD-HKD group prior to exposure to MPH and control group on each of the tasks. The control group were not re-tested and exited the study at this point. The AD-HKD group were randomised under double-blind conditions into three treatment groups. Two weeks after the initial baseline test session, the AD-HKD boys were given a single oral dose acute challenge with MPH at between 0800 hours and 0900 hours, at one of three doses (group 1=placebo, group 2=0.3 mg/kg, group 3=0.6 mg/kg) and re-tested on the neuropsychological tasks using the first parallel test version 90 min later. For the chronic challenge, MPH administration was continued for a further three periods of 28 days immediately following the acute challenge. This phase of the study was also conducted under randomised, double-blind, placebo-controlled, conditions in a cross-over design, with each subject taking MPH twice daily (at 0800 hours and 1200 hours) at each of the three doses (placebo, 0.3 mg/kg and 0.6 mg/kg per dose), starting with the dose given at the acute

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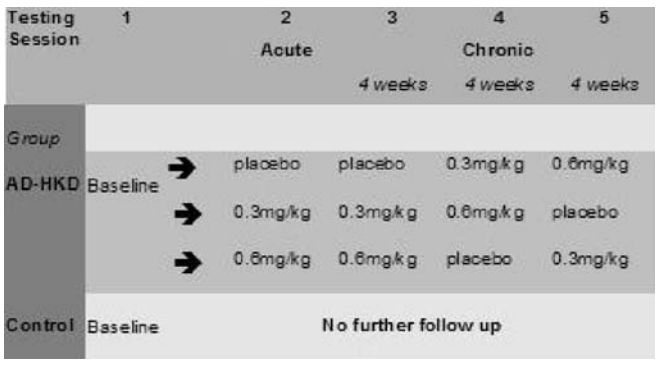


Fig. 1 Flow chart of procedure

challenge and rotating around the other two doses (Fig. 1). Subjects were re-tested using the second, third and fourth parallel task batteries 90 min after taking their morning medication at the end of each 28-day block.

Data analysis

All baseline comparisons between AD-HKD and control boys were analysed using ANCOVA with BPVS percentile rank scores as a covariate. Performance at the simultaneous condition of the DMtS task was analysed separately using univariate ANCOVA, whilst performance at delay conditions of this task and BSE on the SWM task were analysed using repeated-measures ANCOVA (0, 4, 12-s delays for DMtS; 3, 4, 6, 8 boxes for BSE in SWM).

Acute challenge data were analysed using repeated-measures ANOVA for both simultaneous and delay conditions on the DMtS task and all measures on the SWM task. Percentage correct scores on the pattern recognition task failed to meet normality and homogeneity of variance assumptions and hence were analysed using the non-parametric Wilcoxon Sign test for repeated measures.

For chronic data, a mixed-design ANOVA was used with repeated measures on treatment taken (placebo, 0.3 mg/kg or 0.6 mg/kg MPH) and the order in which it was taken (1st, 2nd or 3rd). No effects of order in which the drug was taken were found for any task. Following ANCOVA/ANOVA, further exploration of the data was conducted by determination of simple effects or interactions.

Alpha for the primary outcome measures of the three tasks were adjusted using the Bonferroni method in order to keep the alpha-level overall at 0.05. As a result, alpha for each task was lowered to 0.017.

Results

Subject characteristics

The AD-HKD group comprised 75 boys (mean age 10.8 years) and the healthy control group comprised 70 boys (mean age 10.7 years). There was no significant age difference between the AD-HKD and the healthy control group ($t_{1,113}$<1). The AD-HKD group had significantly lower BPVS scores than controls (F=27.2, P<0.001); thus, BPVS scores were used as a covariate in the baseline analyses. As would be expected, the AD-HKD group scored significantly higher than the healthy control group with respect to ADHD index scores on the parent (F=1571.4, P<0.001) and teacher (F=103.9, P<0.001) Conners' rating scales.

With respect to the acute and chronic challenge analyses, there were no significant differences between the three AD-HKD treatment groups (placebo, 0.3 mg/kg and 0.6 mg/kg) with respect to age (F<1), BPVS percentile rank (F<1), parent-rated ADHD composite score (Conners' scale) (F<1), and teacher-rated ADHD composite score (Conner's scale) (F<1). There were also no significant differences between these groups with respect to the incidence of most co-morbid diagnoses conduct disorder (F<1), oppositional defiant disorder (F<1), social phobia (F<1), generalised anxiety disorder (F=2.1, P>0.05), and tic disorder (F<1). However, there was a significant difference between the treatment groups with respect to separation anxiety disorder (F=3.4, P<0.04). All three boys diagnosed with this co-morbid condition were in one treatment group (those taking placebo at the acute and first chronic session). Separation anxiety disorder is not considered to be associated with neuropsychological impairment (Table 2).

Neuropsychological performance

Baseline

Delayed matching to sample. At baseline (Table 3), the AD-HKD group demonstrated deficits, relative to controls, at both the simultaneous ($F_{1,142}$=8.7, P<0.004,

Table 2 Demographic characteristics

	AD-HKD boys (N=75) mean (SD)	Healthy boys (N=70) mean (SD)	P
Age	10.85 (2.46)	10.74 (2.47)	>0.05
BPVS percentile rank	35.43 (27.93)	58.94 (26.25)	<0.001*
Conners' parent (T scores)			
Oppositionality	75.57 (11.38)	45.25 (6.42)	<0.001*
Cognitive	72.94 (7.07)	44.16 (3.47)	<0.001*
Hyperactive	83.08 (8.88)	46.12 (3.43)	<0.001*
ADHD index	77.01 (6.09)	43.96 (3.37)	<0.001*
Conners' teachers (T scores)			
Oppositionality	65.05 (19.52)	49.15 (9.49)	<0.001*
Cognitive	62.77 (12.78)	47.66 (7.95)	<0.001*
Hyperactive	71.0 (14.34)	47.36 (7.42)	<0.001*
ADHD index	72.23 (14.93)	47.79 (8.12)	<0.001*

Table 3 Summary of findings: baseline functioning

Measure	AD-HKD mean (SD)	Control mean (SD)	*F*	*P*	ES (*d*)
Delayed matching to sample					
Simultaneous % correct	90.93 (15.5)	97.14 (7.03)	8.7	<0.004*	0.52
Delay % correct (0 s, 4 s, 12 s combined)	59.52 (17.84)	75.66 (17.91)	27.18	<0.001*	0.90
Spatial working memory					
Total between-search errors (3, 4, 6, & 8 boxes combined)	50.84 (21.0)	34.99 (21.1)	18.8	<0.001*	0.75
Strategy score	36.32 (5.11)	32.73 (5.11)	16.52	<0.001*	0.70
Pattern recognition					
% correct	80.78 (13.1)	90.95 (8.37)	−5.3 (z)	<0.001*	0.89

Table 4 Summary of findings: acute responses

Measure	Placebo mean (SD)	0.3 mg/kg mean (SD)	0.6 mg/kg mean (SD)	*F*	*P*
Delayed matching to sample					
Simultaneous % correct	90.0 (15.6)	91.2 (19.22)	98.26 (5.76)	1.4	>0.05
Delay % correct (0 s, 4 s, 12 s combined)	55.55 (14.67)	61.6 (20.3)	78.84 (12.97)	7.11	<0.001*
Spatial working memory					
Total between-search errors (3, 4, 6, & 8 boxes combined)	47.08 (22.92)	40.8 (19.95)	38.83 (19.9)	<1	>0.05
Strategy score	35.67 (5.3)	35.56 (4.23)	35.46 (4.29)	<1	>0.05
Pattern recognition					
% correct	84.38 (11.07)	86.33 (10.93)	91.15 (7.40)	1.4	>0.05

d=0.52) and delay ($F_{1,142}$=26.4, p<0.001, d=0.90) conditions (Fig. 2a). There was a significant interaction between performance accuracy and duration of task delay (F=4.7, P<0.01). AD-HKD subjects made fewer correct responses with increasing delay, showing greatest performance deficits at the 12-s delay condition (F=4.6, P<0.03), whilst control boys performed equally across all delays. To investigate the relationship between performance under both simultaneous and delay conditions, performance under the delay conditions was re-analysed with accuracy at the simultaneous condition as a second covariate. No significant effect of the simultaneous condition as a covariate was found. There remained a significant interaction between performance accuracy and duration of task delay ($F_{2,282}$=3.6, P<0.03)] and boys with AD-HKD still made fewer correct responses with increasing delay, showing greatest performance deficits at the 12-s delay condition (F=5.6, P<0.02).

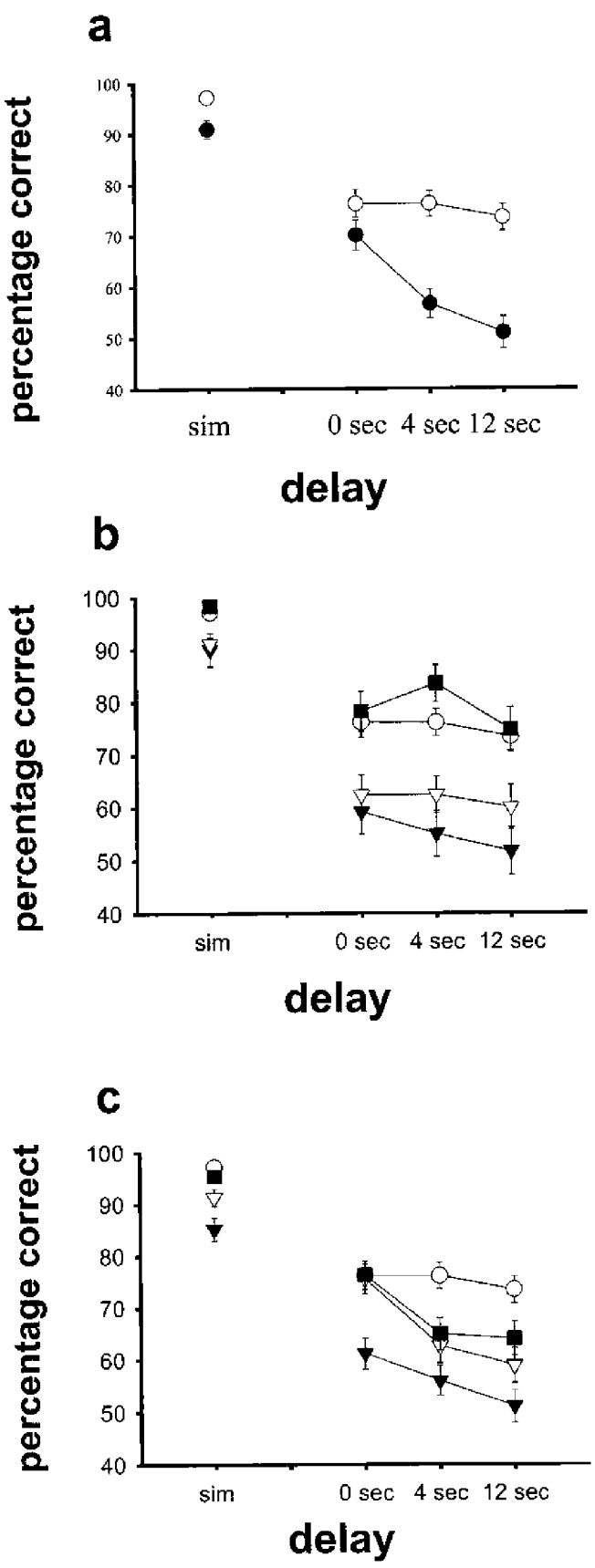
Incorrect responses were not associated with shorter response latencies for either group at the simultaneous condition (F<1). Under delay conditions, incorrect responses were associated with significantly shorter response latencies in the AD-HKD group ($F_{1,74}$=9.5, P<0.003). There were, however, no differences between response latencies across the three delay conditions for either group. Regression analysis revealed that latencies for incorrect responding did not predict accuracy of responding at the simultaneous, 4-s or 12-s delay conditions for AD-HKD boys. Shorter latencies were associated with increased error at the 0-s delay condition ([F=9.1, P<0.004]), but this contributed only a small proportion of the total variance for incorrect responses (r^2=0.145).

Spatial working memory. AD-HKD boys made more BSE on the SWM task ($F_{1,142}$=19.43, P<0.001, d=0.75). There was a significant interaction between group and difficulty level ($F_{1.6,223}$=15.1, P<0.001), and post-hoc tests revealed that AD-HKD boys made more errors at the eight-box stage than at three-box stages (P<0.001), four-box stages (P<0.001) or six-box stages (P<0.02). AD-HKD boys also had higher strategy scores indicating a lower use of strategy ($F_{2,142}$=16.52, P<0.001, d=0.70). There was no group difference in the number of WSE made. Strategy score was significantly correlated with total BSE for both AD-HKD (r=0.513, P<0.001) and control (r=0.588, P<0.001) boys.

Pattern recognition. AD-HKD boys made fewer correct responses on the pattern-recognition task (z=−5.267, P<0.001, d=0.89). There was no significant difference between the groups in latencies for correct responses. AD-HKD boys had shorter response latencies for incorrect choices ($F_{1,121}$=5.8, P<0.02). However, regression analysis revealed that the latencies for incorrect responses did not predict overall accuracy of responding for the AD-HKD boys.

Acute challenge

Delayed matching to sample. Acute oral MPH had no effect, at either dose, on performance accuracy under simultaneous test conditions (Table 4). MPH at a dose of 0.6 mg/kg, restored performance accuracy in AD-HKD boys, across each of the delay conditions, to the levels observed in controls ($F_{1,88}$=1.2, P>0.05) (Fig. 2b). How-



ever, the AD-HKD group continued to show impaired functioning across each of the delay conditions under both placebo ($F_{1,91}$=29.9, P<0.001) and 0.3 mg/kg MPH ($F_{1,90}$=10.8, P<0.001). Enhanced performance under MPH 0.6 mg/kg was not accompanied by significant changes in latencies to make correct responses.

Spatial working memory. Acute MPH did not affect performance on any of the key measures from the SWM task. There was no significant effect of treatment group on BSE. A significant effect of session ($F_{1,70}$=19.0, P<0.001) revealed that, overall, boys showed a reduction in BSE at the acute challenge session. There was no significant session × treatment group interaction ($F_{2,70}$ <1); however, showing that reduction of errors at the acute challenge session cannot be attributed to MPH. There were no other significant interactions between task difficulty, treatment group and session. MPH had no effect on WSE or strategy score.

Pattern recognition. MPH did not affect performance or latencies on the pattern-recognition task. There was no significant effect of treatment group on percentage of correct responses ($F_{2,70}$=1.1, P=0.34). Whilst subjects demonstrated improved responding at the acute challenge session ($F_{1,70}$=18.9, P<0.001), there was no significant treatment group × session interaction.

Fig. 2 Delayed matching to sample. **a** Percentage correct responses under simultaneous and delay conditions at baseline. AD-HKD group (*closed circles*) made fewer correct responses under both simultaneous and delay conditions than control group (*open circles*). There was a significant interaction between performance accuracy and duration of task delay. AD-HKD group made fewer correct responses with increasing delay, showing greatest performance deficits at the 12-s delay condition, whilst control group performed equally well across all delays. **b** Acute responses to oral methylphenidate (MPH). Acute oral MPH had no effect, at either dose, on performance accuracy under simultaneous test conditions. Planned contrasts revealed that MPH 0.6 mg/kg (*closed squares*) significantly enhanced performance accuracy across each of the delay conditions when compared with placebo (*closed triangles*). Indeed, task performance accuracy following MPH 0.6 mg/kg was restored to those levels observed in healthy controls (*open circles*). However, the AD-HKD group continued to show impaired functioning across each of the delay conditions when administered either placebo (*closed triangles*) or 0.3 mg/kg MPH (*open triangles*). **c** Chronic responses to oral methylphenidate (MPH). Chronic administration of MPH at 0.3 mg/kg (*open triangles*) and 0.6 mg/kg (*closed squares*) enhanced accuracy of responding under both simultaneous and delay conditions when compared with placebo (*closed triangles*). Although MPH continued to enhance visual memory performance in the AD-HKD group when administered chronically, this effect was smaller than that observed following acute challenge. Performance was improved, but not normalised. The AD-HKD group continued to display significant impairment in functioning under delay conditions compared with controls (*open circles*) despite MPH 0.3 mg/kg and 0.6 mg/kg

Table 5 Summary of findings: chronic responses

Measure	Placebo mean (SD)	0.3 mg/kg mean (SD)	0.6 mg/kg mean (SD)	*F*	*P*
Delayed matching to sample					
Simultaneous % correct	85.22 (18.03)	91.34 (13.58)	95.38 (9.2)	9.8	<0.001*
Delay % correct (0 s, 4 s, 12 s combined)	56.04 (19.21)	65.78 (21.23)	68.82 (16.29)	15.4	<0.001*
Spatial working memory					
Total between-search errors (3, 4, 6, & 8 boxes combined)	39.0 (20.11)	37.09 (22.95)	35.08(19.83)	2.85	>0.05
Strategy score	35.04 (4.08)	33.96 (5.32)	34.22 (5.28)	1.09	>0.05
Pattern recognition					
% correct	81.28 (14.41)	86.09 (12.79)	87.57 (12.42)	6.02	<0.001

Chronic treatment

Delayed matching to sample. Chronic administration (Table 5) of MPH at both doses enhanced accuracy of responding under both simultaneous ($F_{2,114}$=9.8, P<0.001) and delay ($F_{2,116}$=15.4, P<0.001) conditions (Fig. 2c). This effect was smaller than that observed following acute challenge, with performance improved, but not normalised. The AD-HKD group continued to display significant impairment in functioning under delay conditions compared with controls, despite MPH 0.3 mg/kg ($F_{1,135}$=10.4, P<0.002) and 0.6 mg/kg ($F_{1,132}$=6.2, P<0.01). Chronic MPH treatment slowed response latencies for correct choices at both 0.3 mg/kg (P<0.03) and 0.6 mg/kg (P<0.01). However, a positive correlation between response latencies and accuracy of responding was only observed for children taking the 0.3-mg/kg dose at the 4-s (r=0.344, P<0.004) and 12-s (r=0.347, P<0.005) delays. More detailed evaluation of this relationship using linear regression analysis revealed that the predictive association was modest (4 s, r^2=0.119; 12 s, r^2=0.120).

Spatial working memory. Chronic MPH did not affect performance on the SWM task. There was no significant effect of treatment group on BSE, although effects narrowly failed to reach significance ($F_{2,116}$=2.85, P=0.067). There was a significant effect of difficulty level on BSE ($F_{3,174}$=279.6, P<0.001), but no significant task difficulty × treatment group interaction revealing that treatment groups performed similarly according to difficulty level. Likewise, there was no significant effect of treatment group on WSE, although this narrowly failed to reach significance ($F_{2,116}$=2.9, P=0.06), or on strategy score.

