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Towards an understanding of unique and shared pathways in the psychopathophysiology of ADHD

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Abstract

Most attention deficit hyperactivity disorder (ADHD) research has compared cases with unaffected controls. This has led to many associations, but uncertainties about their specificity to ADHD in contrast with other disorders. We present a selective review of research, comparing ADHD with other disorders in neuropsychological, neurobiological and genetic correlates. So far, a specific pathophysiological pathway has not been identified. ADHD is probably not specifically associated with executive function deficits. It is possible, but not yet established, that ADHD symptoms may be more specifically associated with motivational abnormalities, motor organization and time perception. Recent findings indicating common genetic liabilities of ADHD and other conditions raise questions about diagnostic boundaries. In future research, the delineation of the pathophysiological mechanisms of ADHD needs to match cognitive, imaging and genetic techniques to the challenge of defining more homogenous clinical groups; multi-site collaborative projects are needed.

Background

Comparisons between ADHD and other disorders are needed for several purposes. Nosologically, it is desirable to establish the discriminative as well as the predictive validity of a condition, and so far this has only been partly achieved. Etiologically, it is crucial to understand whether biological associations are for psychopathology in general or ADHD in particular. Developmentally, it seems that ADHD is heterogeneous clinically (Biederman *et al.*, 1992), genetically (Willcutt, Penninton & DeFries, 2000) and neurophysiologically (Banaschewski *et al.*, 2003a) – and clues to understanding this should come if some components of ADHD can be identified as common to several disorders while others are unique. Clinically, the co-existence of several disorders is so common that it cannot be understood unless we know whether the co-existent conditions are truly different disorders with different associations. If ADHD and the comorbid disorder are each associated with different correlates, a double dissociation between the clinical disorders can be obtained, that is, both disorders can be separated by the profile of their correlates. Examining the profile of correlates of the comorbid group relative to the single-disorder groups may then suggest the etiology of comorbidity between the two disorders. Such comparisons between groups, however, may fail to be illuminating if the groups are themselves heterogeneous (Mirowsky & Ross, 1989). As long as etiological pathways are unknown, the question of whether the samples investigated are pathophysiologically homogeneous cannot be answered conclusively.

The central focus of this selective review of research in the fields of neuropsychology, neuroimaging and genetics is the specificity of the associations of ADHD and the etiological pathways they suggest, understood on the basis of comparisons between ADHD and some other disorders: schizophrenia, autism, oppositional defiant disorder/conduct disorder (ODD/CD), and reading disability (RD). We have not tried to be comprehensive, and recognize the frequency with which ADHD co-occurs with still more problems such as developmental co-ordination disorders, mental retardation, tics and anxiety states. Rather, we have selected disorders for comparison that seem likely to be of particular interest for illuminating the nature of ADHD.

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Neuropsychology

ADHD

Numerous studies indicate that ADHD is associated with deficits on a variety of neuropsychological measures which come from different psychological models of ADHD (Sergeant, Geurts, Huijbregts, Scheres & Oosterlaan, 2003). Strong evidence indicates that children with ADHD are impaired in various executive function (EF) domains (Barkley, Grodzinsky & DuPaul, 1992; Pennington & Ozonoff, 1996; Sergeant, Geurts & Oosterlaan, 2002). However, mean effect sizes for EF measures seem to be only moderate, suggesting that none of these deficits is a necessary or sufficient cause of ADHD (Willcutt *et al.*, 2003). Furthermore, evidence for other abnormalities has been presented, for example, altered motivational processes (Sagvolden, Johansen, Aase & Russell, in press; Sonuga-Barke, 2002), or an insufficient ability to regulate the state of activation (Kuntsi, Oosterlaan & Stevenson, 2001; Sergeant *et al.*, 2002). Response variability across a variety of tasks is one of the most consistent findings associated with ADHD, particularly when motor decision or effortful response organization is required (Castellanos & Tannock, 2002; Rubia *et al.*, 1999a; Sergeant & Scholten, 1985). Neuropsychological and event-related potential (ERP) studies have found that measures of domains with less of an executive component, such as processing speed, rapid naming, fine and gross motor skills, timing functions, and early and automatic information processing stages, are impaired as well (Banaschewski *et al.*, 2003a; Brandeis *et al.*, 2002; Rubia *et al.*, 1999a; Smith, Taylor, Rogers, Newman & Rubia, 2002; Tannock, Martinussen & Frijters, 2000). An association between ADHD and motor inhibitory control deficits is one of the most consistent findings (Nigg, 2001; Willcutt *et al.*, 2003). Some results suggest that deficient response inhibition may be a marker for a genetic susceptibility to ADHD (Crosbie & Schachar, 2001), but inhibitory control deficits as such are not a unique marker for ADHD, and have also been found in CD, ADHD + ODD/CD (Oosterlaan, Logan & Sergeant, 1998), RD (Purvis & Tannock, 2000; Willcutt *et al.*, 2003), and autism (Geurts, Verte, Oosterlaan, Roeyers & Sergeant, 2004; Nyden, Gillberg, Hjelmquist & Heiman, 1999). Nevertheless, inhibition deficits may be more pervasive in children with ADHD, and different mechanisms may be involved in ADHD from those in other disorders (Purvis & Tannock, 2000).

