Neuropsychological assessment and functional magnetic resonance imaging of verbal declarative memory performance in relatives of schizophrenia patients and controls

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Thesis submitted for the degree of

Doctor of Philosophy

University of Edinburgh

2004

Acknowledgements

I acknowledge that this thesis has evolved both through my own efforts and with the collaboration of all those mentioned below.

I would like to extend my gratitude to my supervisors Dr Stephen Lawrie and Professor Eve C Johnstone for their guidance and support throughout the course of my studies. For their help and advice, thank you also to my departmental colleagues, in particular Enrico Simmonotto, Heather Whalley, Patrick Miller, Dominic Job, Elvina Gountouna and Andrew McIntosh.

Thank you to all the Edinburgh High Risk Study (EHRS) participants, for without their patience and commitment this project would not have been possible. Given the magnitude of the EHRS, it would not be possible to name all those who have collaborated on this project over the past ten years. However, I would like to acknowledge the contribution of Majella Byrne and all others who took part in the recruitment and data collection over time.

Finally, thank you to all my family for their tolerance and understanding.

Declaration of Authorship

My contribution to the Edinburgh High Risk Study (EHRS) and to the data presented in this thesis:

Systematic Review

I was solely responsible for the literature search, data collection, and meta-analysis for the systematic review. Andrew McIntosh aided in the construction of meta-analysis plots.

Neuropsychological Assessment data collection and analysis

For the second phase of neuropsychological testing (November 2001- July 2003), I was involved in the administration and scoring of neuropsychological assessments, along with Lesley Harrison, Kirsten Russell, Caroline Brett, and Jonathan Harris. Majella Byrne and Richard Cosway collected data between 1994 and 2000. I was solely responsible for the conduct of the data analyses presented in this thesis, based on the data collected between 1994 and 2004.

Functional MRI encoding & retrieval paradigm data collection and analysis

Enrico Simmonotto and Susanna Flett are responsible for the pilot project of the event related functional MRI verbal memory task in the EHRS (October 2000- October 2001). I was responsible for the operation of the Integrated Functional Imaging System (IFIS) for the functional MRI scanning of the EHRS, at the Western General Hospital between November 2001 and January 2004. Enrico Simmonotto, Susanna Flett, Heather Whalley, and Dominic Job collected data prior to this period between October 2000 and October 2001, and Elvina Gountouna after January 2004. Radiologists of the Department of Clinical Neuroscience operated the GE MRI scanner during the MRI sessions. Enrico Simmonotto devised scripts for the pre-processing and first level analysis of the functional MRI data. I manually carried out all other processes on SPM.

I declare that this thesis is my own work and composition, and the contribution of others to the data collection and analysis has been clearly documented here.

Signed Dated 7/11/05

Abstract of thesis:

Background: While the aetiology of schizophrenia has yet to be established, genetic liability is currently the most robust determinant of propensity for the development of schizophrenia, with a risk rate of between 15 and 20% in first-degree relatives of schizophrenia patients. Unaffected relatives of schizophrenics have shown similar, but less severe neuropsychological impairments, to those seen in schizophrenia patients, which are stable over time in individuals beyond the age of risk for the disorder. Such deficits may be reflective of a genetic vulnerability to the disorder (Byrne et al 2003; (Faraone et al 1999). Declarative memory has emerged as a core cognitive impairment in schizophrenia (Cirillo and Seidman 2002) and evidence shows functional brain response differences between patients and controls in frontal, temporal, and parietal areas during tests of memory (Ragland et al 2004). Nonetheless, it is unclear how far behavioural and functional deficits reflect increased risk, at what stage, if at all, these deteriorate in those who develop the disorder, or whether pre-morbid impairments in those who go on to develop schizophrenia could be predictive of psychosis. The Edinburgh High Risk Study recruited 162 individuals (16-25 years) with at least one first or second degree relative with schizophrenia and 43 closely matched controls. A broad neuropsychological and clinical assessment battery was administered every 18-24 months over 10 years, while participants underwent between 1 and 3 functional magnetic resonance imaging (fMRI) scans during a verbal memory and executive function task over 5 years. Methods: Baseline predictors of schizophrenia, performance changes over 2 neuropsychological assessments, and the influence of genetic liability were examined in high risk participants with (HR+) and without psychotic symptoms (HR-), those who are now ill (Scz) and controls (C), using one-way ANOVAs and repeated measures ANCOVAs. Aspects of verbal and non-verbal learning and memory were also compared between the HR and C in the first 100 participants to undergo a functional MRI scan using one-way ANOVAs. In the same participants, differences between groups in blood oxygen level dependent (BOLD) fMRI brain responses during an event related verbal encoding (word classification) and retrieval task were investigated using fixed and random effects general linear models. Results: On a test of verbal learning at baseline, Scz performed significantly less well than HR However, there were no significant interactions of time by group, and HR showed stable impairments relative to controls on immediate and delayed prose recall, delayed list recall and response suppression across both assessments before and after controlling for IQ. A measure of quantitative genetic liability was inversely correlated with delayed prose recall over time. HR showed poorer cued delayed recall, and less word retention between short and long delay recall trials on a verbal learning test. A visual recognition test also significantly discriminated between HR and C. Behavioural analysis of the fMRI verbal encoding and retrieval task revealed no differences between groups in reaction time or accuracy. However, during a word classification task (encoding) there was a greater BOLD response in the right inferior frontal lobe (BA45/44) in HR relative to C and in the right inferior parietal lobule (BA7/40) in HR+ relative to C and HR-. A greater bilateral cerebellar and left inferior frontal response was also apparent in HR relative to C, and an increased ventral anterior thalamus response in HR- relative to HR+, during correct recognition compared to correct rejection responses. Conclusions: Stable differences in NP performance over time suggest a trait deficit, which is relatively unaffected by the presence of psychotic symptoms and schizophrenia onset, although small numbers might have precluded detection of significant time by group interactions. Poorer verbal memory performance overall in Scz suggests that this deficit is more pronounced in those who go on to develop schizophrenia. Non-verbal learning impairments reflect encoding deficits, while verbal learning impairments reflect encoding and retention difficulties in the HR group. Increased BOLD response in frontal and cerebellar areas in the HR group could be due to a requirement for greater effort to perform the task equivalently to C, and may reflect a biological trait deficit in the brains of relatives of schizophrenia patients. Subtle differences in the inferior parietal lobe between HR+ and HR- and C may be indicative of state related functional abnormalities, which possibly herald the onset of schizophrenia.