Pattern recognition. Chronic administration of MPH improved accuracy of responding on the pattern-recognition task ($F_{2,116}$=6.02, P<0.001) at both the 0.3-mg/kg (P<0.02) and 0.6-mg/kg (P<0.003) doses relative to placebo. There were no significant effects of MPH on latencies for correct or incorrect responding on the pattern-recognition task.

Discussion

Stimulant-naive boys with AD-HKD showed profound deficits in visual memory performance on a simultaneous and DMtS task and on a pattern-recognition task both known to be sensitive to temporal and amygdalo-hippocampal dysfunction, but on which patients with frontal lobe excisions show relatively intact performance (Owen et al. 1995). They also showed deficits on a SWM task known to be associated with activations of the dorsolateral and ventrolateral PFC and posterior parietal cortex, in functional neuroimaging studies, in children (Nelson et al. 2000). These performance deficits are not readily explained by existing neuropsychological models of AD-HKD. Acute MPH administration restored the deficit observed on the DMtS task but did not alter performance on the pattern-recognition or SWM tasks. Chronic MPH also improved, but did not normalise, performance on the DMtS task, improved performance on the pattern-recognition task but, again, did not alter performance on the SWM task. A facilitatory effect of MPH on inhibitory control does not explain the acute effects and can only offer a partial explanation for the chronic effects. There was evidence of a reduced effect of MPH on the DMtS task with chronic administration, perhaps reflecting the development of tolerance.

Limitations of the study

There are several limitations of the current study. The present sample comprises a group of children and young people meeting the rigorous ICD 10 criteria for HD. As such, these results may not be generalisable to those with DSM IV ADHD who fail to meet ICD 10 criteria. This may explain some of the differences between the current results and some previous studies and it will be important for future studies to include a range of subjects so that similarities and differences between the diagnostic systems can be fully explored. In order to include subjects representative of those referred to UK clinical services, we did not exclude subjects with co-morbid diagnoses. As expected, oppositional defiant disorder and conduct disorder were the most common co-morbidities. There is a debate in the literature as to whether or not these disorders are themselves associated with deficits in neuropsychological functioning (Pennington and Ozonoff 1996; Morgan and Lilienfeld 2000). Further studies are required to investigate the moderating effects of co-morbidity on baseline neuropsychological performance and the neuropsychopharmacological effects of MPH. Finally, intel-

lectual functioning in the present study was measured using the BPVS, a standardised measure of verbal abilities, which in UK samples correlates highly with measures of general intelligence (Dunn et al. 1997), and which was used as a covariate in the baseline analyses to ensure that group differences were not a result of the lower verbal abilities of the AD-HKD subjects. Unfortunately measures of non-verbal or full-scale IQ were not available for these subjects and no comment can be made with respect to these aspects of functioning.

Neuropsychological performance of drug naive boys with AD-HKD

Our results support extension of the range of neuropsychological deficits ascribed to AD-HKD to include non-executive visual memory functioning. The performance deficits demonstrated on the SWM task were expected. Similar deficits have been demonstrated in previous studies (Nigg et al. 2002), two of which (Barnett et al. 2001; Kempton et al. 1999) used the same task as in the present study. However, unlike these two studies, the significant positive correlation between BSE and strategy scores, in both the AD-HKD and control groups, suggests that poor use of strategy may contribute to the poor task performance. These differences may be explained by the much larger sample size in the present study (n=15 Kempton et al. versus n=75 present study) and differences in the diagnostic status of the samples (DSM IV in Kempton et al. versus ICD 10 in present study).

With respect to the DMtS task, our results support, to an extent, those reported in previous studies. Kempton et al. (1999) used an identical task and reported delay-independent performance deficits in un-medicated ADHD subjects. Chelonis et al. (2002), using a different DMtS task, reported delay-dependent deficits in ADHD subjects withdrawn from stimulants for at least 18 h. Our data support and extend these findings to drug-naive subjects with AD-HKD. The finding in both the present study and that of Chelonis et al. (2002) of no deficit at a 0-s delay suggests that these recognition memory deficits result from difficulties in retention or recall rather than encoding or attending to information at presentation. The deficits observed on the pattern-recognition task in the present study were not predicted. Previous studies have reported no group differences on this (Kempton et al. 1999) and other recognition memory tasks (Douglas 1988). The differences between the present and previous studies may again be related to differences in sample size, rigor of diagnostic assessment, diagnostic classificatory system used and medication status of subjects.

Are these deficits in non-working recognition memory adequately explained by current theories of AD-HKD? Working memory deficits would not impact upon tasks with no requirement to manipulate information on line. Inhibition theories such as that described by Barkley (1997) would predict that AD-HKD-related performance deficits on these tasks should be associated with shorter response latencies, with "impulsive" responding pre-empting accurate solution of the discrimination. Hence, incorrect response latencies should be the shortest. No such association was found at the simultaneous condition of the DMtS. Whilst incorrect response latencies were shorter at the delay condition of the DMtS, this association was delay independent, making it unlikely that the reduced performance accuracy at longer delay intervals was attributable to impulsive responding. Furthermore, regression analysis demonstrated that, for AD-HKD boys, shorter response latencies made only a small contribution to the total variance at the 0-s delay condition and did not predict accuracy of responding at the 4-s or the 12-s delay conditions. Similarly, the shorter incorrect response latencies on the pattern-recognition task did not predict poor performance on this task.

Further, our data do not support the proposition that the performance deficits seen on the DMtS are due to classically defined "delay aversion" (Sonuga-Barke et al. 1992). The simultaneous and DMtS task imposes a range of fixed delays, presented in a pseudorandom order, such that, within each trial, subjects do not know whether the pattern to be remembered will disappear and, if so, for how long. The "delay aversion" hypothesis would predict that when children with AD-HKD have no control over the inter-trial delay and cannot respond in a manner that might reduce the subjective experience of delay, they would show no impairment of performance. Sonuga-Barke has recently argued that delay aversion can provide a motivational route into cognitive deficits in as much as it limits the opportunities to acquire the experience of working under delay conditions and so developing the necessary skills for effective performance (Sonuga-Barke 2002). It is not possible to conclusively discount this explanation from the current data, and further studies explicitly investigating the relationship between visual memory performance and delay aversion are required.

Our data also suggest that the conceptualisation of AD-HKD as a "frontal" disorder of monoaminergic neurocircuitry may be overly restrictive. Whilst performance on this SWM task has been shown to be associated with activations of the dorsolateral and ventrolateral PFC and posterior parietal cortex, both the pattern-recognition and DMtS tasks appear to have different neuroanatomical substrates. Performance on this version of the pattern-recognition task has been demonstrated to be sensitive to temporal and amygdalo-hippocampal damage, but not to frontal lobe damage (Owen et al. 1995). Animal data suggest that a comparable version of the DMtS task is also particularly sensitive temporal and amygdalo-hippocampal damage (Mishkin 1982; Bachevalier and Mishkin 1986). Further, patients with frontal, temporal and amygdalo-hippocampal excisions performed accurately on the simultaneous condition of the DMtS task, whilst temporal and amygdalo-hippocampal, but not frontal, patients were impaired when a delay was introduced (Owen et al. 1995). Similar patterns of delay-dependent impairment on this DMtS task have previously been described in patient groups with medial temporal lobe

damage or disease notably senile dementia of Alzheimer's type (SDAT) (Sahakian et al. 1988), elderly depressives (Abas et al. 1990) and healthy males exposed to the muscarinic antagonist scopolamine (Robbins et al. 1997). Other patient groups have shown delay-independent deficits on this task, for example, patients with Parkinson's disease (Sahakian et al. 1988). Our data suggest a potential role for the temporal lobes, the amgydala and/or hippocampus in AD-HKD. This supports recent magnetic resonance imaging studies, one of which described reduced white and grey matter volumes in temporal, parietal and occipital areas in addition to frontal areas (Castellanos et al. 2002) and the other reported reduced brain volume in the anterior temporal lobe and increased grey matter in the posterior temporal lobe and inferior parietal lobe (Sowell et al. 2003). Further, the striking similarities between the delay-dependent DMtS deficits found in the AD-HKD group and those reported for patients with SDAT and healthy adult males following administration of scopolamine raise the possibility of altered cholinergic neurotransmission in children with AD-HKD. This is of interest given that both nicotinic agonists (Wilens et al. 1999) and donepezil, an acetylcholinesterase inhibitor which improves memory function in SDAT (Rogers et al. 1998), have been demonstrated to exert beneficial effects in AD-HKD (Wilens et al. 2000).

Intriguingly, in addition to demonstrating a striking delay-dependent deficit on the DMtS task, boys with AD-HKD were also impaired at the simultaneous condition. Such impairment has previously been reported in patients with Parkinson's disease (Sahakian et al. 1988). Patients with frontal, temporal or amygdalo-hippocampal damage (Owen et al. 1995), SDAT (Sahakian et al. 1988), elderly depressives (Abas et al. 1990) and healthy males exposed to scopolamine (Robbins et al. 1997) did not show such impairment. A previous small study that reported delay-independent impairment on the DMtS task in children with ADHD found no impairment at the simultaneous condition (Kempton et al. 1999). The performance deficit in AD-HKD boys during the simultaneous matching component of the task did not account for poor performance during the delayed matching components. Hence, there may be two discrete deficits that can be identified. Much less is known about the mediating neural substrates of simultaneous matching components of this task. The Parkinson's disease-related deficits in simultaneous matching and the chronic MPH amelioration of the AD-HKD-related deficit may point towards a dopaminergic substrate and frontostriatal circuitry. Further studies will be required to address these observations.

The effects of methylphenidate on neuropsychological performance

It is currently hypothesised that the pharmacological actions of MPH are mediated by its ability to inhibit the reuptake of dopamine and noradrenaline through blockade of the dopamine transporter (DAT). However, the precise effects of MPH in any particular brain region depends on the balance between tonic and phasic catecholamine release at baseline, the distribution of DATs and pre-synaptic autoreceptors within that region and the interaction between catecholaminergic neurotransmission and other neurotransmitter systems (Mehta et al. 2001). Our findings that MPH did not alter performance on the SWM task contrast strikingly with those of Kempton et al. (1999) and Mehta et al. (2000a,2000b). It is again possible that these differences are related to methodological differences. Both previous studies reported results on much smaller samples diagnosed using DSM IV criteria, and used less rigorous medication strategies than the present study; this non-replication of previous findings is important and raises the possibility of differential impacts of MPH between differently diagnosed samples on this important area of functioning. Interestingly, a recent re-analysis of the influential Multimodal Treatment of ADHD Study (MTA Cooperative Group 1999) has found that diagnostic status (ICD-10 HD versus DSM IV ADHD) is a moderator of treatment response (E. Taylor, personal communication). Also principle differences in monoamine metabolism between mild and severe forms of AD-HKD have been reported (Uzbekov and Misionzhnik 2003).

Whilst we have some understanding of how MPH may act on catecholamine systems in the prefrontal cortex and striatum (Volkow et al. 2001a), there has been limited study of the potential actions of MPH within other brain structures. Our results raise the possibility that the effects of MPH on aspects of visual memory function in AD-HKD may involve interaction between catecholaminergic and cholinergic neurotransmission. Whilst a single dose of MPH, at a dose of 0.6 mg/kg, did not affect performance on the pattern-recognition task, it restored performance accuracy on the DMtS delay conditions to the levels observed in controls. These observations support and extend the work of Chelonis et al. (2002) who also reported normalisation of DMtS performance following administration of stimulant medication. Chronic MPH treatment resulted in less pronounced effects than were observed after the acute challenge, with performance being improved but not normalised. This suggests the possibility that, at least with respect to this task, tolerance develops after chronic MPH administration. Whilst acute tolerance has been demonstrated with clinical doses of oral MPH (Swanson et al. 1999), the MPH literature to date has suggested that long-term tolerance does not occur in clinical cases (Greenhill et al. 2001). There are, however, some suggestions from the literature that long-term tolerance may occur. For example, increases in the mean daily MPH dose required to optimally control ADHD symptoms were reported over the 14 months of the Multimodal Treatment of ADHD study (Vitiello et al. 2001).

Unlike the study of Chelonis et al. (2002) enhanced performance on DMtS in the current study following acute 0.6 mg/kg MPH was not accompanied by significant changes in latencies to make correct responses.

Therefore, enhanced accuracy of responding in the AD-HKD group in this condition was not a consequence of either increased deliberation time or reduced impulsivity. Chronic MPH treatment with either dose did not alter response latencies for the pattern-recognition task but did slow response latencies for correct choices on DMtS. This observation supports a presumed therapeutic mechanism of action whereby chronic MPH may enhance inhibitory control (Barkley 1997). However, positive correlations between response latencies and accuracy of responding were only observed for children taking the lower dose and only at the 4-s and 12-s delays. Linear regression analysis revealed that this predictive association was modest, suggesting that the therapeutic effects of MPH are, at best, only partially attributable to an enhancement of inhibitory control.

The dissociation with respect to the impact of MPH on the working memory and non-working memory tasks suggests that, at least in those children with the more refined ICD 10 HD phenotype, whilst treatment with MPH may result in significant improvement in behavioural symptoms and in some aspects of neuropsychological functioning, it does not normalise all aspects of functioning in all patients.

Conclusions

Our data highlights the heterogeneity of AD-HKD, challenges single-cause theories of AD-HKD and supports a multi-pathway model whereby AD-HKD is the phenotypic consequence of several endophenotypic risk factors (Castellanos and Tannock 2002). We propose that deficits in non-working visual memory may constitute a novel independent endophenotype for AD-HKD. In contrast to previous pathophysiological explanations of AD-HKD, this impairment is consistent with medial temporal lobe, but not frontal lobe dysfunction, and may implicate cholinergic neurotransmission. Further, we have demonstrated that, whilst none of the observed deficits resulted from previous exposure to stimulant medication, the deficit in DMtS performance was restored by acute administration of MPH and, on both DMtS and pattern recognition, was improved by chronic administration.

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Appendix 7

Neuropsychological functioning in stimulant-naïve boys with hyperkinetic disorder

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Neuropsychological functioning in stimulant-naive boys with hyperkinetic disorder

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ABSTRACT

Background. Although children with hyperkinetic disorder and/or attention deficit hyperactivity disorder (ADHD) show disordered executive neuropsychological functioning, the nature of these changes remains controversial. Additionally, impairments in non-executive neuropsychological functioning have been relatively unexplored. Here, the authors describe the neuropsychological functioning of a sample of stimulant drug-naive boys with hyperkinetic disorder on a battery of neuropsychological tasks sensitive to impairments of both executive and non-executive functions.

Method. Seventy-five stimulant drug-naive boys meeting diagnostic criteria for ICD-10 hyperkinetic disorder were compared with 70 healthy developing controls matched for age but not IQ on computerized tests of neuropsychological functioning from the Cambridge Neuropsychological Test Automated Battery (CANTAB) and a Go/No-Go inhibition task.

Results. Boys with hyperkinetic disorder exhibited impairments on tasks with a prominent executive component – working memory, planning, strategy formation, attentional set-shifting and on a reaction time task. However, they were also impaired on tasks without prominent executive components – pattern and spatial recognition, spatial span, delayed matching to sample and paired associates learning. Contrary to predictions, no impairment was observed on the Go/No-Go inhibition task.

Conclusions. Medication-naive boys with hyperkinetic disorder displayed a broad range of neuropsychological impairments. Deficits were demonstrated on tasks with and without prominent executive components. Impairments were not confined to tasks dependent upon frontostriatal functioning, cannot wholly be explained by deficits in inhibitory control, nor can they be attributed to intelligence or previous exposure to stimulant medication.

INTRODUCTION

Hyperkinetic disorder (ICD-10; WHO, 1992) and attention deficit hyperactivity disorder (DSM-IV; APA, 1994) are characterized by pervasive impaired attention, hyperactivity and impulsivity. These disorders are common, particularly in boys (Swanson *et al*. 1998), with 1 year combined prevalence rates in school-age children of 1·7% for hyperkinetic disorder (Meltzer *et al*. 2000) and between 5 and 10% (Swanson *et al*. 1998) for ADHD. With continuing controversy with respect to nosology, we have adopted the convention suggested by Taylor (1994) and described by Schachar & Tannock (2002) and refer to specific diagnostic terms, such as hyperkinetic disorder (HD) or attention deficit hyperactivity disorder (ADHD) when addressing a particular diagnostic entity and set of criteria. However, we use the acronym AD-HKD when referring to characteristics that are shared by both ADHD and HD.

The impairments associated with AD-HKD are considerable, and core symptoms and associated social, interpersonal, and academic

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problems often persist into adulthood (Klein & Mannuzza, 1991; Hechtman, 1992; Murphy & Barkley, 1996; Barkley *et al*. 2004). Despite considerable study and speculation, the pathophysiology of AD-HKD remains poorly understood (Solanto *et al*. 2001). Converging evidence implicates dysregulation of frontostriatal neural circuits (Castellanos *et al*. 1996*b*; Giedd *et al*. 2001; Rubia *et al*. 2001*b*) and, more specifically, reduced prefrontal dopamine (DA) transmission (Castellanos *et al*. 1996*a*; Pliszka *et al*. 1996; Ernst *et al*. 1998).

Executive neuropsychological functioning (EF) has been used as an umbrella term to describe those functions that mediate 'the ability to maintain an appropriate problem-solving set for attainment of a future goal' (Luria, 1996). EF includes, for example, diverse processes such as response inhibition, planning, working memory, and flexibility of thinking or responding. Performance deficits on executive tasks of working memory have been observed in prefrontal cortex (PFC)-lesioned animals (Goldman-Rakic, 1996) and humans (Owen *et al*. 1990). Similarly, inhibitory control, attentional set-shifting and planning are impaired in patients with frontal lobe resections (Owen *et al*. 1990, 1991; Braun *et al*. 1992). Hence, executive dysfunction might reasonably be predicted in association with the altered frontostriatal functioning reported in AD/HKD. However, no consensus has been derived within the literature concerning EF impairments in AD-HKD (Tannock, 1998; Kempton *et al*. 1999; Castellanos *et al*. 2000). Neuropsychological investigation has undoubtedly been hampered by a lack of clearly defined, specific, sensitive and valid measures of EF other than inhibition (Tannock, 1998) and persistent failure to deploy task batteries sensitive to a broad range of impairments. Other important methodological limitations have included small sample sizes (e.g. Kempton *et al*. 1999), the use of rating scales rather than structured clinical interviews for case definition (e.g. Scheres *et al*. 2001), and the inclusion of children who were either taking, or had recently stopped taking stimulant medication (e.g. Seidman *et al*. 1997; Aman *et al*. 1998). These latter issues are crucial since methylphenidate (MPH), the first-line pharmacological treatment for AD-HKD, significantly enhances various aspects of neuropsychological functioning, including EF (Kempton *et al*. 1999; Mehta *et al*. 2000).