Schizophrenia

Subtle cognitive, developmental and social impairments can be observed in children long before the onset of psychosis (Hollis, 1995). Children of adults with schizophrenia show abnormalities on tasks involving executive control, motor function, sustained attention and rapid information processing – similar to those of children with ADHD (Marcus *et al.*, 1987). Inattention and EF deficits occur in both disorders. In a recent meta-analysis of schizophrenia case-control studies, the largest effect sizes are found for cognitive flexibility (Wisconsin Card Sorting Task, WCST), verbal fluency, interference control (Stroop) and planning (Tower of London/Hanoi, ToH) – very similar to the pattern found in ADHD (Pennington & Ozonoff, 1996). Working memory (WM) impairments have been found both in adult schizophrenia (Gold, Carpenter, Randolph, Goldberg & Weinberger, 1997) and ADHD (Kempton *et al.*, 1999). Similar deficits in verbal and spatial WM performance were found in children with early-onset schizophrenia and children with ADHD (Karatekin & Asarnow, 1998). Evidence to support the hypothesis that a deficit in response inhibition might be more central than a working memory deficit for the pathophysiology of ADHD comes from comparison of eye movement measures. While both schizophrenic and ADHD adult subjects show disinhibition on the delayed oculomotor response task, only schizophrenic subjects show evidence of decreased WM for saccades (Ross, Olincy, Harris, Sullivan & Radant, 2000).

Autism

EF deficits are common in autism too (Pennington & Ozonoff, 1996). Children with autism may also show problems less associated with ADHD – in theory of mind (though studies are contradictory) and in weak central coherence (Booth, Charlton, Hughes & Happe, 2003). A few studies have compared autism and ADHD directly. Ozonoff and Jensen (1999) found a double dissociation between both disorders. Children with autism showed difficulties in planning and cognitive flexibility, but not in inhibition, whereas children with ADHD showed the opposite pattern. Nyden *et al.* (1999) failed to replicate this finding. Both ADHD and autism were associated with a response inhibition deficit, and only children with ADHD showed deficits in flexibility. Geurts *et al.* (2004) also failed to obtain a double dissociation. Children with High Functioning Autism (HFA) demonstrated deficits in all EF domains, except interference control and working memory. ADHD was associated with EF deficits in inhibiting a prepotent response and verbal fluency. Strikingly, EF measures hardly discriminated between ADHD and HFA. Compared to children with ADHD, the HFA group showed more difficulties only with cognitive flexibility and planning.

ODD/CD

Most studies found that ADHD, but not ODD/CD, is associated with deficits in EF. With almost 400 children included, the largest study found evidence for planning deficits in children with ADHD combined type (not inattentive type) that were independent of oppositional and conduct disorders (Klorman *et al.*, 1999). Cognitive flexibility did not discriminate between groups. Clark, Prior and Kinsella (2000) found that adolescents with ADHD performed worse on two EF measures independently of ODD/CD. Similar results were obtained using three different measures of WM (Kalff *et al.*, 2002). In a meta-analysis of the stop task (response inhibition), Oosterlaan *et al.* (1998) concluded that both disorders are associated with inhibitory deficits. More recent studies, however, showed that ADHD, but not ODD or CD, was associated with inhibitory dysfunction (Kooijmans, Scheres & Oosterlaan, 2000; Oosterlaan & Sergeant, 1998; Schachar, Mota, Logan, Tannock & Klim, 2000). Other studies are consistent with the idea that both ADHD and ODD/CD are associated with EF deficits. Thus, adolescents with ADHD as well as those with CD performed poorly on the Stroop task (MacLeod & Prior, 1996). Aronowitz *et al.* (1994) found that CD was associated with poor cognitive flexibility (WCST) and several other EF deficits (Rey-Osterreith complex figure test), while ADHD was associated only with poor flexibility, suggesting that ADHD and ODD/CD may differ in terms of their profile of EF deficits.