Relevant publications based on data within this thesis

Invited speaker at the London Institute of Psychiatry 'Cognition in schizophrenia: improving real life function' conference (16th of September 2004)- 'Cognitive performance over time in a high-risk group'

Marie-Claire Whyte, Caroline Brett, Lesley Harrison, Majella Byrne, Patrick Miller, Stephen M Lawrie and Eve C Johnstone 'Neuropsychological performance changes over time in people at high risk of developing schizophrenia and controls'. Submitted to Biological Psychiatry (revised submission November 2004).

Marie-Claire Whyte, Enrico Simonotto, Heather Whalley, Susanna Flett, Nigel Goddard, Ian Marshall, Richard Shillcock, Eve C Johnstone and Stephen M Lawrie 'Event related fMRI study of a verbal encoding and retrieval task in individuals at high-risk of developing schizophrenia' (in preparation).

Marie-Claire Whyte, Andrew Macintosh, Eve C Johnstone and Stephen M Lawrie 'A systematic review of declarative memory performance in unaffected relatives of schizophrenia patients and controls' (Resubmitted to Schizophrenia Research following changes).

Oral Presentation at the 12th Biennial Winter Workshop on Schizophrenia (2004)- 'Neuropsychological performance over time in people at high risk of schizophrenia and controls' Schizophrenia Research 67 (1), supplement, p18.

Oral Presentation at the Mount Sinai conference on Cognition in Schizophrenia (February 2004)- 'Neuropsychological performance over time in people at high risk of schizophrenia and controls'.

Poster Presentation at the 12th Biennial Winter Workshop on schizophrenia- *Marie-Claire Whyte, Enrico Simmonotto, Heather Whalley, Susanna Flett, Nigel Goddard, Ian Marchall, Richard*

Shillcock, Eve C Johnstone and Stephen M Lawrie (2004) 'An event related fMRI study of verbal encoding and retrieval in subjects at high risk of schizophrenia and controls' Schizophrenia Research 67 (1), supplement, p93.

Poster Presentation at the Edinburgh Neuroscience Day- *Marie-Claire Whyte, Enrico Simmonotto, Heather Whalley, Susanna Flett, Nigel Goddard, Ian Marchall, Richard Shillcock, Eve C Johnstone and Stephen M Lawrie* (2004) 'An event related fMRI study of verbal encoding and retrieval in subjects at high risk of schizophrenia and controls'.

Brief outline of thesis

Neuropsychological assessment

Chapter 1 is a review of the neuropsychology of cognition in schizophrenia and in biological relatives of people with schizophrenia, and includes a systematic meta-analytic review of declarative memory in biological relatives of schizophrenic patients. This is an introduction to chapters 2-5, in which the methods, results and discussions of investigations 1-4 are presented. Investigation 1 compares baseline neuropsychological performance in the high-risk group and those who are now ill. Investigations 2 and 3 analyse performance of these groups and the controls over time, and the influence of predisposition to psychotic symptoms and genetic liability. Investigation 4 explores declarative memory and learning in the first 100 participants to participate in a functional MRI-scanning paradigm. Appendices 1,2 and 3 contain tables and figures to accompany these chapters.

FMRI verbal memory task

Chapter 6 is a review of structural neuroimaging and functional neuroimaging of language and verbal memory in schizophrenia and close relatives of people with schizophrenia. This is an introduction to investigation 5, an event-related fMRI verbal memory task in a high-risk and control group. The methods, results and discussion for this investigation are presented in chapters 7, 8 and 9 respectively. Appendices 6, 7 and 8 contain tables and figures to accompany these chapters.