One influential neuropsychological account of AD-HKD emphasizes behavioural impulsiveness and postulates a primary deficit in inhibitory control leading to secondary deficits in other EF (Barkley, 1998). However, no empirical evidence has been provided to support the primacy of inhibition. It is increasingly implausible that AD-HKD could represent the clinical manifestation of a single neuropsychological or neurophysiological abnormality. Recently developed models have, instead, proposed (Castellanos & Tannock, 2002; Sonuga-Barke, 2002) that AD-HKD be viewed as the behavioural consequence of a combination of several risk factors, present to varying degrees in different individuals, with heterogeneity of EF deficits (Pennington & Ozonoff, 1996; Denney & Rapport, 2001). It has further been suggested that only a proportion of those with AD-HKD may demonstrate neuropsychological deficits (Doyle *et al*. 2000; Sonuga-Barke, 2002; Nigg *et al*. 2004). These views are supported by empirical evidence regarding inhibitory function (Rubia *et al*. 2001*b*); working memory and attentional set-shifting (Kempton *et al*. 1999; Tripp *et al*. 2002) and planning ability (Kempton *et al*. 1999). In addition, children with AD-HKD are impaired on tasks with low executive demands, for example a spatial span task (Kempton *et al*. 1999), and on tasks traditionally associated with parietal rather than frontal functioning, such as mental rotation (the Turning task) and visuospatial processing (Aman *et al*. 1998). Similarly, neuroimaging studies in AD-HKD describe abnormalities in several areas of the brain other than the PFC, including the temporal and parietal lobes and the cerebellum (Filipek *et al*. 1997; Castellanos *et al*. 2002). Encouraging an integrative approach that takes these observations in account, Castellanos & Tannock (2002) have proposed four candidate 'endophenotypes' for AD-HKD; delay aversion, deficits in working memory, deficits in time estimation and behavioural inhibition. Compelling empirical evidence for each is awaited.

We have examined the neuropsychological functioning of a large sample of stimulant-naive boys with ICD-10 hyperkinetic disorder (who also met criteria for a diagnosis of DSM-IV

ADHD combined subtype), using tasks from the CANTAB neuropsychological test battery and a computerized Go/No-Go task. The CANTAB battery (Fray & Robbins, 1996) has been extensively validated in both child (Luciana & Nelson, 1998; Hughes *et al*. 1999; Williams *et al*. 2000; Curtis *et al*. 2002) and adult populations (Robbins *et al*. 1994) and has been shown to be differentially sensitive to dysfunction in several brain regions, including frontal, temporal and amygdalo-hippocampal regions (Owen *et al*. 1995). We have previously reported data from the same clinical group on the Spatial Working Memory, Delayed Matching to Sample and Pattern Recognition tasks from the CANTAB battery (Rhodes *et al*. 2004). Having included these data in the correlational and regression analyses that follow, the results are briefly summarized alongside those that represent the present report.

METHOD

Participants

We tested two groups of boys aged between 7 and 15 years. One was an experimental cohort of 75 stimulant-medication-naïve participants with ICD-10 HD, but who also met criteria for DSM-IV ADHD combined subtype (AD-HKD group, mean age 10·8 years). The other contained 70 healthy control boys (Controls, mean age 10·7 years).

AD-HKD group

Participants were recruited from consecutive male out-patient referrals to the Tayside Child and Adolescent psychiatric service using a two-stage screening procedure. Potential participants were first screened using the Child Behaviour Checklist (Achenbach *et al*. 1991) and the Conners' Parent and Teaching Rating Scales (Conners, 1997*a*, *b*). Subjects with a T-score greater than 65 on all subscales of the 27 item Conners' Parent Rating Scale–Revised (S) (CPRS-48) and the Conners' Teacher Rating Scale–Revised (S) (CTRS-28) were interviewed by an experienced child and adolescent psychiatrist using the Kiddie-SADS Present and Lifetime (K-SADS-PL) Version 1.0 semi-structured interview (Kaufman *et al*. 1996, 1997). Each AD-HKD subject met diagnostic criteria on K-SADS interview for both ICD-10 HD, and DSM-IV attention-deficit/hyperactivity disorder, combined type. Although co-morbidity is not formally permitted within the ICD-10 system, the presence of a range of commonly occurring co-morbid conditions; including oppositional defiant disorder, conduct disorder, and anxiety disorder, did not result in exclusion from the study (see Table 1). This was to ensure recruitment representative of the clinical populations seen in routine practice within the UK National Health Service. All co-morbid diagnoses were considered secondary to the primary diagnosis of HD. Five children met criteria for multiple co-morbid diagnoses.

Table 1. *Co-morbid diagnoses in AD-HKD group*

	n	% of sample
Pure hyperkinetic disorder	18	24
Co-morbid diagnoses		
Oppositional defiant disorder (no CD)	31	41·3
Conduct disorder (CD)	21	28
Depressive disorder	3	4
Generalized anxiety disorder	2	2·7
Separation anxiety disorder	3	4
Tic disorder	2	2·7
Social phobia	1	1·3

Controls

Healthy developing boys were recruited from local schools and screened as above. Symptom-free (T-score <60 on all subscales of the CPRS-48, CTRS-28 and CBCL subscale T-scores <60), age-matched participants and their parents were interviewed using the K-SADS-PL to confirm health. A previous or current history of any psychiatric disorder led to exclusion, as did a history of neurological impairment, learning disability, chronic physical illness, sensory or motor impairment, current or previous exposure to prescribed stimulant medication, and abuse of any illegal drugs. The British Picture Vocabulary Scale, second edition (BPVS; Dunn *et al*. 1997) was used to estimate general intellectual ability. The BPVS assesses verbal intelligence and was chosen for its ease of administration and ability to be used with children aged between 3 and 15 years (Dunn *et al*. 1997). Informed written consent to participate in the study was obtained from each child's parent(s)/guardian. The characteristics of both groups are summarized in Table 2.

Table 2. *Demographic characteristics*

	AD-HKD boys ($n=75$) Mean (S.D.)	Control boys ($n=70$) Mean (S.D.)	p
Age	10·85 (2·46)	10·74 (2·47)	$>0·05$
BPVS percentile rank	35·43 (27·93)	58·94 (26·25)	$<0·001$
Conners: parent (T-scores)			
Oppositionality	75·57 (11·38)	45·25 (6·42)	$<0·001$
Cognitive	72·94 (7·07)	44·16 (3·47)	$<0·001$
Hyperactive	83·08 (8·88)	46·12 (3·43)	$<0·001$
ADHD index	77·01 (6·09)	43·96 (3·37)	$<0·001$
Conners: teachers (T-scores)			
Oppositionality	65·05 (19·52)	49·15 (9·49)	$<0·001$
Cognitive	62·77 (12·78)	47·66 (7·95)	$<0·001$
Hyperactive	71·0 (14·34)	47·36 (7·42)	$<0·001$
ADHD index	72·23 (14·93)	47·79 (8·12)	$<0·001$

BPVS, British Picture Vocabulary Scale.

Neuropsychological assessment

A total of 10 tasks were used and each subject performed all tasks in the same order. A computer-based Go/No-Go task was used to assess inhibitory control and nine tasks were selected from the three batteries (working memory and planning, visual memory, and attention) of CANTAB (Morris *et al.* 1987). All tasks were presented on a high-resolution colour monitor with CANTAB tasks utilizing a touch-sensitive screen. A scheduled break of approximately 10 minutes was taken midway through the testing session and subjects were informed that they could take further breaks as required. In practice few subjects requested additional breaks.

Go/No-Go

This task assessed the ability to detect and respond to a target stimulus and to inhibit responding to distractor stimuli. A random sequence of 18 letters and numbers (nine of each) were rapidly presented in the centre of a colour computer screen, one by one. Stimuli were presented on screen for 300 ms, with an inter-stimulus interval of 900 ms. Subjects were instructed to respond to target stimuli (letters) by pressing the space bar as quickly as possible, but not to respond to distractors (numbers). Response contingencies alternated between numbers and letters with two 'switching' and two 'non-switching' blocks. The dependent measures are the mean number of errors for distractors (false positive responses) and reaction time to target stimuli across eight test trials. This version of the Go/No-Go task has not previously been used in the study of neuropsychiatric disorders or psychopharmacological manipulations; however, the test parameters are identical to those previously used, in several studies, to demonstrate impaired inhibitory control in AD-HKD subjects.

CANTAB

Task descriptions and order for presentation of the CANTAB tasks are described in Table 3.

Statistical analysis

All analyses were conducted using SPSS for Windows (v.10) (SPSS Inc., Chicago, IL, USA). As AD-HKD boys tended to score lower on the BPVS percentile rank scores and despite there being no correlation between task performance and BPVS scores on any task, the BPVS percentile rank scores were used as a covariate in all parametric analyses. In addition, a separate analysis of an age- and BPVS-matched subsample was conducted. Data meeting assumptions of normality and homogeneity of variance were analysed using analysis of covariance (ANCOVA) and, thereafter, by determination of simple effects or interactions (Winer *et al.* 1991). All other data were compared using appropriate non-parametric tests (e.g. Mann–Whitney U test). To explore the potential contribution of disordered impulse control on task performance both accuracy measures and reaction times are reported. For analysis of

Table 3. *Descriptions and order of presentation of CANTAB tasks*

Task	Main outcome measures	Description	References for fuller task description
Working memory and planning battery			
Spatial Span	Span	A test of spatial short-term memory capacity based on the Corsi block-tapping task.	Milner, 1971; Kempton *et al.* 1999
Spatial Working Memory	Between-search errors, Strategy score	A self-ordered search task that assesses working memory for spatial stimuli and requires a subject to use mnemonic information to work towards a goal.	Petrides & Milner, 1982; Kempton *et al.* 1999; Rhodes *et al.* 2004
Stockings of Cambridge	Problems solved in minimum moves	Derived from the 'Tower of Hanoi' task, measuring spatial planning, working memory, and behavioural inhibition.	Shallice, 1982; Kempton *et al.* 1999
Visual memory battery			
Pattern Recognition	Percentage correct	Tests the ability to recognize a previously presented abstract pattern in a forced choice procedure.	Kempton *et al.* 1999
Spatial Recognition	Percentage correct	Tests the ability to recognize the spatial locations of target stimuli.	Kempton *et al.* 1999; Rhodes *et al.* 2004
Delayed Matching to Sample	Percentage correct	Tests the ability to remember the visual features of a complex, abstract, target stimulus and to select from a choice of four patterns after a variable delay.	Kempton *et al.* 1999; Rhodes *et al.* 2004
Paired Associates Learning	Stage reached, total errors, Total trials	Tests the ability to learn the locations of a progressively increasing number of abstract stimuli. The main measures in this task are the number of trials taken to complete the task and the total number of errors across all trials.	Sahakian & Owen, 1992
Attention battery			
Attentional Set-Shifting task/ID-ED	Stage reached	Tests the ability to focus attention on specific attributes of compound stimuli (intradimensional stages) and to shift attention when required to a previously irrelevant stimulus dimension (extradimensional stages).	Kempton *et al.* 1999
Reaction Time	Reaction time, Movement time	Tests reaction and movement times in response to a stimulus under a simple one-choice and a five-choice condition.	Sahakian & Owen, 1992

ID-ED, Intradimensional-extradimensional set-shifting.

performance on the Go/No-Go task, trials were divided into two blocks: Block 1 represented the 'switch' blocks where the task changed from letters to numbers (or vice versa) and Block 2 the 'non-switch' block. Blocks were entered into a repeated-measures ANOVA for analysis. Multiple regression analyses were conducted using a backwards deletion entry method with a probability of F for entry set at 0·05 and removal at 0·10. As each of the neuropsychological tasks is designed to measure a different aspect of functioning, and therefore can be seen as representing a separate experiment, α levels were not adjusted for the main comparative analyses. For the correlational analyses α was adjusted to 0·008 to reflect the multiple comparisons.

RESULTS

All subjects completed each of the tests. Mean performance (raw scores and those adjusted for covariate), statistical comparisons and effect sizes (d) for each task, for both groups, are summarized in Table 4. As the Spatial Working Memory, Pattern Recognition, and Delayed Matching to Sample tasks been previously reported (Rhodes *et al.* 2004), data are only briefly summarized here.

AD-HKD boys showed no impairments on the Go/No-Go task. There was no difference between groups for errors to distractors at either the shift or non-shift block [$F(1, 142) < 1$], or in reaction times to targets [$F(1, 142) = 3{\cdot}1$, $p > 0{\cdot}05$].

Table 4. *Summary of findings*

	AD-HKD		Controls				
Measure	Raw mean (S.D.)	Adjusted mean (S.D.)	Raw mean (S.D.)	Adjusted mean (S.D.)	Sig.	ES raw	ES adj.
Go/No-Go							
Errors for Distractors (Block 1)	2·31 (1·5)	2·4 (1·42)	2·23 (1·35)	2·13 (1·56)	N.S.		
Errors for Distractors (Block 2)	2·21 (1·66)	2·27 (1·59)	1·94 (1·46)	1·88 (1·65)	N.S.		
Reaction time to Targets B1 (log_{10})	2·66 (0·09)	2·66 (0·08)	2·64 (0·08)	2·64 (0·09)	N.S.		
Reaction time to Targets B2 (log_{10})	2·67 (0·09)	2·66 (0·08)	2·64 (0·08)	2·64 (0·09)	N.S.		
Spatial Span							
Span Score	5·08 (1·47)	5·08 (1·26)	5·93 (1·5)	5·94 (1·47)	**	0·57	0·6
Spatial Working Memory							
Total between-search errors	50·71 (19·49)	50·84 (21·0)	35·13 (20·7)	34·99 (21·82)	***	0·77	0·75
Strategy score	36·31 (4·54)	36·32 (5·11)	32·74 (5·17)	32·73 (5·28)	***	0·73	0·70
Stockings of Cambridge							
No. solved in minimum moves	7·13 (2·04)	7·2 (2·11)	8·07 (2·01)	7·99 (2·17)	*	0·46	0·38
Pattern Recognition							
% Correct	0·70	81·29 (11·71)	90·95 (8·37)	90·4 (12·12)	***	0·92	0·89
Spatial Recognition							
% Correct	0·70	68·21 (13·9)	77·64 (13·68)	78·2 (13·8)	***	0·89	0·72
Delayed Matching to Sample							
Simultaneous	90·93 (15·5)	90·77 (12·38)	97·14 (7·03)	97·32 (1·53)	**	0·53	0·52
Delay (0, 4 + 12)	59·38 (18·8)	59·52 (17·84)	75·81 (17·66)	75·66 (17·91)	***	0·91	0·90
Paired Associates Learning							
Stage reached	7·96 (0·26)	7·96 (0·26)	7·97 (0·24)	7·97 (0·25)	N.S.		
Total errors	11·61 (11·5)	11·14 (9·71)	6·71 (7·1)	7·22 (10·39)	**	0·51	0·47
Total trials	12·76 (4·09)	12·61 (4·07)	10·7 (2·93)	10·86 (3·89)	**	0·57	0·58
ID-ED							
Stage reached	7·55 (1·08)	7·5 (1·04)	7·94 (0·97)	7·99 (1·13)	*	0·38	0·46
Reaction Time							
Reaction time latency (5 choice)	2·61 (0·13)	2·62 (0·09)	2·58 (0·11)	2·57 (0·17)	*	0·24	0·71
Movement time latency (5 choice)	2·61 (0·14)	2·63 (0·26)	2·55 (0·34)	2·53 (0·25)	*	0·23	0·39

ID-ED, Intradimensional-extradimensional set-shifting.
* $p<0·05$, ** $p<0·05$, *** $p<0·001$.

There was a significant group difference in performance on the Spatial Span task with AD-HKD boys obtaining a lower Spatial Span score than control boys [$F(1, 142)=9·89$, $p<0·002$, $d=0·6$]. AD-HKD boys also made more between-search errors on the spatial working memory task [$F(1, 142)=18·8$, $p<0·001$, $d=0·75$]. There was a significant interaction between group and difficulty level and *post hoc* tests revealed that AD-HKD boys made more errors at the 8-box stage relative to the 3-, 4- or 6-box stages. AD-HKD boys also had higher (impaired) strategy scores [$F(2, 142)=16·52$, $p<0·001$, $d=0·70$] but there were no differences in within-search errors [$F(1, 142)=1·5$, $p>0·05$].

AD-HKD boys solved fewer problems in the minimum number of moves on the SoC task [$F(1, 142)=4·7$, $p<0·03$, $d=0·38$] but there was no significant difference in the average moves made [$F(1, 141)=3·5$, $p>0·05$] and no significant interaction between group and difficulty level in average moves [$F(2·3, 321)=1·6$, $p>0·05$]. There was no significant overall difference between the two groups with respect to either initial [$F(1, 141)=1·1$, $p>0·05$] or subsequent [$F(1, 141)<1$] thinking times but there was a significant interaction between group and difficulty level [$F(2·5, 349)=3·8$, $p<0·02$] for subsequent but not for initial [$F(1·7, 236)<1$] thinking times. Planned contrasts revealed that controls had longer subsequent thinking times for 5-move problems relative to 3-move problems ($p<0·01$).

AD-HKD boys made fewer correct responses on the Pattern Recognition task ($z=-5·267$, $p<0·001$, $d=0·89$) but latencies for correct responses did not differ. AD-HKD boys had shorter response latencies for incorrect choices.

However, regression analysis revealed that the latencies for incorrect responses did not predict overall accuracy of responding for the AD-HKD.

AD-HKD boys obtained a lower percentage of correct responses on the Spatial Recognition task [$F(2, 142) = 17{\cdot}4$, $p < 0{\cdot}001$, $d = 0{\cdot}72$]. There was no significant difference in latencies for correct responses [$F(1, 142) = 1{\cdot}07$, $p > 0{\cdot}05$], but AD-HKD boys had shorter latencies to respond when making incorrect choices [$F(1, 141) = 13{\cdot}9$, $p < 0{\cdot}001$]. Again, however, regression analysis revealed that latencies for incorrect responses did not predict overall accuracy of responding for the AD-HKD boys [$F(1, 72) < 1$].

AD-HKD boys demonstrated deficits at both the simultaneous and delay conditions of the Delayed Matching to Sample task. There was a significant interaction between performance accuracy and duration of task delay [$F(2, 284) = 4{\cdot}7$, $p < 0{\cdot}01$] and AD-HKD boys made fewer correct responses with increasing delay, whilst control boys performed equally across all delays. This performance deficit was not explained by differences in response latency on the task.

Groups did not differ as to the Stage Reached on the Paired Associates Learning task [$F(1, 142) < 1$]. AD-HKD boys, however, made more errors [$z = -2{\cdot}9$, $p < 0{\cdot}003$, $d = 0{\cdot}47$] and required more trials [$z = -3{\cdot}7$, $p < 0{\cdot}001$, $d = 0{\cdot}58$].