Reading disability

Individuals with RD are impaired in several abilities in which children with ADHD are also weak: processing speed (Rucklidge & Tannock, 2002; Tannock *et al.*, 2000), time processing (Smith *et al.*, 2002), EF domains such as verbal WM (Rucklidge & Tannock, 2002; Willcutt *et al.*, 2003), cognitive flexibility (Weyandt, Rice, Linterman, Mitzlaff & Emert, 1998), planning (Klorman *et al.*, 1999), and response inhibition (Purvis & Tannock, 2000; Willcutt *et al.*, 2003). Deficits in phonological processing are more specific to RD (Pennington, Groisser & Welsh, 1993; Wagner & Torgesen, 1987), which may be related to an auditory temporal processing deficit (Tallal, 1980), deficits in rapid sequential processing (Wagner & Torgesen, 1987) or a deficit in the automatization of skills (Nicolson, Fawcett & Dean, 2001). Pennington *et al.* (1993) reported that the comorbid group exhibited significant phonological processing deficits in the absence of the EF deficits typically associated with ADHD. This may have been an artefact of subject selection: most later studies with larger samples found that the comorbid group exhibited the deficits of both single groups in an additive fashion (Rucklidge & Tannock, 2002; Willcutt *et al.*, 2003).

Neurobiology

ADHD

Structural studies in ADHD have shown reduced volumes – especially in right frontal brain regions, caudate, corpus callosum and cerebellum – and also in parietal, temporal and occipital brain regions (Castellanos *et al.*, 2002; Sowell *et al.*, 2003). The largest structural study conducted so far using combined cross-sectional and longitudinal design revealed that these volumetric abnormalities seem to be evident early in life, persist with age, and show parallel and non-progressive developmental growth curves (except for the caudate where group differences disappeared with age, Castellanos *et al.*, 2002). Abnormalities were not related to medication. Functional imaging studies using SPECT and fMRI have found abnormal brain activation patterns during attention tasks and response inhibition – predominantly in frontal lobes and caudate, but also in parietal lobes. The reduced caudate activation was consistent across all these studies, while the prefrontal lobe has been reported both as overactivated (Vaidya *et al.*, 1998) and underactivated (Rubia, Sergeant, Taylor & Taylor, 1999b).

Schizophrenia

In schizophrenia, as in ADHD, reduced grey matter has been observed in frontal, temporal and parietal brain regions (Rapoport *et al.*, 1997), but with different developmental trajectories. As opposed to the parallel growth curves in ADHD, strikingly *progressive* decline has been found in early-onset schizophrenia in region-specific grey matter loss of parietal, temporal and frontal lobes without changes in white matter (Thompson *et al.*, 2001), suggesting a progressive neurodevelopmental process. Ventricular volume enlargement is described in schizophrenia rather than ADHD (Rapoport *et al.*, 1997). The only study comparing functional imaging data between the two disorders found mirror image activation patterns between adolescent ADHD and adult schizophrenic patients in prefrontal lobes (underactivation in right dorsolateral prefrontal lobe in ADHD, but in left dorsolateral prefrontal lobe in schizophrenia) and in caudate (underactivation in ADHD and overactivation in schizophrenia) during response inhibition (Rubia, 2002). This last finding is in line with anatomical studies finding larger sized caudate, putamen and globus

pallidus in schizophrenia (Gordon *et al.*, 1994), as opposed to the reduced size of these regions in ADHD. A preattentional information processing deficit has been reported both in adolescents with schizophrenia and ADHD (Rund, Oie & Sundet, 1996). Abnormal early sensory processing – evidenced by lack of normal P50 suppression to a second paired auditory stimulus – appears specific for schizophrenia (Olincy *et al.*, 2000). The P50 effect in schizophrenia has a large effect size (1.5) and may reflect specific temporal lobe pathology (Bramon, Rabe-Hesketh, Murray & Frangou, 2004). In contrast, the P300 amplitude attenuation is a non-specific finding. However, differences in lateralization of the P300 are reported: reduction over the left temporal lobe in schizophrenia (Salisbury *et al.*, 1998) and the right hemisphere in ADHD (Oades, Dittmann-Balcar, Schepker, Eggers & Zerbin, 1996).