AD-HKD boys achieved lower stage-reached scores on the Intradimensional-Extradimensional Set-Shifting (ID-ED) attentional set-shifting task [$F(1, 142) = 7{\cdot}0$, $p < 0{\cdot}009$, $d = 0{\cdot}46$]. They made more errors prior to the ED shift stage [$F(1, 142) = 10{\cdot}17$, $p < 0{\cdot}002$]. Fewer AD-HKD boys completed the ED shift stage [$F(1, 142) = 6{\cdot}7$, $p < 0{\cdot}01$], and examination of errors made by boys who did reach the ED Reversal stage (AD-HKD boys, $n = 26$; control boys, $n = 40$), revealed that AD-HKD boys made more errors at this stage [$F(1, 63) = 5{\cdot}4$, $p < 0{\cdot}02$].

Groups differed significantly at the most complex (5-choice) condition of the Reaction Time task. AD-HKD boys were *slower* to respond than controls both in terms of reaction times [$F(1, 133) = 5{\cdot}5$, $p < 0{\cdot}02$, $d = 0{\cdot}71$] and movement times [$F(1, 133) = 3{\cdot}94$, $p < 0{\cdot}05$, $d = 0{\cdot}39$]. Groups did not differ in reaction or movement times at the simple condition (both $F < 1$).

In view of the group differences in BPVS scores a further analysis was conducted on a subset of the sample comprising 47 AD-HKD boys and 47 controls matched for age and BPVS. This broadly confirmed findings for the total group analyses above. Some differences narrowly failed to reach statistical significance [SoC number of problems solved in minimum moves ($F = 3{\cdot}66$, $p = 0{\cdot}059$); total errors on the Paired Associates Learning task ($F = 3{\cdot}33$, $p = 0{\cdot}07$); and stage reached on the ID-ED task ($F = 2{\cdot}87$, $p = 0{\cdot}09$); and movement time latency on the 5-choice condition of the Reaction Time task ($F = 3{\cdot}81$, $p = 0{\cdot}054$). It is likely that these findings simply reflect reduced statistical power due to smaller sample size.

Inter-relationships among tasks

To further examine the role of short-term memory span, strategy, and spatial recognition memory on spatial working memory performance, correlations were conducted between these variables and total between-search errors (BSE) on the Spatial Working Memory task. In view of the multiple comparisons α was adjusted to 0·008. Spatial short-term memory span correlated significantly with BSE for AD-HKD boys ($r = -0{\cdot}473$, $p < 0{\cdot}001$) and control boys ($r = -0{\cdot}533$, $p < 0{\cdot}001$). Strategy score was significantly correlated with total BSE for both AD-HKD boys ($r = 0{\cdot}513$, $p < 0{\cdot}001$) and control boys ($r = 0{\cdot}588$, $p < 0{\cdot}001$). Accuracy on the Spatial Recognition task was also correlated with total BSE for the control ($r = -0{\cdot}351$, $p < 0{\cdot}001$) but not the AD-HKD ($r = -0{\cdot}253$, $p < 0{\cdot}05$) group.

In view of the significant correlations between several task measures and performance on the Spatial Working Memory task, exploratory multiple regression analyses were performed. BSE score was the dependent variable and short-term memory span, strategy score and spatial recognition score were the predictors. Separate analyses, using a backward deletion entry method, were carried out for the AD-HKD boys and the control boys. Spatial span and strategy score were retained in the best fit equation for both groups. For AD-HKD boys these two variables together accounted for approximately 37% of the total variance [$r^2 = 0{\cdot}372$, $F(2, 72) = 21{\cdot}3$, $p < 0{\cdot}001$]. For the control boys, these two variables predicted for

approximately 49% of the total variance [$r^2 = 0{\cdot}493$, $F(2, 68) = 33{\cdot}0$, $p < 0{\cdot}001$]. Accuracy on the spatial recognition task did not predict performance on the Spatial Working Memory task for either group. There was no evidence of significant multi-co-linearity and the similarities of the values of r^2 and the adjusted r^2 suggest that the models are generalizable. Part correlations indicate that both span and strategy score make independent contributions to BSE score for both the AD-HKD (span $r^2 = 0{\cdot}11$, strategy $r^2 = 0{\cdot}15$) and control (span $r^2 = 0{\cdot}15$, strategy $r^2 = 0{\cdot}21$) groups.

DISCUSSION

These data confirm and extend those published previously (Rhodes *et al*. 2004). AD-HKD boys showed profound impairments of EF in terms of visual working memory, strategy formation, planning, attentional set-shifting and were significantly *slowed* on a reaction time task. Contrary to predictions, inhibitory performance on a Go/No-Go task was unimpaired. Our data suggest that EF impairments cannot be explained on the basis of inhibitory dysfunction. Additionally, profound neuropsychological impairment was evident in aspects of non-executive neuropsychological functioning. AD-HKD boys showed impairments in tasks assessing recognition of patterns and spatial locations, spatial short-term memory span, visual recognition memory, and a spatial delayed response task. Perhaps most importantly, these impairments in executive and non-executive functioning cannot be attributed to exposure to stimulant medications, nor can they be accounted for by differences in verbal intelligence.

Several aspects of the present study design may account for the important differences between these data and those from other studies. Our sample was considerably larger than those previously reported, hence the power to detect differences between AD-HKD boys and healthy boys was increased. One possible consequence of this increased power would be to report statistically significant, but clinically irrelevant, differences between the groups. However, we do not believe this to be the case in the current sample. The effect sizes reported above were all in the medium to strong range and are broadly consistent with those reported in the existing literature (Pennington & Ozonoff, 1996). In addition to meeting DSM-IV criteria for ADHD, the boys in this study also met criteria for the more rigorously defined hyperkinetic disorder as described in ICD-10. Previous studies have, arguably, recruited more homogeneous populations by excluding subjects with co-morbid conditions. Future studies will need to compare neuropsychological functioning across the phenotypic spectrum and to include additional tasks which measure other important processes such as delay aversion and time perception (Castellanos & Tannock, 2002).

EF changes in AD-HKD boys encompass working memory, strategy formation, planning, attentional set-shifting abilities and reaction times. The Spatial Working Memory deficit has previously been described (Rhodes *et al*. 2004). This deficit was negatively correlated with Spatial Span; shorter spans were associated with a greater number of Between Search Errors. Kempton and co-workers (1999) reported similar correlations between these tasks and concluded that impairment was related to a decreased ability to hold multiple elements of spatial information in memory rather than an inability to manipulate this information. Unlike the Kempton study, however, we found impairments in strategy use. Further, strategy use was significantly correlated with between-search error score. Multiple regression analysis confirmed that both Spatial Span and strategy score, along with performance on the Go/No-Go task, correlated significantly with Spatial Working Memory total task variance for both groups. However, in view of the lack of impairments detected on the Go/No-Go task, it is unlikely that inhibition deficits contribute significantly. Thus, the Spatial Working Memory impairment is more likely related to a deficit in spatial short-term memory span and/or strategy formation. Interestingly, performance on the Spatial Recognition task, considered to be an intrinsic component of the Spatial Working Memory task and thus a developmental prerequisite for accurate performance, was not predictive of accuracy on Spatial Working Memory. Thus, recognition impairment does not appear to explain the working memory impairments of the AD-HKD boys.

AD-HKD boys had slower reaction times and were impaired in terms of planning ability and

solved fewer problems in the minimum required moves on the SoC task. SoC performance activates the PFC and connecting areas including the anterior cingulate, striatum, thalamus, and cerebellum (Morris *et al*. 1993; Baker *et al*. 1996; Elliott *et al*. 1997). AD-HKD boys also had lower stage-reached scores on the ID-ED attentional set-shifting task and evident difficulty at the Extra-Dimensional stages. This pattern supports suggestions that frontal lobe functioning is impaired (Owen *et al*. 1991). In particular, these data implicate the anterior frontal lobe (Rogers *et al*. 2000) and support, to an extent, existing dysexecutive models of AD-HKD (Morton & Frith, 1995; Castellanos & Tannock, 2002).

However, in marked contrast to previous studies (e.g. Shue & Douglas, 1992; Iaboni *et al*. 1995; Rubia *et al*. 1999*a*, *b*; 2001*a*, *b*; Castellanos *et al*. 2000), AD-HKD boys performed as well as controls on a Go/No-Go task. One possible criticism of our Go/No-Go task is the relatively high presentation rate of No-Go stimuli (50%). Some positive studies have used lower No-Go rates (e.g. Van der Meere *et al*. 1999, 20%; Rubia *et al*. 2001*a*, 30%) and it is, therefore, possible that the task used in the present study may have been less likely to tax inhibitory processes. However, as several positive studies using a Go/No-Go task have used the same 50% No-Go presentation rate (Shue & Douglas, 1992; Iaboni *et al*. 1995; Castellanos *et al*. 2000) it seems unlikely that differences in this task parameter alone could account for our data. There are, of course, several task parameters that influence performance. We utilized a fast presentation rate with an inter-stimulus interval of 900 ms – a rate which previous studies have shown to be particularly sensitive in detecting impairments in children with AD-HKD (Van der Meere *et al*. 1999). It also seems unlikely that the lack of impairment on the Go/No-Go in our sample was due to sampling differences. Our sample of AD-HKD boys were diagnosed as meeting the more restrictive ICD-10 criteria for HD and were stimulant-medication-naive – both of which factors would probably predict a greater level of impairment. Thus whilst it remains possible that this task is not sensitive to the type of response inhibition that is impaired in AD-HKD, we can see no obvious simple explanations for the absence of inhibitory impairments in our sample. The design could be improved by including other measures of inhibitory ability, such as the Stop Signal Task, and further studies comparing performance on CANTAB tasks with such measures are indicated.

It has been suggested that impairments observed in aspects of EF other than inhibition in AD-HKD are, in fact, secondary to impaired inhibitory responding (Barkley, 1998). Our findings, whilst not ruling out inhibitory dysfunction as a component of AD-HKD, do suggest that inhibitory deficits cannot solely account for the range of executive impairments observed in these children.

Our data do not support earlier conceptualizations of AD-HKD as a dysfunction in a single aspect of EF. They do, however, support the growing literature suggesting impairment across a range of EF (e.g. Kempton *et al*. 1999; Nigg *et al*. 2002; Tripp *et al*. 2002). Development of future models, or refinement of existing models of EF must incorporate the range and complexity of interacting systems involved. Further, our data implicate non-executive neuropsychological impairments as important features of AD-HKD. We have shown impairments on a range of tasks without a prominent executive component. Whilst impairment on the Spatial Recognition task may mirror the performance of frontal lobe damaged patients on this task (Owen *et al*. 1995), the intact performance of lesion patients on Pattern Recognition and Delayed Matching to Sample (Owen *et al*. 1995) differs from our AD-HKD boys. In fact, the performance of AD-HKD boys on these tasks more closely mirrors that of patients with temporal lobe and amygdalo-hippocampal damage. We have, as above, considered the possibility that these deficits may reflect inhibitory dysfunction. AD-HKD boys were more impulsive when responding incorrectly on both tasks. However, latencies for incorrect responding did not predict accuracy of responding on either task. Consequently, as with the EF deficits described above, these impairments are unlikely to be solely ascribable to impaired inhibitory responding.

These deficits in executive and non-executive functioning cannot be accounted for by differences between the two groups with respect to their levels of verbal intelligence. Despite there

being a scheduled break at the mid-point of the testing session and subjects being given the opportunity to take further breaks if required we cannot however rule out the possibility that a proportion of the observed deficit was related to fatigue effects in those tasks carried out later in the testing session.

Our data suggest a potentially important role for the temporal lobes, the amgydala and/or hippocampus in the neuropsychological deficits found with AD-HKD. These are consistent with a recent structural MRI study describing reduced white and gray matter volumes in temporal, parietal, and occipital areas in addition to frontal areas (Castellanos *et al*. 2002). Hence, neuropsychological and structural brain imaging data suggest that AD-HKD is rather more than a 'frontostriatal' disorder of monoaminergic neurocircuitry. Unfortunately, although the current sample is considerably larger than those previously reported in the AD-HKD literature, it is not sufficiently large to conduct a reliable exploratory factor analysis to search for latent variables or fully to explore for heterogeneity. These analyses will be crucial in furthering our understanding of the neuropsychological underpinnings of AD-HKD.

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Appendix 8

Acute neuropsychological effects of methylphenidate in stimulant drug-naive boys with ADHD II – broader executive and non-executive domains

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Acute neuropsychological effects of methylphenidate in stimulant drug-naïve boys with ADHD II – broader executive and non-executive domains

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Background: Accumulating evidence supports methylphenidate-induced enhancement of neuropsychological functioning in attention deficit hyperactivity disorder (ADHD). The present study was designed to investigate the acute effects of the psychostimulant drug, methylphenidate (MPH), on neuropsychological performance in stimulant naïve boys with ADHD. **Methods:** Seventy-three drug-naïve boys (age 7–15) with ADHD (combined type) completed neuropsychological tasks from the CANTAB battery under randomised, placebo controlled, double-blind conditions following an acute challenge with either placebo ($n = 24$), .3 ($n = 25$) or .6 ($n = 24$) mg/kg oral MPH. **Results:** MPH did not impair performance on any task. MPH (.6 mg/kg) lengthened response latencies on a task of Spatial Recognition, shortened response times on a Reaction Time task and restored performance on a Delayed Matching to Sample visual, non-working memory task. Contrary to predictions, MPH did not enhance performance on tasks with a prominent executive component, including Go/NoGo, Spatial Working Memory, Stockings of Cambridge and Attentional Set shifting tasks. **Conclusions:** Acute administration of MPH to drug-naïve boys with ADHD did not impair neuropsychological performance. Acute MPH enhanced performance on some aspects of non-executive functioning. MPH-induced slowing of responding on a relatively complex Spatial Recognition memory task and quickened responding on a reaction time task requiring less cognitive resources suggests that MPH may act by improving self-regulatory ability. MPH may not exert its effects on neuropsychological functioning by enhancing executive processes. **Keywords:** ADHD, stimulant, methylphenidate, cognition, executive functioning, self-regulation. **Abbreviations:** BPVS: British Picture Vocabulary Scale; CANTAB: Cambridge Automated Neuropsychological Testing Automated Battery; DMtS: Delayed Matching to Sample; ID/ED: Intradimensional/Extradimensional shifting; K-SADS-PL: Kiddie-SADS Present and Lifetime; MPH: methylphenidate; PAL: Paired Associates Learning; SOC: Stockings of Cambridge; SWM: Spatial Working Memory.

Attention deficit hyperactivity disorder (ADHD) combined type (DSM-IV – American Psychiatric Association, 1994) is characterised by pervasive behavioural symptoms of inattention, hyperactivity and impulsivity. Hyperkinetic disorder (ICD-10 – World Health Organisation, 1992) is a more restrictive definition requiring higher degrees of pervasiveness and impairment and, as such, describes those with severe ADHD. Current models of ADHD and hyperkinetic disorder (collectively referred to here as ADHD) emphasise a causal pathway from genetic variations generating functional abnormalities in dopaminergic and noradrenergic neurotransmission within fronto-striatal circuitry leading to deficits in executive neuropsychological functioning and, ultimately, to the behavioural manifestations of ADHD (Castellanos & Tannock, 2002).

A range of executive functioning deficits, including inhibition (Barkley, 1997), working memory (Rhodes, Coghill, & Matthews, 2004; Kempton et al., 1999) attentional set shifting and planning (Kempton et al., 1999; Rhodes, Coghill, & Matthews, 2005) have been described in ADHD. Studies utilising broad neuropsychological testing, such as the Cambridge Automated Neuropsychological Testing Automated Battery (CANTAB) (Robbins et al., 1994), suggest that ADHD is associated with deficits in non-executive as well as executive functioning. These include tasks such as spatial recognition and spatial span in addition to tasks upon which performance depends on intact temporal or parietal lobe function – Delayed Matching to Sample (DMtS) and Pattern Recognition (Kempton et al., 1999; Rhodes et al., 2004). Further, deficits in cerebellar timing tasks (Toplak, Rucklidge, Hetherington, John, & Tannock, 2003) and in delay aversion tasks for which the neuroanatomical substrates are unclear (Sonuga-Barke, 2003) have been described.

Conflict of interest statement: Dr David Coghill is an advisory board member for Eli Lilly, Janssen Cilag, Shire, Cephalon and UCB and has research funding from Eli Lilly and Janssen Cilag. Prof. Keith Matthews and Dr Sinead Rhodes have nothing to disclose.

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Despite this evidence for broad neuropsychological dysfunction in ADHD, prevailing models continue to emphasise an assumed primacy of inhibitory and working memory deficits (Barkley, 1997; but see Coghill, Nigg, Rothenberger, Sonuga-Barke, & Tannock, 2005; Castellanos & Tannock, 2002).

Stimulant medication, of which methylphenidate (MPH) is the most widely studied (Greenhill, Halperin, & Abikoff, 1999), remains the cornerstone of the pharmacological management of children with ADHD (Safer & Malever, 2000). However, an understanding of the relationship between the pharmacological actions of MPH and its therapeutic effects remains elusive. A generalised, simplistic explanation suggests that, since oral MPH at therapeutic doses increase the availability of extracellular dopamine (Volkow et al., 2001) and executive functioning can be modified by even small manipulations in catecholamine release (Mehta, Sahakian, & Robbins, 2001), the therapeutic effects of MPH in ADHD may arise from catecholamine-mediated improvements in executive functioning (Volkow et al., 2001). Indeed, it has been proposed that MPH may act relatively selectively to enhance executive functioning (Mehta et al., 2000; Elliott et al., 1997). If deficits in inhibitory control and working memory reflect the core psychopathology of ADHD, and MPH acts as above, performance on inhibition and working memory tasks should improve following administration of MPH. Numerous studies support this hypothesis, whereby MPH appears to enhance inhibitory control, reducing impulsive and variable responding and errors on tasks with prominent inhibitory components (e.g. Berman, Douglas, & Barr, 1999; Shue & Douglas, 1992; Trommer, Hoeppner, & Zecker, 1991; Scheres et al., 2003). However, other studies have failed to demonstrate enhanced inhibitory performance in medicated children with ADHD (Ross, Hommer, Breiger, Varley, & Radant, 1994; Van der Meere, Gunning, & Stemerdink, 1999).

The CANTAB test battery is increasing utilised in child and adolescent neuropsychopharmacological studies because of its extensive validation (Luciana, 2003; Curtis, Lindeke, Georgieff, & Nelson, 2002), its availability in parallel forms for repeated testing, and its sensitivity to pharmacological manipulation. A previous controlled study in healthy adults (Elliott et al., 1997) and previous controlled (Bedard, Martinussen, Ickowicz, & Tannock, 2004; Mehta, Goodyer, & Sahakian, 2004) and uncontrolled (Kempton et al., 1999; Barnett et al., 2001) studies in children with ADHD have reported that MPH enhanced performance on the CANTAB Spatial Working Memory task but have reported inconsistent effects on other tasks. Each of the ADHD studies has significant methodological limitations which limit their interpretation. The two earliest studies were both uncontrolled and non-randomised (Barnett et al., 2001; Kempton et al., 1999). The studies of Kempton and colleagues (1999) and Mehta et al. (2004) reported on small samples with non-standard clinical assessment procedures. Also, both of the previously reported controlled studies included non-medication-naïve subjects (Mehta et al., 2004; Bedard et al., 2004) and utilised a within-subjects crossover design which permits practice effects in addition to potential carryover and/or withdrawal effects of MPH.

The aim of the present study was to address these methodological limitations. We have used a randomised, placebo-controlled, double-blind, parallel design in a large sample of rigorously diagnosed medication-naïve boys with ADHD. We have examined their neuropsychological responses to the first administration of MPH using a broad range of range neuropsychological tasks from the CANTAB battery. We predicted that MPH would enhance performance on a range of tasks with (Go/NoGo, SWM; SOC, ID/ED), and without (e.g. Spatial Span, DMtS), a significant executive component. MPH enhancement of performance was further predicted to be dose-dependent.

We have previously reported the effects of acute MPH on the SWM, DMtS and Pattern Recognition tasks from the CANTAB battery (Rhodes et al., 2004). In this paper we reported that acute MPH did not affect performance on the SWM Task; MPH had no significant effect on Between or Within Search Errors or Strategy Score. Acute MPH also did not affect performance on the Pattern Recognition Task or performance accuracy under simultaneous test conditions of the DMtS task. In contrast, acute MPH at a .6 mg/kg dose restored performance accuracy across each of the delay conditions of the DMtS task to the levels observed in healthy controls (see Rhodes et al., 2004) and this improvement was not associated with significant changes in response latencies. Impaired functioning, however, continued to be seen across each delay condition with placebo and MPH .3 mg/kg. Here we report the effects of acute MPH on performance of the previously unpublished tasks from the CANTAB battery and the Go/NoGo task.

Method

This study was approved by the Tayside Committee on Medical Research Ethics. All participants and their parents/guardians provided written informed consent.

Participants

Seventy-three stimulant medication-naive boys participated in the study. Participants were selected from consecutive male outpatient referrals to the Tayside Child and Adolescent Psychiatric Service (Tayside, UK). There was a two-stage screening procedure. Potential participants were first screened using the Child Beha-

viour Checklist (Achenbach, 1991) and the Conners' Parent and Teaching Rating Scales (Conners, 1997). Participants with a T-score greater than 65 on all subscales of the parent *and* teacher Conners' Rating Scales entered the second stage of screening. Thereafter, participants were assessed and screened by an experienced child and adolescent psychiatrist using the Kiddie-SADS Present and Lifetime (K-SADS-PL) Version 1.0 semi-structured interview (Kaufman, Birmher, Brent, Rao, & Ryan, 1996). Standardised school reports covering in-school behaviours, with particular emphasis on impairments related to attention, impulsivity and overactivity, relationships with peers and teachers and academic performance, were requested for all cases. Teachers were interviewed only in cases where there were discrepancies between this information and parent report. All of the diagnostic information was reviewed by a senior child and adolescent psychiatrist (DC). The K-SADS-PL interviews were videoed and a selection (every fifth interview) was also reviewed by DC for reliability. Symptom ratings, impairment, pervasivity and duration of illness were collated and compared to the research versions of ICD-10 and DSM-IV. All participants met diagnostic criteria for both DSM-IV Attention-Deficit/Hyperactivity Disorder, Combined Type, and ICD-10 Hyperkinetic Disorder. Our intention was to ensure recruitment of a group of children representative of those seen in typical clinical practice. Hence, the presence of comorbid conditions did not result in exclusion from the study (see Table 1). All boys completed the British Picture Vocabulary Scale (BPVS) (Dunn, Dunn, Whetton, & Burley, 1997) [2nd Edition], providing an estimate of general intellectual ability. The BPVS assesses verbal intelligence and was chosen for its ease of administration and ability to be used with children aged between 3 and 15 (Dunn et al., 1997). It is an individually administered, norm-referenced wide-range test of receptive vocabulary for Standard English which has been demonstrated to be significantly correlated with verbal IQ.

There were no significant differences between treatment groups with respect to age [$F < 1$], socioeconomic deprivation score [$F < 1$], verbal intelligence (BPVS Percentile Rank) [$F < 1$], or baseline performance on parent-rated and teacher-rated ADHD composite scores (Conners' Scale) [both with $F < 1$] (Table 1). There were also no significant differences with respect to the presence of comorbid disorders other than separation anxiety disorder [$F = 3.4$, $p < .04$]. All three boys diagnosed with this comorbid condition were in the treatment group taking placebo. Separation anxiety disorder is not considered to be associated with neuropsychological impairment.

Procedure

All participants were tested on two occasions: at baseline (drug-naïve) and two weeks later, following randomisation by the trial pharmacist. The randomisation code was developed using a computer random number generator to select random permuted blocks (block length 6). The trial pharmacist was not involved in subject selection and all other researchers and subjects were blind to the randomisation procedure and block length. Subjects were randomised into three groups for acute challenge with placebo ($n = 24$), MPH .3 mg/kg ($n = 25$), or MPH .6 mg/kg ($n = 24$). We have previously described the wide range of executive and non-executive deficits at baseline (summarised in Table 2) (Rhodes et al., 2004, 2005). Testing for all participants started at 10.00 a.m., 90 minutes after taking their first-ever dose of MPH.

Computerised neuropsychological assessment. Subjects performed a computer-based Go/NoGo task at the beginning of each testing session. The remaining tasks were selected from the CANTAB battery (Robbins et al., 1994). CANTAB comprises a series of computerised tests presented on a high-resolution

Table 1 Patient details for each treatment group as recorded at baseline testing

	Placebo	MPH.3 mg/kg	MPH.6 mg/kg
Age (mean, s.d.)	11.08 (2.48)	10.40 (2.42)	10.92 (2.57)
BPVS percentile rank (mean, s.d.)	37 (30.42)	32.36 (25.22)	38.63 (28.96)
Social deprivation (DepCat score)	4.17 (1.85)	3.96 (1.40)	3.77 (1.85)
Conners: Parent (T scores)			
Oppositionality	74.43 (9.78)	74.6 (13.73)	78.36 (9.01)
Cognitive	73.65 (5.6)	72 (8.26)	72.91 (7.41)
Hyperactive	81.48 (9.03)	82.16 (9.20)	85.18 (8.48)
ADHD index	77.09 (5.37)	76 (7.12)	77.5 (5.7)
Conners: Teachers (T scores)			
Oppositionality	63 (20.12)	61.54 (21.41)	71.1 (16.37)
Cognitive	63.45 (11.27)	61.21 (16.34)	63.71 (9.91)
Hyperactive	76 (9.78)	66.08 (17.75)	71.14 (12.22)
ADHD index	71.95 (18.76)	71.13 (16.63)	73.76 (8.25)
Comorbid Conditions (N)			
Oppositional defiant disorder (No CD)	11	12	8
Conduct disorder (CD)	7	6	7
Depressive disorder	1	1	1
Generalised anxiety disorder	2	0	1
Separation anxiety disorder	3	0	0
Tic disorder	1	1	1
Social phobia	0	1	1

Table 2 Summary of baseline findings shown by subsequent treatment group allocation

Measure	Placebo Mean (s.d.)	MPH.3 mg/kg Mean (s.d.)	MPH.6 mg/kg Mean (s.d.)	*F*	*p*
Go/NoGo					
Errors for Distractors Block 1 ('shift' block)	2.31 (1.49)	2.24 (1.55)	2.38 (1.52)	$F < 1$	N.S.
Errors for Distractors Block 2	1.97 (1.69)	2.21 (1.67)	2.46 (1.64)	$F < 1$	N.S.
Reaction Time to targets Block 1 (log10)	2.64 (.09)	2.66 (.09)	2.66 (.07)	$F < 1$	N.S.
Reaction Time to targets Block 2 (log10)	2.67 (.07)	2.65 (.09)	2.66 (.07)	$F < 1$	N.S.
Spatial Span					
Span Score	4.88 (1.3)	5.32 (1.18)	5.04 (1.31)	$F < 1$	N.S.
Spatial Working Memory					
Total Between Search Errors	54.84 (14.8)	49 (21.8)	48.28 (21.23)	$F < 1$	N.S.
Strategy Score	36.92 (5.63)	35.84 (3.98)	36.16 (3.91)	$F < 1$	N.S.
Stockings of Cambridge					
No. Solved in Minimum Moves	7.08 (2.16)	7.20 (2.31)	7.12 (1.67)	$F < 1$	N.S.
Average Moves (5 move problems)	7.2 (1.23)	7.99 (1.82)	7.54 (1.19)	$F = 1.88$	N.S.
Initial Thinking Times (5 move problems) (log10)	3.51 (.31)	3.67 (.38)	3.6 (.31)	$F < 1$	N.S.
Pattern Recognition					
% Correct	78.83 (16)	81.5 (11.35)	82 (11.7)	$F < 1$	N.S.
Spatial Recognition					
% Correct	65.6 (13.25)	66.8 (16.69)	73.8 (10.13)	$F = 2.6$	N.S.
Latency Correct (log10)	3.3 (.11)	3.32 (.16)	3.3 (.16)	$F < 1$	N.S.
Latency Incorrect (log10)	3.26 (.15)	3.28 (.16)	3.27 (.13)	$F < 1$	N.S.
Delayed Matching to Sample					
% Correct					
Simultaneous	89.6 (14.28)	91.2 (16.41)	92 (16.33)	$F < 1$	N.S.
0 s delay	71.2 (25.87)	65.2 (29.31)	73.6 (21.39)	$F < 1$	N.S.
4 s delay	58.33 (22.78)	53.66 (24.3)	66.4 (19.77)	$F = 2.0$	N.S.
12 s delay	45.6 (28.59)	51.2 (25.87)	56 (27.08)	$F < 1$	N.S.
Paired Associates Learning					
Stage Reached	8 (0)	8 (0)	8 (0)	$F < 1$	N.S.
Total Errors	13.28 (12.51)	12.08 (12.57)	9.48 (9.36)	$F < 1$	N.S.
Total Trials	13.84 (5.09)	12.44 (3.49)	12 (3.4)	$F = 1.39$	N.S.
ID/ED					
Stage Reached Score	7.56 (.87)	7.36 (1.41)	7.72 (.89)	$F < 1$	N.S.
Pre-ED Errors	9.64 (7.46)	9.64 (5.24)	8.72 (5.88)	$F < 1$	N.S.
Errors at ED Shift	20. 4 (11.13)	20.33 (8.6)	19.68 (9.67)	$F < 1$	N.S.
Reaction Time (all log10)					
Reaction Time Latency: Simple	2.6 (.17)	2.57 (.13)	2.58 (.15)	$F < 1$	N.S.
Movement Time Latency: Simple	2.62 (.16)	2.6 (.18)	2.6 (.14)	$F < 1$	N.S.
Reaction Time Latency: 5 choice	2.61 (.11)	2.59 (.09)	2.62 (.18)	$F < 1$	N.S.
Movement Time Latency: 5 Choice	2.61 (.15)	2.63 (.14)	2.6 (.15)	$F < 1$	N.S.

N.S. indicates non-significant.

colour monitor with a touch-sensitive screen. Nine tests taken from the three batteries, (1) working memory and planning, (2) visual memory and (3) attention, were used in this study.

Go/NoGo. This task is a measure of the ability to detect and respond to a target stimulus and to inhibit responding to distractor stimuli, when all stimuli are presented in a randomly changing order. A random sequence of eighteen letters and numbers (nine of each) are rapidly presented in the centre of the screen, one by one. Stimuli are presented on screen for 300 ms, with an inter-stimulus interval of 900 ms. Subjects are instructed to respond to target stimuli by pressing the space bar as quickly as possible but not to respond to distractors. Trials were divided into two blocks: Block 1 represents the 'switch' block where the task stimuli have changed from letters to numbers (or vice versa) and Block 2 represents a 'non-switch' block. The principal dependent measures in this task were the mean number of errors for distractors (false positive responses) and reaction time to target stimuli across eight test trials.

CANTAB. Task descriptions and order of presentation of the CANTAB tasks are provided in Table 3. The standard battery was used to test all subjects at the baseline session and the first parallel battery at the acute session.

Data analysis

All analyses were conducted using SPSS for Windows (v.10) (SPSS Inc. Chicago, Ill.)

Where necessary, data were subjected to square root transformation [SQRT] or logarithmic transformation [log10] to stabilise variance and to diminish skewness depending on the relationship between the variance and the group means (Tukey, 1977). Preliminary analysis was conducted to check if data met the assumptions of homogeneity of variance and normality assumptions. A mixed design ANOVA with one between-subjects factor, TREATMENT GROUP (placebo [PBO], MPH .3 mg/kg, MPH .6 mg/kg) and with one within-subject factor, SESSION (2 levels, baseline and acute), was used. Measures with several levels of task difficulty [SOC

Table 3 Descriptions and order of presentation of CANTAB tasks

Task	Main outcome measures	Description	References for fuller task description
Working Memory and Planning Battery			
Spatial Span	Span	A test of spatial short-term memory capacity based on the Corsi block-tapping task.	Milner (1971) Kempton et al. (1999)
Spatial Working Memory (SWM)	Between search errors, strategy score	A self-ordered search task that assesses working memory for spatial stimuli and requires a subject to use mnemonic information to work towards a goal.	Petrides & Milner (1982) Kempton et al. (1999) Rhodes et al. (2004)
Stockings of Cambridge (SOC)	Problems solved in minimum number of moves	Derived from the 'Tower of Hanoi' task, measuring spatial planning, working memory, and behavioural inhibition.	Shallice (1982) Kempton et al. (1999)
Visual Memory Battery			
Pattern Recognition	Percent correct	Tests the ability to recognise a previously presented abstract pattern in a forced choice procedure.	Kempton et al. (1999)
Spatial Recognition	Percent correct	Tests the ability to recognise the spatial locations of target stimuli.	Kempton et al. (1999) Rhodes et al. (2004)
Delayed Matching to Sample (DMtS)	Percent correct	Tests the ability to remember the visual features of a complex, abstract, target stimulus and to select from a choice of four patterns after a variable delay.	Kempton et al. (1999) Rhodes et al. (2004)
Paired Associates Learning (PAL)	Stage reached, total errors, total trials	Tests the ability to learn the spatial locations of a progressively increasing number of abstract stimuli. The main measures in this task are the number of trials taken to complete the task and the total number of errors across all trials.	Sahakian & Owen (1992)
Attention Battery			
Attentional Set-Shifting task/ID-ED (Intradimensional/ Extradimensional Set Shifting)	Stage reached	Tests the ability to focus attention on specific attributes of compound stimuli (intradimensional stages) and to shift attention when required to a previously irrelevant stimulus dimension (extradimensional stages).	Kempton et al. (1999)
Reaction Time	Reaction time, movement time	Tests reaction and movement times in response to a stimulus under both one choice and five choice conditions.	Sahakian & Owen (1992)

(average moves, Initial and Subsequent Thinking Times)] were analysed using repeated-measures ANOVA with an additional within-subject factor, TASK DIFFICULTY.

Where ANOVA revealed significant effects or interactions, planned comparisons comparing placebo to the two doses of MPH were conducted. For repeated-measures data with two within-subject factors, TASK DIFFICULTY and SESSION, the most difficult level (e.g., 5 moves SOC) was compared with all other levels.

Results

Mean performance and statistical comparisons for each of the treatment groups on each task are summarised in Table 4. F and p values reported in Table 4 represent SESSION × TREATMENT interactions. Main effects of TREATMENT GROUP, TASK DIFFICULTY and SESSION are reported only when significant.

Go/NoGo

Whilst subjects showed a significant reduction in Errors for Distractors from baseline to acute challenge, this improved performance was not due to MPH which had no effect on either performance accuracy or reaction times, at either dose, for either of the blocks.

Spatial Span

MPH had no effect on spatial span score at either dose.

Stockings of Cambridge

MPH did not influence performance on the SOC Task either in terms of the number of problems Solved in Minimum Number of Moves, average moves, or on Initial and Subsequent Thinking times. There were

Table 4 Summary of acute challenge findings for each treatment condition

Measure	Total ADHD sample (baseline)	Placebo Mean (s.d.)	MPH.3 mg/kg Mean (s.d.)	MPH.6 mg/kg Mean (s.d.)	*F*	*p*
Go/NoGo						
Errors for Distractors Block 1 ('shift' block)	2.39 (1.47)	1.85 (1.6)	1.8 (1.5)	1.81 (1.9)	$F < 1$	N.S..
Errors for Distractors Block 2	2.27 (1.65)	1.41 (1.6)	1.81 (1.7)	2 (2)	$F < 1$	N.S.
Reaction Time to targets Block 1 (log10)	2.66 (.09)	2.69 (.06)	2.66 (.10)	2.66 (.08)	$F < 2.7$	N.S.
Reaction Time to targets Block 2 (log10)	2.67 (.09)	2.69 (.07)	**2.65 (.13)**	**2.67 (.09)**	$F < 1.3$	N.S
Spatial Span						
Span Score	5.07 (1.47)†	4.75 (1.4)	**5.48 (1.3)**	**5.54 (1.3)**	$F = 2.6$	N.S.
Spatial Working Memory						
Total Between Search Errors	50.84 (21)†	47.08 (22.9)	40.8 (19.9)	38.83 (19.9)	$F < 1$	N.S.
Strategy Score	36.32 (5.1)†	35.67 (5.3)	**35.6 (.4.2)**	**35.46 (4.3)**	$F < 1$	N.S.
Stockings of Cambridge						
No. Solved in Minimum Moves	7.2 (2.1)	7.96 (1.5)	8.04 (2)	**8.5 (1.8)**	$F < 1$	N.S.
Average Moves (5 move problems)	7.58 (1.5)	6.85 (1.3)	6.97 (1.6)	**6.79 (1.6)**	$F < 1$	N.S.
Initial Thinking Times(5 move problems) (log10)	3.59 (.34)	3.47 (.31)	3.69 (.37)	**3.73 (.3)**	$F < 1$	N.S.
Pattern Recognition% Correct	80.78 (13.1)†	84.4 (11.08)	**86.3 (10.9)**	**91.1 (7.4)**	$F = 1.4$	N.S.
Spatial Recognition						
% Correct	68.21 (13.9)†	57.7 (13.3)	61.4 (16.7)	65.22 (16.8)	$F < 1$	N.S.
Latency Correct (log10)	3.32 (.15)	3.26 (.13)	3.32 (.12)	3.44 (.24)	$F = 3.4$	*
Latency Incorrect (log10)	3.27 (.14)†	3.3 (.16)	**3.39 (.15)**	**3.55 (.32)**	$F = 7.3$	**
Delayed Matching to Sample						
% Correct						
Simultaneous	90.93 (15.5)†	90 (15.6)	91.2 (19.2)	98.26 (5.8)	$F = 1.4$	N.S.
0 s delay	70 (25.63)†	59.17 (20.8)	62.4 (24.7)	78.26 (18)	$F = 7.1$	**
4 s delay	56.52 (24)†	55 (21.5)	62.4 (23.3)	83.48 (16.7)	$F = 11.84$	***
12 s delay	50.93 (27.2)†	51.67 (22)	**60 (27.7)**	**74.78 (20.2)**	$F = 5.75$	**
Paired Associates Learning						
Stage Reached	7.96 (.26)	8 (0)	8 (0)	8 (0)	$F < 1$	N.S.
Total Errors	11.61(11.5)†	11.67(7.9)	13.04 (12.4)	6.5 (5)	$F = 2.8$	N.S.
Total Trials	12.76 (4.1)†	9.25 (2.7)	**8.84 (2.1)**	**7.21 (2.4)**	$F = 1.5$	N.S.
ID/ED						
Stage Reached Score	7.5 (1)†	7.83 (.96)	**8.16 (.99)**	**8.04 (.96)**	$F = 1.1$	N.S.
Pre-ED errors	9.33 (6.2)	8.21 (3.5)	6.96 (3.8)	7.58 (3.3)	$F < 1$	N.S.
Errors at ED Shift	21. 4 (9.74)	18.79 (10.0)	15.79 (11.05)	16.17 (10.68)	$F < 1$	N.S.
Reaction Time (all log10)						
Reaction Time Latency: Simple	2.58 (.15)	3.10 (1.7)	3.06 (1.6)	2.57 (.11)	$F = 1.2$	N.S.
Movement Time Latency: Simple	2.60 (.16)	2.73 (.47)	2.71 (.36)	2.61 (.15)	$F < 1$	N.S.
Reaction Time Latency: 5 choice	2.62 (.09)	2.89 (1.2)	2.62 (.09)	2.6 (.10)	$F = 3.3$	*
Movement Time Latency: 5 Choice	2.63 (.26)	2.68 (.37)	**2.61 (.11)**	**2.62 (.14)**	$F < 1$	N.S.