Autism

In autism, as opposed to ADHD, anatomical studies found *larger* total brain and white matter volumes in most cortical brain regions and in the cerebellum, caudate and globus pallidum (Piven, Arndt, Bailey & Andreasen, 1996). A shared anatomical dysmorphology between autism and ADHD appears to be a smaller corpus callosum (Saitoh, Courchesne, Egaas, Lincoln & Schreibman, 1995). In functional imaging studies, the most consistent finding has been that of reduced frontal and parietal activation during a wide range of tasks (Baron-Cohen *et al.*, 1999), which may not be very different for ADHD.

ODD/CD

No modern imaging studies exist on pure CD independent from its comorbidity with ADHD. Recent ERP studies (Bauer & Hesselbrock, 1999) did show abnormalities in prefrontal lobe activation. Furthermore, electrophysiological activity has been observed to differ between comorbid ADHD + ODD/CD groups and pure ADHD or pure ODD/CD groups (Banaschewski *et al.*, 2003a; Rothenberger *et al.*, 2000). Interestingly, comorbid children appear to be less deviant than either children with ADHD only or children ODD/CD only regarding performance parameters and P3a-amplitudes to cues linked to attentional orienting (Banaschewski *et al.*, 2003a).

Reading disability

The most consistent imaging findings in dyslexia have been those of reduced volume in specific focal brain regions mediating speech and learning such as bilateral inferior prefrontal lobes (pars triangularis) and anterior lobe of the cerebellum, but also left hemispheric temporal and parietal brain regions, in particular planum temporale and parietale (Klingberg *et al.*, 2000; Pennington *et al.*, 1999). In line with these structural findings, functional imaging studies have observed abnormal left prefrontal and left temporo-parietal brain activation in relation to linguistic stimuli (Breier *et al.*, 2003).

Genetics

Twin studies have shown considerable heritability of ADHD with genetic factors explaining 70% to 80% of the phenotypic variance in the population (Thapar, Holmes, Poulton & Harrington, 1999). Molecular genetic studies have linked ADHD to various polymorphisms. However, the known risk alleles are widely distributed in the population and each accounts only for a small increase of risk. No single allele is either necessary or sufficient. Twin and family studies strongly support the role of genetic factors in schizophrenia (explaining about 80% of the phenotypic variance, Harrison & Owen, 2003), autism (about 90%, Shastry, 2003), RD (30–60%, Stevenson, Pennington, Gilger, DeFries & Gillis, 1993), and to some extent in ODD/CD, depending on the source of information. Several regions of the chromosomes, which, it has been suggested, harbour risk genes for autism – 2q24, 15q, 16p13, 17p11 – have also been highlighted in genome-wide scans for ADHD (Smalley *et al.*, 2002). Some common genetic influences may also contribute to the comorbidity of RD and ADHD. A quantitative trait locus study revealed significant bivariate linkage of the chromosome 6p region to both disorders (Willcutt *et al.*, 2002). More recently, suggestive linkage to RD was found in four chromosomal regions including regions on 16p and 17q that had previously been implicated in ADHD (Loo *et al.*, 2004).

Implications for understanding ADHD pathophysiology

(1) Unique and shared pathways

The studies we have reviewed indicate a mixed pattern: many of the findings in ADHD characterize other disorders too, but some may be more specific. The most specific seem to be some of the anatomical changes. Some good candidates (such as delay aversion) have not yet been tested in other disorders. ADHD may not be fully explainable by a primary deficit of behavioural inhibition

causing secondary deficits in other EFs, and thus leading to behavioural symptoms (as proposed by Barkley, 1997). Inhibitory control problems may also be a secondary consequence of attentional problems (Banaschewski *et al.*, 2004; Brandeis *et al.*, 2002), altered motivational processes (Sagvolden *et al.*, in press; Sonuga-Barke, 2002), or an insufficient ability to regulate the state of activation (Kuntsi *et al.*, 2001; Sergeant *et al.*, 2003). More fundamental, simpler problems could also be underlying ADHD deficits, such as a more generalized deficit of processing speed, time processing, motor response organization, or attentional orienting (Brandeis *et al.*, 2002; Sagvolden *et al.*, in press; Sergeant, Oosterlaan & Van der Meere, 1999; Smith *et al.*, 2002). While there is evidence for the hypothesis that EF deficits play a role in the etiology of ADHD (Willcutt *et al.*, 2003), many deficits are shared with other disorders and some differences between ADHD and other disorders may be quantitative rather than qualitative. Comparative neurofunctional and neuroanatomical studies between different psychopathological disorders are needed to establish the specificity of aetiopathophysiology of ADHD. At the present state of research, it appears that while identical brain regions, including the association cortices, the basal ganglia and the cerebellum, are sensitive to a wide range of developmental abnormalities, there seem to be specific differences between ADHD and the other psychiatric disorders in either the development of these brain abnormalities, the exact location, the size of abnormalities, or the laterality.