†indicates tasks on which ADHD boys demonstrated baseline performance deficits compared to healthy boys (Rhodes et al., 2004, 2005). N.S. indicates non-significant, * = $p < .05$, ** = $p < .01$, *** = $p < .001$.

significant effects of SESSION on each of these measures. Overall, subjects showed improved performance during the second test session. However, as there were no significant SESSION × TREATMENT interactions, these improvements cannot be attributed to MPH. There was a significant effect of TASK DIFFICULTY on average moves [$F(3,207) = 944.6$, $p < .001$], Initial [$F(3,207) = 68.8$, $p < .001$], and Subsequent Thinking [$F(3,207) = 79.7$, $p < .001$] times. There were no significant TASK DIFFCULTY × TREATMENT GROUP interactions.

Spatial Recognition

MPH had no effect on accuracy but did increase the time to respond on the Spatial Recognition Task. Whilst accuracy was significantly improved at the acute challenge session compared with baseline [$F(1,69) = 12.0$, $p < .001$], there was no significant SESSION by TREATMENT GROUP interaction. MPH (.6 mg/kg) slowed responding for both correct and incorrect choices on the Spatial Recognition Task. Although there was no significant effect of SESSION on latency to make correct responses, there was a significant SESSION × TREATMENT GROUP interaction [$F(2,69) = 3.36$, $p < .04$]. Planned contrasts showed that the MPH .6 mg/kg group showed longer latencies when making correct responses at the acute challenge session than did those taking placebo ($t(45) = -2.07$, $p < .04$). There was also a significant effect of TREATMENT GROUP [$F(2,68) = 4.91$, $p < .01$] on latencies to make incorrect responses, a significant effect of SESSION [$F(1,68) = 25.8$, $p < .001$] and a significant TREATMENT GROUP by SESSION interaction [$F(2,68) = 7.27$, $p < .001$]. Planned contrasts revealed that the MPH .6 mg/kg group showed longer latencies when making incorrect responses at the acute challenge session ($t(45) = -2.43$, $p < .003$) compared with placebo.

Paired Associates Learning

MPH did not affect performance on PAL. For stage reached and mean error scores there was no effect of TREATMENT GROUP, SESSION, nor an interaction between the two. There was a significant effect of TREATMENT GROUP [$F(2,70) = 3.5$, $p < .04$] and of SESSION [$F(1,70) = 170.8$, $p < .001$] on total number of trials, but no interaction indicating an absence of effect of MPH. The significant effect of TREATMENT GROUP seems likely to reflect a non-statistically significant trend towards a smaller number of trials taken by the .6 mg/kg MPH treatment group at baseline in comparison to the placebo group.

ID/ED

MPH did not affect performance on the ID/ED attentional set shifting task. There was no effect of TREATMENT GROUP on Stage Reached, errors up to and including ID reversal, errors at the ED shift or at the ED reversal stages. There was a significant effect of SESSION [$F(1,70) = 12.05$, $p < .001$] on the proportion successfully completing the Extra-Dimensional Reversal stage (stage 9) but no significant effects of TREATMENT GROUP [$F(2,70) < 1$] or significant TREATMENT GROUP by SESSION interaction.

Reaction time

There were no significant effects of MPH on reaction time or movement time in the simple reaction test condition. However, MPH .6 mg/kg shortened latencies to respond during the 5-choice condition. While there was no significant effect of TREATMENT GROUP or SESSION on Reaction Time latencies, there was a significant TREATMENT GROUP by SESSION interaction [$F(2,68) = 3.30$, $p < .05$]. Planned contrasts revealed that the MPH .6 mg/kg group had shorter latencies during the acute challenge session ($t(46) = 2.13$, $p < .03$). MPH did not improve movement time latencies in the 5-choice condition.

Discussion

The acute administration of oral MPH (.3 and .6 mg/kg) under randomised, placebo-controlled, double-blind conditions to a cohort of 73 medication-naïve boys with ADHD improved neuropsychological performance on three tasks without a prominent executive component. *Shortened* response latencies were reported on a complex reaction time task and *lengthened* response latencies (which were not associated with increased task accuracy) were found on a Spatial Recognition memory task. As we previously reported (Rhodes et al., 2004), performance on a Delayed Matching to Sample task was restored to that described for healthy developing children. Contrary to predictions, acute MPH failed to improve performance on neuropsychological tasks with a prominent executive component. This absence of effect was observed on sensitive tests of inhibition, working memory, strategy formation, planning, and attentional set-shifting. These findings are striking in that they contradict the existing literature. Specifically, the hypothesis that MPH selectively enhances performance on neuropsychological tasks with a prominent executive component was not supported.

Whilst it was not appropriate to examine clinical response to a single dose of medication, the results presented do not support the hypothesis that the therapeutic effects of MPH in children with ADHD are mediated by improved executive neuropsychological performance. Further, the present study fails to support the findings of two earlier studies which

utilised the Go/NoGo task and demonstrated an enhancement of inhibitory processes with acute MPH (Trommer et al., 1991; Broyd et al., 2005). However, Van der Meere and colleagues also conducted a double-blind, placebo-controlled study of strictly defined drug-naïve children with ADHD (Van der Meere et al., 1999) and found that stimulant medication (chronically administered) failed to enhance performance on a Go/NoGo task. It is also possible that the differences between these studies could be a consequence of the Go/NoGo tasks used. The current study and that of Van der Meere used tasks with visual targets whereas the Trommer and Broyd studies used an auditory Go/NoGo task. Further, the current study used a relatively fast presentation rate with an inter-stimulus interval of .9 whilst both the Trommer and the Broyd studies used a medium presentation rate with an inter-stimulus interval of between 3 and 4 seconds. This explanation seems less likely as Van der Meere and colleagues investigated performance across several inter-stimulus intervals (1, 4 and 8 secs) and found no relationship between presentation rate and medication effects.

The present findings also fail to fully replicate those from previous comparable studies using the CANTAB tasks (Bedard et al., 2004; Kempton et al., 1999; Mehta et al., 2004; Barnett et al., 2001). Each of these studies reported that MPH reduced BSE on the SWM task, and both studies that included the ID/ED task reported improvement with MPH (Kempton et al., 1999; Mehta et al., 2004). However, studies using the SOC planning task reported mixed findings (Kempton et al., 1999; Bedard et al., 2004). We found no effects on these three tasks. This may relate to differences in study design. The two earliest studies were both uncontrolled and non-randomised (Barnett et al., 2001; Kempton et al., 1999). The studies of Kempton and colleagues (1999) and Mehta et al. (2004) reported on small samples with non-standard clinical assessment procedures. Also, both of the previously reported controlled studies included non-medication-naïve subjects (Mehta et al., 2004; Bedard et al., 2004). Both also utilised a within-subjects crossover design which permits practice effects in addition to potential carryover and/or withdrawal effects of MPH. We observed improvements on several tasks between baseline and acute challenge in the present study that cannot be attributed to MPH. Finally, unlike these previous studies, the statistical analyses for the present study included unmedicated baseline performance when estimating the significance of MPH effects.

Stimulant drug effects on tasks without a prominent executive component are relatively understudied. Using an uncontrolled study design, Kempton et al. (1999) suggested that MPH enhanced performance on several tasks without a prominent executive component: Spatial Span, Pattern Recognition and Delayed Matching to Sample, but not on others: Spatial Recognition and Paired Associates Learning (PAL). Controlled studies have included only small subsets of these tasks. MPH improved performance on the Spatial Span task as reported by Bedard, Ickowicz, and Tannock (2002) but did not improve performance on the Spatial Recognition task (Bedard et al., 2004; Mehta et al., 2004) or on the Pattern Recognition task (Mehta et al., 2004). The present study found that acute MPH (.6 mg/kg) exerted significant effects on response latencies on two such tasks. MPH .6 mg/kg lengthened latencies for both correct and incorrect responses on the Spatial Recognition task and shortened reaction time latencies on the 5-choice condition of the Reaction Time task. These findings support the contention that MPH exerts therapeutic effects by improving '*regulatory ability*' – slowing performance during the difficult conditions of tasks and shortening response times during easier stages (Douglas, 1999; Berman et al., 1999). These beneficial effects may be dependent upon memory load. Berman et al. (1999) demonstrated that at a low memory load, improvement in performance accuracy occurred with no cost to reaction time, irrespective of dose of MPH, whereas at higher loads there was a dose-dependent effect of MPH to slow reaction times. In support of this model, we found that acute MPH did not uniformly slow or speed responding. MPH lengthened responding on the Spatial Recognition task, but shortened response times on the Reaction Time task. While MPH has contrasting effects on reaction times on these two tasks, both effects can be regarded as enhancements of cognitive functioning. The Spatial Recognition task is a relatively complex task in comparison to the lighter cognitive processing burden of the Reaction Time task; hence lengthened responding in the former and shortened responding in the latter can be regarded as an enhancement of performance in both tasks. Whilst these results support those found in other studies, it should be noted that the reported p values for each of these effects were in the .5 to .1 range. Considering the number of tasks investigated, it remains possible that these results represent Type 1 errors. Further significant effects were found on another task without a prominent executive component, the DMtS task, which assesses the ability to hold information in memory over a short delay (Rhodes et al., 2004).

The present study also supports the notion that MPH selectively enhances discrete aspects of neuropsychological functioning (Gao & Goldman-Rakic, 2003) and that these effects extend beyond baseline impairments (Rapport & Kelly, 1991). Within the present sample, baseline assessments revealed a wide range of deficits in neuropsychological functioning (see Table 2) (Rhodes et al., 2005). Acute MPH, however, failed to enhance performance on many of these tasks. Indeed, apart from the amelioration of deficits on the DMtS task and the slowing of incorrect responses (but *without*

improved accuracy) on Spatial Recognition, MPH-related enhancements were restricted to aspects of neuropsychological functioning in which boys showed *no* impairment at baseline. Importantly, despite there being no evidence for MPH-related improvement on other aspects of neuropsychological performance, there was no evidence of MPH-related performance deficits. Specifically, there was no evidence for MPH reducing cognitive flexibility (see ID/ED results) as has previously been suggested (Robbins & Sahakian, 1979; Dyme, Sahakian, Golinko, & Rabe, 1982).

Several potential limitations of this study should be addressed. The recruitment of participants meeting criteria for both DSM-IV ADHD Combined Type and ICD-10 Hyperkinetic Disorder may have generated a more severely affected clinical sample than previous studies. However, a recent re-analysis of the Multimodal Treatment Study for ADHD (MTA) data (E. Taylor, pers. comm.) suggests that such a population is more, rather than less, likely to respond to MPH. Presumably, this ought to increase rather than decrease the chances of detecting clinically meaningful changes. The inclusion of only male subjects reduces the generalisability of the findings to females with ADHD.

No attempt was made to measure clinical response to the acute MPH challenge. However, in view of the highly structured, controlled and relatively novel environment required for neuropsychological testing, it is unlikely that such ratings (even with relatively objective measures such as from an actometer) would accurately capture clinically relevant symptom changes. Also, although participants were randomised following baseline testing, it is possible that the present findings are a consequence of latent differences between the treatment groups in either clinical or neuropsychological characteristics. However, there were no statistically significant differences between the three treatment groups on a wide range of clinical variables: age, BPVS Percentile Rank, the presence of a wide range of comorbid conditions, or on neuropsychological functioning at baseline. Whilst our sample size was modest, it easily exceeds that of previous, comparable studies. The use of a single session between-subjects rather than multiple session within-subject design results in a reduction in power; however, as detailed above, such repeated measures designs also add potential confounding factors. To evaluate the first-ever neuropsychological response to MPH in drug-naïve subjects mandates a between-subjects design. The *F*-ratios reported above are frequently <1, suggesting that the loss of power of a between-subjects design is unlikely to have been a major issue with respect to the negative findings. It is also worth noting that the consistently negative results across multiple neuropsychological domains reinforce the possibility that MPH may not exert the previously anticipated effects.

One possible explanation for the absence of effects of MPH on executive functioning is that we have only studied the acute response to a first-ever dose and chronic administration may have very different effects. Clinically, the positive impact of MPH on behaviour within approximately an hour of administration has traditionally been interpreted as evidence that its therapeutic effects are immediate and are not mediated by long-term neurobiological adaptation (Solanto, 1998). Perhaps this is incorrect? Previous controlled study designs, utilising these same tasks, have considered the possibility that the 'enhanced' performance seen with MPH may be a consequence of neuropsychological rebound secondary to acute medication withdrawal. Definitive prospective studies comparing acute and chronic responses in stimulant-naïve subjects are awaited.

ADHD is associated with a wide range of neuropsychological deficits. While findings from this study do not support the popular hypothesis that MPH enhances performance on executive functioning tasks, they do suggest selective enhancement of several aspects of non-executive cognitive functioning which may reflect increased capacity for self-regulation. As a majority of children with ADHD demonstrate positive clinical responses to MPH, this suggests that clinically important cognitive deficits may not all be 'executive' in nature. Importantly, MPH does not impair performance on any of the tasks studied.

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Appendix 9

The Neuropsychological Effects of Chronic Methylphenidate on Drug-Naive Boys with Attention-Deficit/Hyperactivity Disorder

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ORIGINAL ARTICLES

The Neuropsychological Effects of Chronic Methylphenidate on Drug-Naive Boys with Attention-Deficit/Hyperactivity Disorder

David R. Coghill, Sinead M. Rhodes, and Keith Matthews

Background: The reported neuropsychological effects of methylphenidate (MPH) in attention-deficit/hyperactivity disorder (ADHD) are inconsistent. The assumed relationships between these neuropsychological effects and clinical efficacy have not been substantiated. We therefore investigated the effects of chronic MPH administration on neuropsychological functioning.

Methods: We conducted a 12-week, placebo-controlled, double-blinded, randomized, crossover trial (MPH .3 and .6 mg/kg/dose and placebo). Participants were 75 boys aged 7–15 years with ADHD. Neuropsychological performance was assessed with tests taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB) battery and a GoNoGo task.

Results: Chronic MPH improved performance ($p < .001$) on aspects of the GoNoGo task ($p < .02$) and on three CANTAB tasks which together contributed to a "recognition memory" component identified through principal components analysis (delayed matching to sample [DMtS], pattern and spatial recognition). There were no effects on other, high or low "executive demand" tasks ($p > .05$). GoNoGo performance improvements were the only neuropsychopharmacological changes associated with clinical response. Poor performance on the DMtS task was the sole baseline neuropsychological predictor of clinical response.

Conclusions: Chronic MPH predominantly enhanced neuropsychological functioning on "recognition memory" component tasks with modest "executive" demands. Neuropsychological measures offer only modest contributions to the prediction of clinical responses to MPH in ADHD.

Key Words: Attention deficit hyperactivity disorder, cognition, executive functioning, methylphenidate, randomized controlled trial, stimulant

Conceptual models of attention deficit hyperactivity disorder (DSM-IV)(American Psychiatric Association 1994) and hyperkinetic disorder (ICD-10) (World Health Organization 1992), emphasize causal pathways by which genetic variation generates functional changes within frontostriatal dopamine and noradrenaline neurotransmission. In turn, these alterations mediate deficits in "executive" aspects of neuropsychological functioning that are proposed to elicit the core phenotypic manifestations of ADHD (Castellanos and Tannock 2002). Executive functioning deficits ascribed to ADHD include inhibition (Barkley 1997), working memory (Kempton *et al.* 1999; Rhodes *et al.* 2004) attentional set shifting and planning (Kempton *et al.* 1999; Rhodes *et al.* 2005). However, executive deficits are neither necessary, nor sufficient, to account for all presentations of the ADHD phenotype (Willcutt *et al.* 2005). Further, recent studies have linked ADHD with deficits on neuropsychological tasks with minimal 'executive demands' (spatial span and spatial recognition memory, delayed matching to sample (DMtS) and pattern recognition) (Kempton *et al.* 1999; Rhodes *et al.* 2004), including tasks (e.g. DMtS, Pattern Recognition) previously ascribed as reliant upon intact temporal and parietal, rather than frontal, lobe functioning (Owen *et al.* 1995). Similarly, consistent performance deficits on cerebellar timing (Toplak *et al.* 2003) and delay aversion tasks (for which the neural substrates remain unclear (Sonuga-Barke 2003)), have been described. Hence, the anatomical and neurochemical neural substrates mediating core features of ADHD are likely to be complex and heterogeneous (Coghill *et al.* 2005).

Stimulant medication, of which methylphenidate (MPH) is the most commonly prescribed and studied (Greenhill *et al.* 1999), remains the dominant, yet still controversial, pharmacological contribution to the management of ADHD (Safer and Malever 2000) Several studies have demonstrated MPH-mediated enhancement of inhibitory control in ADHD, with reduced impulsive responding, response variability and errors (Berman *et al.* 1999; Scheres *et al.* 2003; Shue and Douglas 1992; Trommer *et al.* 1991). However, these findings are not robust (Ross *et al.* 1994; Van der Meere *et al.* 1999) Thus, proposed mechanisms linking the pharmacological actions of MPH to core neuropsychological processes remain highly speculative (Elliott *et al.* 1997; Mehta *et al.* 2000), and often fail to make any meaningful distinction between acute and chronic pharmacological actions. We have previously described acute responses on a range of neuropsychological tasks in a large sample of rigorously diagnosed, medication-naive boys with ADHD following their first ever exposure to MPH in a randomized, placebo-controlled, double-blind, parallel group design (Rhodes *et al.* 2004, 2006) In this study, acute MPH failed to enhance performance on tasks with a prominent executive component, but significantly enhanced performance on three tasks without prominent executive demands (a reaction time task, spatial recognition memory, and DMtS). Other acute MPH administration studies (also using tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB) test system (Morris *et al.* 1987)) have described enhanced Spatial Working Memory (SWM) performance in healthy adults (Elliott *et al.* 1997) and in children with ADHD

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Table 1. Comorbid Diagnoses in ADHD Group

	n	% Of Sample
Pure ADHD	18	24
Comorbid Diagnoses		
Oppositional Defiant Disorder (No CD)	31	41.3
Conduct Disorder (CD)	21	28
Depressive Disorder	3	4
Generalised Anxiety Disorder	2	2.7
Separation Anxiety Disorder	3	4
Tic Disorder	2	2.7
Social Phobia	1	1.3

ADHD, attention deficit hyperactivity disorder.

(Bedard *et al.* 2004; Mehta *et al.* 2004), enhanced strategy and planning (Stockings of Cambridge (SOC) in healthy adults (Elliott *et al.* 1997) (but not in ADHD subjects (Bedard *et al.* 2004; Mehta *et al.* 2004)), and enhanced attentional flexibility/set-shifting (ID/ED task) in ADHD subjects only (Mehta *et al.* 2004). Two uncontrolled, acute MPH studies also reported improved SWM (Barnett *et al.* 2001; Kempton *et al.* 1999), ID/ED and SOC task performance (Kempton *et al.* 1999) in ADHD subjects.

Further detailed studies of the chronic effects of MPH on executive neuropsychological functions in children with ADHD are required because effective therapeutic use mandates chronic administration. Chronic, but not acute, studies permit exploration of the relationships between neuropsychological performance, medication response and clinical status. Further, experimental designs must accommodate potential withdrawal effects, as well as manifestations of tolerance or sensitization. To date, there has been only one such study. Using a randomized, placebo-controlled design, Van der Meere and colleagues described impaired performance of ADHD boys on a GoNoGo response inhibition task (van der Meere *et al.* 1999) and the failure of chronic MPH administration to improve performance. Thus, the reported neuropsychological effects of MPH in ADHD are inconsistent. Further, the assumed, intuitively attractive, relationship between neuropsychological effects of MPH, dose and clinical efficacy has not been substantiated.

We now describe neuropsychological performance in a clinical sample of medication-naive boys with ADHD in response to chronic MPH (.3 and .6 mg/kg twice daily) using a randomized, placebo-controlled, double-blind, parallel group design. We have previously reported elements of these data from the SWM, DMtS and Pattern Recognition tasks (Rhodes *et al.* 2004). We aimed to test the following hypotheses: 1) Chronic exposure to MPH would enhance performance on tasks with a prominent executive component; 2) neuropsychological responses to chronic MPH would demonstrate dose-dependency; and 3) if, as is proposed in several prominent causal theories of ADHD, neuropsychological performance deficits contribute significantly to the clinical presentation and impairments associated with ADHD, then those study participants exhibiting the largest neuropsychological responses to MPH would also demonstrate the greatest clinical responses.

Methods and Materials

This study was approved by the Tayside Committee on Medical Research Ethics (NHS Tayside, Dundee, United Kingdom). All participants and parents/guardians provided written informed consent.

Participants

Seventy-five boys were recruited from consecutive out-patient referrals (aged 7 to 15) to the Tayside Child and Adolescent Psychiatric Service (Tayside, United Kingdom). Exclusion criteria included history of neurological impairment, learning disability (IQ $<$ 80), chronic physical illness, sensory or motor impairment, current or previous exposure to stimulant medication, and abuse of any illegal drugs. The presence of commonly comorbid conditions; oppositional defiant disorder, conduct disorder, and anxiety disorder, did not result in exclusion (see Table 1). Eligible boys (scoring $>$ 1.5 standard deviations from the mean on both Conners' Parent Rating Scale short version (CPRS-26) and Conners' Teacher Rating Scale short version (CTRS-28)) were interviewed by an experienced child and adolescent psychiatrist using the Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime (K-SADS-PL) (Kaufman *et al.* 1996 unpublished data) interview schedule. Those meeting criteria for hyperkinetic disorder (HD) (F90 ICD-10) and ADHD combined subtype (DSM-IV) were invited to participate. The British Picture Vocabulary Scale (BPVS) (Dunn *et al.* 1997) [2nd Edition] was used to estimate general intellectual ability.

Design

Participants were randomized by an independent clinical trials pharmacist (using a computer-generated random number sequence with block design to ensure equal numbers in each treatment arm) to receive placebo (n = 25), .3mg/kg/dose MPH (n = 25), or .6mg/kg/dose MPH (n = 25) (hereafter referred to as; placebo, .3mg/kg and .6mg/kg) twice daily. These doses were chosen to reflect low and high dose regimes respectively. Neuropsychological performance was assessed prior to exposure to MPH (Rhodes *et al.* 2004, 2005) {Rhodes, 2005 12848 /id}and again two weeks after baseline testing, to minimize practice effects, following the first dose of MPH (Rhodes *et al.* 2006) Subsequently, MPH administration was continued for three cross-over periods of 28 days under randomized, double-blinded conditions. MPH was taken at 08:00 and midday (Figure 1). Participants were tested 90 min after taking morning medication at the end of each 28-day block. Clinical status was assessed by interview conducted by an experienced, blinded child and adolescent psychiatrist (Clinical Global Impressions - Improvement scale (CGI-I) (National Institute of Mental Health 1985), Parent and Teacher-rated 10-item Conners' Global Index rating scales (CGI-P and CGI-T) (Conners 1997)). Treatment adherence was assessed by pill count and clinical enquiry.

	1		2	3	4	5
Testing Session			**Acute**		**Chronic**	
				4 weeks	*4 weeks*	*4 weeks*
Group						
AD-HKD	Baseline	➔	placebo	placebo	0.3mg/kg	0.6mg/kg
		➔	0.3mg/kg	0.3mg/kg	0.6mg/kg	placebo
		➔	0.6mg/kg	0.6mg/kg	placebo	0.3mg/kg
Control	Baseline		**No further follow up**			

Figure 1. Study design.

Table 2. Descriptions and Order of Presentation of Cambridge Neuropsychological Test Automated Battery (CANTAB) Tasks

Task	Main Outcome Measures	Description	References for Fuller Task Description
Working Memory and Planning Battery			
Spatial Span	Span	A test of spatial short-term memory capacity based on the Corsi block-tapping task	Milner (1971) Kempton et al. (1999)
Spatial Working Memory (SWM)	Between search errors, strategy score	A self-ordered search task that assesses working memory for spatial stimuli and requires a subject to use mnemonic information to work towards a goal.	Petrides and Milner (1982) Kempton *et al.* (1999) Rhodes *et al.* (2004)
Stockings of Cambridge (SOC)	Problems solved in minimum moves	Derived from the 'Tower of Hanoi' task, measuring spatial planning, working memory, and behavioral inhibition	Shallice (1982) Kempton *et al.* (1999)
Visual Memory Battery			
Pattern Recognition	Percent correct	A test of the ability to recognize a previously presented abstract pattern in a forced choice procedure	Kempton *et al.* (1999)
Spatial Recognition	Percent correct	A test of the ability to recognize the spatial locations of target stimuli	Kempton *et al.* (1999) Rhodes *et al.* (2004)
Delayed Matching to Sample (DMtS)	Percent correct	A test of the ability to remember the visual features of a complex, abstract, target stimulus and to select from a choice of four patterns after a variable delay	Kempton *et al.* (1999) Rhodes *et al.* (2004)
Paired Associates Learning (PAL)	Stage reached, total errors, total trials	A test of the ability to learn the locations of a progressively increasing number of abstract stimuli. The main measures in this task are the number of trials taken to complete the task and the total number of errors across all trials	Sahakian and Owen (1992)
Attention Battery			
Attentional Set-Shifting Task/ID-ED (Intradimensional-Extradimensional Set Shifting)	Stage reached	A test of the ability to focus attention on specific attributes of compound stimuli (intradimensional stages) and to shift attention when required to a previously irrelevant stimulus dimension (extradimensional stages)	Kempton *et al.* (1999)
Reaction Time	Reaction time Movement time	A test of reaction and movement times in response to a stimulus under a simple one choice and a five choice condition	Sahakian and Owen (1992)

Neuropsychological Testing

Participants performed each task in the same order on each occasion. A GoNoGo task was followed by nine tasks (see Table 2 for descriptions) selected from the CANTAB (Morris *et al.* 1987). All tasks were presented on a high-resolution color monitor with touch sensitive screen. Where available, parallel versions of the CANTAB tasks were used for repeat testing (pattern recognition, spatial recognition, delayed matching to sample, paired associates learning and reaction time).

GoNoGo Task. The GoNoGo task required the detection and response to target stimuli with inhibition of responding to distractors. Stimuli were presented as 8 blocks of random 18 character sequences of letters and numbers (9 of each i.e. 50% targets, 50% distractors) in the center of the screen for 300 msec, with an interstimulus interval of 900 msec. Participants were instructed to respond to target stimuli by pressing a computer keyboard space bar. Response contingencies alternated between numbers and letters every second block (i.e. l,l,n,n,l,l,n,n). Dependent measures were mean number of errors for distractors (ERD) and reaction times to target stimuli (RTT). For analysis, trials were divided into those representing 'switch' blocks (1) where task requirements shifted from detection of letters to numbers (or vice-versa) and 'nonswitch' blocks (2).

Cambridge Neuropsychological Test Automated Battery (CANTAB)

Task descriptions and presentation order are summarized in Table 2.

Statistical Analysis

All analyses were conducted using SPSS (SPSS Inc., Chicago, Illinois) for Windows (v.10). Where required, data were subjected to square root transformation or logarithmic transformation to stabilize variance and diminish skewness. Where ORDER effects were not detected, data were pooled (n = 69 for placebo, 68 for .3mg/kg MPH and 65 for .6mg/kg MPH). A mixed design analysis of variance (ANOVA) with one between-subject factor, ORDER (treatment sequence), and with repeated-measures on one within-subject factor, DOSE (placebo, .3mg/kg MPH, or .6mg/kg MPH) was performed. Where ORDER effects were evident, data were analysed by repeated-measures ANOVA with two levels of the within-subjects factor SESSION (baseline and session three scores only) and ORDER as a between-subjects factor. Data failing to meet normality and homogeneity of variance assumptions were analyzed using the nonparametric Wilcoxon Sign test for repeated-measures. Posthoc analyses were conducted using planned contrasts using data from subjects with complete datasets.

Clinical response was described as a continuous variable by calculation of change scores between placebo and MPH dose. In addition, 'responder' status was determined using the clinical significance methods proposed by Jacobson and Truax (1991). "Clinically significant change" was defined as movement from the dysfunctional to the functional range (< 65) on the Conners' Global Index total t-score. Reliable change scores were calculated (defined as reliable change index (RCI) < -1.96) and "response" was defined as requiring both "clinically significant change" and "reliable change". Separate analyses were carried out for each dose of MPH (see Jacobson and Truax 1991 for full consideration of relevant theory and its application). Neuropsychopharmacological response to MPH was defined as score change on the primary measures from each task. Although both parent and teacher ratings of clinical response were obtained,

Table 3. Clinical Response to Methylphenidate

	Placebo Mean (SD)	MPH .3 mg/kg mean (SD)	MPH .6 mg/kg mean (SD)	*F*	*p*	Effect Size	
						Pla vs. .3mg/kg	Pla vs. .6mg/kg
Parent Conners' Global Index							
Restless/impulsive subscale (T score)	77.1 (1.9)	68.4 (13.8)	65.5 (13.6)	14.2	<.001	70	.94
Emotional Lability subscale (T score)	71.6 (13.6)	65.2 (14.2)	65.6 (15.0)	4.0	.02	.46	42
Total subscale (T score)	77.2 (11.1)	67.2 (13.5)	67.0 (14.8)	12.2	<.001	81	.78
Teachers Conners' Global Index							
Restless/impulsive subscale (T score)	71.8 (9.9)	63.7 (13.6)	57.7 (11.4)	17.4	<.001	.68	1.32
Emotional lability subscale (T score)	69.0 (14.1)	62.6 (14.1)	57.8 (14.3)	7.5	.001	45	.79
Total subscale (T score)	73.0 (11.3)	65.0 (14.1)	58.5 (12.8)	15.3	<.001	63	1.20
Clinical Global Impressions - Improvement	3.85 (.65)	2.99 (.81)	2.82 (1.06)	29.4	<.001	1.17	1.17

only parent ratings of response were used in this analysis used due to incomplete teacher data.

Prediction of Response. A principal components Analysis was conducted on the z scores (adjusted for age and BPVS) for the primary dependent measures derived from those neuropsychological tasks for which statistically significant baseline differences were found between the present sample of ADHD boys and healthy matched controls (spatial span, spatial working memory, stockings of Cambridge, pattern and spatial recognition, delayed matching to sample, paired associates learning, reaction time and ID/ED shift) (Rhodes *et al.* 2005) Correlations, multiple regressions, ANOVAs and logistic regressions were used to investigate socio-demographic, clinical, neuropsychological and neuropsychopharmacological predictors of clinical response.

Results

Participant Characteristics

There were no differences between groups at baseline with respect to age [$F < 1$], BPVS percentile rank [$F < 1$], parent-rated, or teacher-rated ADHD composite Conners' scores [both $F < 1$]. There were also no differences with respect to the incidence of co-morbid disorders other than separation anxiety disorder [$F = 3.4$, $p < .04$]. Three boys with this diagnosis took placebo during the first chronic session. Participant progress through the study is described in the CONSORT diagram, which is available online as supplemental information.

Clinical Response to MPH Treatment

Chronic treatment with MPH .3 and .6 mg/kg improved functioning as measured by all subscales of the Conners' scales and by Clinical Global Impression-Improvement scale (see Table 3). There were no differences between the two MPH doses, although there was a nonsignificant trend for increased response with increased MPH dose on teacher-rated Conners' scores. 'Responder' status with MPH .3mg/kg was confirmed for 20 of 59 (33%) and with MPH 6mg/kg for 27 of 63 participants (43%). Fifty-eight participants provided data on both doses of MPH; 24 (41%) were 'nonresponders', 8 (11%) 'responded' to .3, but not .6mg/kg, 15 (26%) 'responded' to .6 but not .3mg/kg, and 11 (19%) 'responded' to both doses.

Effects of MPH on Neuropsychological Performance

Effects of Repeated Testing. Fourteen of the 22 measures reported in Table 4 changed significantly between baseline and chronic placebo testing, with all but one showing robust improvements (Cohen's *d* up to 1.61). It is likely that these changes represent the influence of practice and learning effects. One notable exception was the measure of accuracy on the spatial recognition memory task where performance worsened by .75 standard deviations from baseline to chronic placebo.

Chronic MPH Improved Accuracy and Speeded Performance on a GoNoGo Task

MPH reduced mean errors for distractors (ERD) during both Block 1 (the 'shift' block) [$F(2,116) = 4.1$, $p < .02$] and Block 2 [$F(2,116) = 5.9$, $p < .005$]. MPH .3mg/kg ($p < 03$) reduced errors during Block 2 and .6mg/kg during both Blocks ($p < .01$ and $p < 004$). There was also a significant overall effect of MPH to shorten response latencies during Blocks 1 [$F(2,116) = 4.1$, $p < .02$] and 2 [$F(2,116) = 3.1$, $p = .049$]. This was accounted for by 6mg/kg MPH shortening response latencies relative to placebo ($p < .005$).

Spatial Span and Spatial Working Memory. There was no effect of MPH on spatial span score ($F(2,116) < 1$), nor on any measures from the spatial working memory task (see Rhodes *et al.* 2004).

Stockings of Cambridge. There was no effect of MPH on the number of minimum move solutions [$F(2,116) = 1.9$, $p = .16$], but there was a significant effect of ORDER [$F(2,58) = 5.38$, $p < .007$] and a significant interaction between MPH and ORDER [$F(4,116) = 3.3$, $p < .02$]. Re-analysis with SESSION as a within-subjects and GROUP as a between-subjects factor [$n = 24$ per group] revealed no significant effect of GROUP [$F(2,68) = 2.1$, $p = .13$], although performance improved overall from baseline to chronic challenge [$F(1,68) = 17.6$, $p < .001$]. There was a significant interaction between SESSION and GROUP [$F(2,68) = 3.3$, $p < .04$], but planned contrasts revealed no significant differences between the groups (all $p > .05$). There were no significant effects of MPH on initial (ITT) [$F(2,116) < 1$] or subsequent (STT)[$F(2,116) = 1.6$, $p = .21$] thinking times. There was a MPH and ORDER interaction for STT [$F(4,116) = 3.1$, $p < .02$]; planned contrasts revealed that boys taking placebo at the first chronic test session had longer STT than when taking .3mg/kg ($p < .049$) or .6mg/kg ($p < .043$).

Pattern Recognition Memory. Chronic .3 mg/kg and .6 mg/kg MPH enhanced accuracy on this task but exerted no effect on speed of response (see Rhodes *et al.* 2004).