(2) Heterogeneity

The construct validity of the various psychological processes implicated in ADHD (e.g. attention, response inhibition, working memory, executive function and timing) is often uncertain. The validity of the tasks used to measure these processes needs to be investigated more rigorously (Miyake *et al.*, 2000). Many tasks tap more than one latent dimension of functioning (Tannock, 1998). We also recognize that distinct neuropsychological constructs may partly rely on the same interconnected neuronal circuits (Goldman-Rakic, 1998); and similar neuropsychological processes may rely on different neuronal structures in clinical and control groups. Developmental effects and compensatory processes need to be taken into account. More work needs to be done on the possibility several distinct neuropsychological changes can all result in ADHD behaviour. For instance, Sonuga-Barke (2002) has emphasized the independence of a motivational pathway (delay aversion) and a disinhibitory change; and they seem to be independently associated with the diagnosis of ADHD (Solanto *et al.*, 2001). We do not yet know whether these will be separately associated with other disorders, but it should repay investigation (see Coghill, Nigg, Rothenberger, Sonuga-Barke & Tannock, 2005, this issue). The fronto-striatal circuits considered above may be disrupted at numerous loci with similar functional consequences (Fletcher, 2000). Dysfunctions of these circuits could also be affected by dysfunctions of posterior cortical regions, the cerebellum or ascending arousal systems, which closely interact with the prefrontal cortex and have also been implicated in ADHD. Recent neuropsychological evidence demonstrating temporal processing deficits and non-executive memory deficits suggests the involvement of wider brain systems. The common perception of ADHD as a cortico-striato-thalamo-cortical disorder may be too limited. The overlap of genetic influences on ADHD and comorbid disorders could indicate that some influences have multiple behavioural consequences (pleiotrophy); or could result from uncertainties and overlaps in the definitions of the phenotypes. This raises questions about diagnostic boundaries: the mapping of different cognitive and behavioural abnormalities on to the various DNA changes should be encouraged.

(3) Development

It is difficult to determine through cross-sectional studies whether neurocognitive correlates represent a primary abnormality or a secondary compensation mechanism. Longitudinal studies of developmental trajectories are required using age-appropriate task versions. For example, as long as developmental studies on EF in ADHD are lacking, any hypotheses concerning an etiological primacy of a deficit in EF seems to remain somewhat speculative.

(4) Comorbidity

The specificity of ADHD correlates may be dependent on the presence or absence of comorbid disorders. Stratification according to certain comorbidities is appropriate to study homogeneous ADHD subgroups. For example, ADHD and autism often co-occur, and inclusion of the comorbid group in research is urgently needed. Concerning the comorbidity of ADHD with ODD/CD, some studies suggest that the comorbid condition may constitute a biologically distinct subtype (Banaschewski *et al.*, 2003a; Faraone, Biederman, Mennin, Russell & Tsuang, 1998); others do not. In contrast, recent studies suggest more clearly that the comorbidity of ADHD + RD may represent a true comorbidity, with characteristics of both disorders, caused partly by common genetic influences (Purvis & Tannock, 2000; Willcutt *et al.*, 2003).

Concluding comments

Specific pathophysiological pathways for ADHD have not been identified. Many components of the etiological pathways may well be shared with other conditions, while others may be unique to ADHD. Future studies will need to examine the validity of the complex neurocognitive constructs, decompose the distinct component processes that are involved and develop methods to investigate whether poor task performance reflects the same underlying dysfunction across development and in groups with different disorders. Group differences in cognitive strategies, effort, motivation, or compensation strategies need to be considered. Comparison of pure and comorbid groups will be useful and may need advances in how to measure comorbid states. This will require the use of an extensive battery of well-defined and theoretically based tasks, including several measures of each construct to provide the accurate assessment of the multiple aspects of these multifaceted EF constructs and the investigation of putatively etiologically homogeneous subgroups of the ADHD phenotype. Research on epidemiological samples would be helpful, because at least some inconsistencies across studies using clinical samples, which may be conditioned by referral patterns, might reflect differences in sample composition (Willcutt *et al.*, 2003). The combination of techniques required calls for increasing collaboration between research groups.

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