Spatial Recognition Memory. MPH improved accuracy on the spatial recognition task [$F(2,116) = 16.3$, $p < .001$]. Planned contrasts revealed improved performance when taking both .3mg/kg ($p < .001$) and .6mg/kg ($p < .001$) MPH doses relative to the performance deterioration observed with placebo. There was a significant effect of MPH to slow responses when making correct [$F(2,116) = 10.08$, $p < .001$] and incorrect [$F(2,114) = 3.8$, $p < .03$] responses, attributable to the differences between

Table 4. Neuropsychological Response to Methylphenidate

		Chronic Challenge (collapsed across order)			*p*		Effect Size (d)		Effect Size (d)
Measure	Baseline	Placebo Mean (SD)	.3 mg/kg Mean (SD)	.6 mg/kg Mean (SD)	Pla vs. .3 mg/kg	Pla vs. .6 mg/kg	Pla vs. .3 mg/kg	Pla vs. .6 mg/kg	Baseline vs. Placebo
GoNoGo									
Errors for Distractors b1	2.39 (1.47)	1.59 (1.5)	1.35 (1.4)	1.2 (1.4)	NS	.01		.27	.54
Errors for Distractors b2	2.27 (1.65)	1.62 (1.6)	1.27 (1.4)	1.14 (1.3)	.03	.004		.33	.4
Reaction Time to Targets b1 (log10)	2.66 (.09)	2.70 (.07)	2.68 (.09)	2.67 (.09)	NS	.005		.37	.5
Reaction Time to Targets b2 (log10)	2.67 (.09)	2.69 (.07)	2.68 (.09)	2.69 (.08)	.02	NS	.12		.25
Spatial Span									
Span Score[a]	5.07 (1.47)	5.48 (1.7)	5.7 (1.6)	5.69 (1.5)	NS	NS			.26
Spatial Working Memory									
Total Between Search Errors[a]	50.84 (21)	39.9 (20.6)	38.68 (23.0)	35.9 (19.8)	NS	NS			.53
Strategy Score[a]	36.32 (5.1)	35.15 (4.0)	34.4 (5.0)	34.4 (5.2)	NS	NS			.26
Stockings of Cambridge									
No. Solved in Minimum Moves	7.2 (2.1)	8.33 (1.9)	8.84 (2.2)	8.84 (2.1)	NS	NS			.57
Initial Thinking 5 Move (log 10)	3.59 (.34)	3.54 (.40)	3.63 (.38)	3.64 (.35)	NS	NS			.14
Subsequent Thinking 5 Move (log 10)	2.83 (.58)	1.88 (1.16)	2.08 (1.06)	2.28 (.97)	NS	NS			1.04
Pattern Recognition % Correct[a]	80.78 (13.1)	81.76 (13.3)	86.0 (12.9)	87.8 (12.5)	<.001	<.001	.32	.47	.07
Spatial Recognition % Correct[a]	68.21 (13.9)	57.8 (14.0)	67.2 (14.4)	68.9 (13.4)	<.001	<.001	.66	.81	−.75
Latency Correct (log 10)	3.32 (.15)	3.27 (.16)	3.3 (.15)	3.37 (.15)	NS	<.001		.64	.32
Latency Incorrect (log 10)[a]	3.27 (.14)	3.32 (.17)	3.34 (.2)	3.4 (.15)	NS	.01		.50	.32
Delayed Matching to Sample									
Simultaneous % Correct[a]	90.93 (15.5)	85.20 (18.0)	91.34 (13.6)	95.38 (9.2)	<.001	<.001	.38	.71	.34
Delay (0, 4 and 12 sec combined)[a]									
% Correct	59.52 (17.8)	56.04 (19.2)	65.78 (21.23)	68.82 (16.29)	<.001	<.001	.48	.72	.19
Paired Associates Learning									
Stage Reached	7.96 (.26)	8 (0)	8 (0)	8 (0)	NS	NS	Ceiling Effect		
Total Errors[a]	11.61 (11.5)	6.67 (6.6)	5.73 (5.74)	5.45 (5.6)	NS	NS			.53
Total Trials[a]	12.76 (4.1)	7.7 (2.2)	7.33 (2.03)	7.20 (1.9)	NS	NS			1.61
ID/ED Stage Reached Score[a]	7.5 (1)	7.95 (.99)	8.16 (.95)	8.02 (.97)	NS	NS			.45
Reaction Time									
Reaction Time Latency: 5 Choice (log 10)	2.62 (.09)	2.86 (1.1)	2.62 (.11)	2.62 (.11)	NS	NS			.24
Movement Time Latency: 5 Choice (log10)	2.63 (.26)	2.67 (.35)	2.63 (.12)	2.66 (.12)	NS	NS			.13

ID/ED, Intradimensional-Extradimensional Set Shifting; ADHD, attention deficit hyperactivity disorder.

[a]Measures on which ADHD boys demonstrated baseline performance deficits compared to healthy boys (Rhodes, Coghill, and Matthews 2004, and submitted).

.6mg/kg MPH and placebo [correct ($p < .001$), incorrect ($p < .01$]. There were no correlations between response latencies and accuracy of responding.

Delayed Matching to Sample. Chronic .3 mg/kg and .6 mg/kg MPH enhanced accuracy of performance of simultaneous matching to sample without affecting speed of response. Chronic MPH enhanced accuracy and slowed response latencies for correct choices under the delay conditions of this task (see Rhodes *et al.* 2004).

Paired Associates Learning (PAL). All participants reached the final stage with chronic MPH treatment. There was no effect of MPH on total number of trials required to complete the task [$F(2,114) = 2.1$, $p = .125$], nor on total errors made [$F(2,114) = 1.4$, $p = .2$]. There was a significant interaction between MPH and ORDER for both total trials [$F(4,114) = 4.7$, $p < .002$] and errors [$F(4,114) = 5.6$, $p < .001$]. Planned contrasts revealed that boys who took placebo during the first chronic session required more trials than when taking .3mg/kg ($p < .032$) or .6mg/kg ($p < .002$) MPH. Re-analysis with SESSION and GROUP [$n = 24$ in each treatment group] revealed no significant effect of GROUP on total trials [$F(2,68) < 1$] nor total errors [$F(2,68) < 1$]. There was a significant effect of SESSION for both total trials [$F(1,68) = 196.1$, $p < .001$] and errors, but no significant interaction between SESSION and GROUP (total trials [$F(2,68) < 1$], total errors [$F(2,68) < 1$]), suggesting an improved performance that could not be attributed to MPH.

Reaction Time. There was no effect of MPH on reaction time latencies during simple [$F(2,116) = 2.3$, $p = .13$] or 5-choice [$F(2,116) = 2.9$, $p = .09$] conditions.

Attentional Set-Shifting (ID/ED). There was no significant effect of MPH on stage reached on the ID/ED task [$F(2,116) = 1.78$, $p = .17$]. There was no significant effect of MPH on errors made prior to [$F(1.7, 3.5) = 2.72$, $p > .05$], during [$F(2,116) = 2.1$, $p = .13$], or after [$F(2,116) = 1.1$, $p = .34$] the extradimensional shift stage.

Baseline Predictors of Clinical Response

Four components (Table 5) emerged from a principal components analysis corresponding to "paired associates learning," "working memory and planning," "recognition memory," and "mixed." Baseline prediction of clinical response was assessed separately for each dose level using several statistical methods. Multiple regression analyses with neuropsychological performance on each of these components, sociodemographic and

Table 5. Principal Components Analysis of Baseline Neuropsychological Performance Data

	Component			
	1 "Paired associates learning"	2 "Mixed"	3 "Working memory and planning"	4 "Recognition memory"
Paired Associates Learning, Total Errors	.972			
Paired Associates Learning, Total Trials	.972			
5-Choice Reaction Time		−.737		
ID/ED Shift, Total Trials		−.675		
Spatial Span		.533		
Spatial Working Memory, Strategy Score			−.794	
Spatial Working Memory, Between Search Errors			−.732	
Stockings of Cambridge, Solved in Minimum Moves			.701	
Delayed Matching to Sample, Total Percent Correct				.780
Pattern Recognition, Percent Correct				.619
Spatial Recognition, Percent Correct				.476

ID/ED, Intradimensional-Extradimensional Set Shifting. Extraction Method: Principal Components Analysis. Rotation Method: Oblimin with Kaiser Normalization. Rotation converged in 20 iterations.

baseline clinical variables as predictors and total change score from placebo according to Conners' Global Index—Parent (CGI-P) was the outcome variable. These same predictor variables were entered into two separate ANOVAs with responder status as independent variables.

For .3 mg/kg, only the "recognition memory" component predicted response (multiple regression; $r^2 = .19$, $F(1,43) = 10.1$, $p = .003$, ANOVA $F(1,57) = 5.3$, $p = .025$), poorer baseline performance predicted superior response to medication. For .6mg/kg, no variables predicted response to medication in the multiple regression and only BPVS score differentiated between the groups in the ANOVA [$F(1,61) = 6.7$, $p = .012$] with 'responders' having higher BPVS scores than nonresponders.

Further regression analysis indicated that the baseline "recognition memory" contribution at .3mg/kg was accounted for by delayed matching to sample (DMtS) performance, with poorer (DMtS) baseline performance predicting a better response to medication. (For a fuller discussion of these findings see online supplemental information.)

Neuropsychopharmacological Predictors of Clinical Response

For MPH .3mg/kg 'responders', GoNoGo Block 2 ERD and RTT, spatial and pattern recognition (% correct) and DMtS (total % correct, plus 0, 4 and 12 sec delays) change scores (placebo vs. .3mg/kg) were entered as predictors within a correlational regression analysis with CGI-P change score as the dependent variable. Only Block 2 ERD performance improvement correlated significantly with clinical response ($p = .002$) and was retained in the best fit equation ($r^2 = .17$, $F(1,44) = 8.9$, $p = .005$). For .6 mg/kg 'responders' there were no significant correlations. (For a fuller discussion of these findings see online supplemental information.)

Discussion

With its short half-life and duration of action, MPH only exerts clinically meaningful therapeutic effects when administered chronically. Accordingly, acute effects may be of minor relevance. The present study is the first to have evaluated the neuropsychological effects of chronically administered MPH, in stimulant naive subjects with ADHD, using a prospective, randomized, controlled, crossover design These data, which confirm and extend those published previously (Rhodes *et al.* 2004, 2005, 2006), are important for clinical and scientific reasons.

Consistent with the 'acute response' data that we have previously reported (Rhodes *et al.* 2006), but contrary to predictions based on existing literature, chronic MPH failed to enhance performance on neuropsychological tasks with a prominent 'executive' component, with the exception of aspects of a GoNoGo task. Intriguingly, MPH significantly enhanced performance on two visual memory tasks without prominent executive demands (pattern and delayed matching to sample) and reversed performance decline on a third (spatial recognition memory). A detailed analysis of baseline, drug naive, neuropsychological and neuropsychopharmacological measures as potential predictors of clinical response to MPH suggests that each makes a statistically significant, but modest, predictive contribution.

Study Limitations

Limitations which arise due to the cross-over, repeat-testing design include loss of novelty and the emergence of practice, learning and ceiling effects on neuropsychological performance. Rabbitt (1997) and Lowe and Rabbitt (1998) highlighted the vulnerabilities of tests of "executive functioning" to such factors. It is, possible that the moderate to large practice effects for aspects of spatial working memory, stockings of Cambridge, GoNoGo, ID/ED shift and paired associates learning may have diminished our ability to identify treatment effects on these tasks. However, these factors cannot account for the differences in findings between the current study and previous studies using identical tasks with similar, but less robust, methods. Further studies with large sample sizes and alternative trial designs will be required to fully address these issues.

Interpretation of our data is also hindered by the absence of reliable and valid measures of treatment adherence. Although assigned to a specific treatment for a defined period of time, we cannot be certain that the participant did indeed take medication as prescribed, nor that other stimulant drugs were avoided. It is also unfortunate that we were unable to use teacher ratings of response. There was a suggestion that teachers and parents differentially rated response to medication with a trend for teachers to rate greater improvements with higher dose MPH. It is therefore possible that an analysis of the predictors of teacher-rated response would have produced different results to those reported for parent-rated response.

What Does Chronic MPH Do?

Taken alongside our 'acute response' data (Rhodes *et al.* 2004, 2006) and those of other groups (Barnett *et al.* 2001; Bedard *et al.* 2004; Kempton *et al.* 1999; Mehta *et al.* 2004), the present results support the contention that MPH selectively enhances discrete aspects of neuropsychological functioning (Gao and Goldman-Rakic 2003) However, the current findings are striking in that they fail to substantiate; indeed they contradict, key aspects of existing literature. Specifically, the hypothesis that MPH would selectively enhance performance on neuropsychological tasks with prominent executive demands was not supported. Baseline assessments revealed a wide range of deficits in executive and nonexecutive neuropsychological functioning in ADHD boys compared with healthy controls (see Table 3) (Rhodes *et al.* 2005). MPH failed to restore function across many domains, following both acute (Rhodes *et al.* 2006) and chronic administration. Specifically, previously reported acute MPH performance improvements on Spatial Working Memory (Barnett *et al.* 2001; Bedard *et al.* 2004; Kempton *et al.* 1999; Mehta *et al.* 2004) ID/ED (Kempton *et al.* 1999; Mehta *et al.* 2004) and Stockings of Cambridge (Kempton *et al.* 1999) performance were not replicated. These contradictory findings may relate to differences in study methods, statistical analyses and/or the possible practice effects noted above. Previous studies have made significant design compromises including the use of nonrandomized and uncontrolled protocols (Barnett *et al.* 2001; Kempton *et al.* 1999), small samples with nonstandard assessment procedures (Kempton *et al.* 1999; Mehta *et al.* 2004), inclusion of previously medicated subjects with the potential for withdrawal and carryover effects of medication (Bedard *et al.* 2004; Mehta *et al.* 2004), and the use of only a single dose of MPH. It is also possible that differences in study inclusion criteria may be important. Previous studies' inclusion criteria were based on DSM-IV. We recruited participants meeting diagnostic criteria for both DSM-IV ADHD combined type and ICD-10 hyperkinetic disorder. The similarities and differences in neuropsychological functioning and response to medication between children diagnosed under each of these systems are not well described and merit further investigation. Our data support the contention that the effects of MPH on neurocognitive functioning should not be considered as a simple restoration of baseline impairments (Rapport and Kelly 1991), particularly of psychological processes with high 'executive' demands. Indeed, the only evidence of improved performance on such a task in the present study was that seen with the GoNoGo task. Even here, it is worth recalling that, at baseline, no differences in performance were identified between ADHD and control subjects (Rhodes *et al.* 2005).

Stimulant effects on tasks with relatively modest 'executive' demands have been relatively understudied. We have previously reported that both acute and chronic MPH improved performance on DMtS and pattern recognition tasks (Rhodes *et al.* 2004) We now report that, although performance improvements were not seen on a spatial recognition memory task following acute MPH (Rhodes *et al.* 2006), chronic exposure maintained subjects' performance on this task whereas deterioration in performance was observed under placebo conditions. Interestingly, these three tasks constituted the "recognition memory" component identified through principal components analysis.

As previously reported for the effects of acute MPH on the DMtS and pattern recognition memory tasks, there was again no relationship between accuracy of responding and speed of responding. This suggests that, whilst one effect of MPH may be to improve "regulatory ability" (Berman *et al.* 1999; Douglas 1999), improvements in performance accuracy cannot be solely attributable to these improvements (nor indeed to improved 'behavioral inhibition' as has been suggested (Barkley 1997)), but may instead represent true improvements in nonworking mnemonic functioning. Interestingly, the shortened response latencies in a complex reaction time task which were observed following acute MPH were not replicated with chronic MPH. This, and the previously reported amelioration of medication effects on the DMtS with chronic, as compared to acute, MPH (Rhodes *et al.* 2004), suggests that, at least with respect to these tasks, a form of behavioral tolerance to MPH may develop. Conversely, the improvements in performance on the spatial recognition and GoNoGo tasks seen after chronic, but not acute, administration may reflect a form of behavioral sensitization. These speculative possibilities require further investigation.

Prediction of Clinical Response

We are unaware of previous studies investigating neuropsychological predictors of clinical response to MPH. Evaluation of clinical and demographic predictors of response have yielded conflicting results. For example, whilst both Taylor (1987) and Buitelaar (1995) found younger age to be a positive predictor of clinical response to MPH, Taylor observed greater pretreatment attentional impairment, hyperactivity, and lower IQ scores in 'responders' Buitelaar, however, found the opposite pattern. In the present study, greater hyperactivity at baseline and higher BPVS scores predicted clinically and statistically significant response to MPH (.6 mg/kg). However, these variables accounted for a very small component of the overall variance and their utility in predicting individual response seems negligible. Denney and Rappoport (1999) recently applied a range of theoretical and statistical models to assess predictors of teacher-rated response to MPH. They identified numerous weaknesses in previous studies and failed to replicate many previously reported findings. They concluded that a comprehensive model of MPH response will be dependent upon a wide range of factors that cannot reasonably be reduced down to any single measure. Our data support this. Denney and Rappoport also pointed out that a comprehensive model of MPH response needs to capture several levels of analysis (including both biological and behavioral) as well as the relationships between these levels.

The CANTAB battery is a potentially useful tool to develop causal models as the neural substrates for some of the tasks have been identified. For example, the finding that although MPH improved performance on two tasks conventionally associated with frontal lobe functioning (spatial recognition and GoNoGo) it also improved performance on two visual memory tasks for which the initial patterns of deficits in ADHD boys resembled those seen following medial temporal rather than frontal lobe damage (Owen *et al.* 1995) This, in addition to the finding that baseline performance on the DMtS task contributed to the prediction of clinical response to low dose MPH, supports the hypothesis that nonworking memory dysfunction and aspects of temporal lobe functioning may make an important contribution to ADHD pathophysiology (Castellanos and Tannock 2002; Rhodes *et al.* 2004) However, that clinical response to MPH was only associated with neuropsychological response to MPH on a single measure from a single task (GoNoGo), and that this task did not itself discriminate between ADHD boys and healthy controls at baseline (Rhodes *et al.* 2005), mandates caution. Although there are measurable deficits on a range of neuropsychological tasks, and whilst some of these deficits are, apparently, ameliorated by MPH, we must consider the possibility that

they may not be meaningfully related to the core functional impairments in ADHD. On the other hand, it could be that had we been able to utilize teacher ratings of response we would have identified a greater number of predictors. Also, it remains plausible that improvements in neuropsychological functioning mediate improvements in overall functioning and thus reduce overall behavioral impairment in a manner which is either more subtle, or less easily observed. Further, the incomplete overlap between those responding to high and low doses of MPH and the differential weak predictors for low and higher dose medication raises the possibility that MPH actions are mediated differently at different doses.

In conclusion, the present study supports the contention that MPH selectively enhances neuropsychological functioning in ADHD, with the most prominent effects observed on three tasks which invoke relatively modest 'executive' demands and which were represented in a single component, "recognition memory", identified through principal components analysis. These neuropsychological findings, paired with the positive clinical responses observed in the same participants, strengthen the hypothesis that clinically important ADHD-related neurocognitive deficits are diverse and that, even following clinical improvement with MPH, there remain unaffected deficits. These may require additional, or alternative, therapeutic interventions. These data may assist in the identification of useful cognitive and behavioral endophenotypes for further study. It is important to note that, contrary to previous suggestions (Robbins and Sahakian 1979), MPH does not appear to impair performance on any of the studied tasks.

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All authors had full access to all the data in the study.

Supplementary material cited in this article is available online.

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