Note on terminology

For the purposes of brevity alone, throughout this thesis people with schizophrenia will be described as schizophrenics, schizophrenic patients or patients. Abbreviations and acronyms for terms used are included as far as possible under 'Abbreviations and Acronyms', or noted within the text.

Abbreviations and acronyms

AC	Anterior cingulate
APFC	Anterior prefrontal cortex
BA	Brodmann area
BADS	Behavioural Assessment of the Dysexecutive Syndrome
BOLD	Blood oxygen level dependent
C	Control group
CANTAB	Cambridge Neuropsychological Test Automated Battery
COWA	Controlled oral word association
CPT	Continuous Performance Test
CSF	Cerebro-spinal fluid
CT	Computerised tomography
CVLT	California Verbal Learning Test
DATs	Patients with disease of Alzheimer's type
Ds	Depressed patients
DLPFC	Dorsolateral prefrontal cortex
EHRS	Edinburgh High-Risk Study
FSIQ	Full scale IQ
FE	First Episode
fMRI	Functional magnetic resonance imaging
HR	High Risk
HR-	No psychotic symptoms
HR+	With psychotic symptoms
HSCT	Hayling Sentence Completion Test
HVLT	Hopkins Verbal Learning Test
IFC	Inferior frontal cortex
IPL	Inferior parietal lobe
IQ	Intelligence Quotient
LTM	Long term memory
MMSE	Mini-mental state exam
MDs	Manic depressed patients
MTL	Medial temporal lobes
NART	National Adult Reading Test
NP	Neuropsychological performance
OCs	Obstetric complications
PET	Positron emission tomography
PFC	Prefrontal cortex
PHG	Parahippocampal gyrus
PPL	Posterior parietal lobe
RBMT	Rivermead Behavioural Memory Test
RAVLT	Rey Auditory Verbal Learning Test
RCFT	Rey Complex Figure Test
RT	Reaction time
SAT	Standard Achievement Test
SE/s.e.	Standard error
SD/s.d.	Standard deviation
SCZ	Schizophrenic patients
SCZaff	Schizoaffective disorder patients
SCZfffm	Schizophreniform disorder patients
SPECT	Single photon emission tomography
STG	Superior temporal gyrus
STM	Short-term memory
WAIS	Wechsler Adult Intelligence Test
WCST	Wisconsin Card Sorting Test
WISC	Wechsler Intelligence Test for Children
WMS-R	Wechsler Memory Test Revised
WRAT	Wide Range Achievement Test
WJ-R	Woodcock Johnson Psychological Educational Battery Revised
TD	Thought disorder
VF	Verbal fluency
VLFC	Ventrolateral prefrontal cortex

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1.1 Background to schizophrenia

1.1.1 Prevalence and incidence

Schizophrenia is a debilitating and heterogeneous mental condition characterised by disordered thought, language, behaviour, and social function, and is associated with impairments across a range of cognitive domains. Considered among the top ten causes of disability in developed countries, about 1 in 4,000 people can expect to be positively diagnosed within any one year, while over 250,000 people are estimated to be sufferers in Britain at any one time. Although prevalence and incidence may appear to differ across countries, the World Health Organisation showed comparative profiles of schizophrenia development, independent of culture and socio-economic status (Source: National Institute of Mental Health website: http://www.nimh.nih.gov/healthinformation/statisticsmenu.cfm, accessed 11th of June 2004).

The lifetime expectancy of developing the disorder is approximately 1% in the general population, a risk which increases as a function of the number and proximity of affected relatives, such that there is a 10% likelihood of development in individuals with one affected first degree relative, and almost 50 % in the monozygotic twin of someone with schizophrenia (McGuffin et al 1995). Genetic predisposition is therefore the most robust indicator of risk for schizophrenia. However, the less 100% concordance rate emphasises the additional impact of non-genetic factors on the development of this condition. Current research supports the theory of a neurodevelopmental disorder, apparent along two dimensions-the combined genetic and environmental continuum, and the maturational continuum, which continues to impact at various developmental stages throughout life, most notably in early adulthood, prior to the onset of psychosis (Cannon et al 2003).

The manifestation of a disabling symptomatology normally occurs in late adolescence/early adulthood and rarely in individuals under ten or over forty-five years old. While the age of onset is typically earlier in males (peaking in 25 to 34 years age group) than in females (peaking in 35 to 44 years age group), the incidence of schizophrenia is equivalent across genders (Hafner 1987; Mueser and

McGurk 2004). This further suggests that although the genes responsible for the divergence of the sexes early in development may impact on the earlier psychosis onset and the different manifestations of personality and behaviour deviations in childhood, they do not effect the underlying causes of schizophrenia (Crow et al 1995).

In most cases, following an insidious onset, schizophrenia will become a chronic condition leading to life long dependence on welfare services, relatives etc. This, in addition to an uncertain aetiology, disappointing relapse rates (i.e. 11% relapse per month in patients failing to comply with medication treatment plans (Brenner et al 1990; Lang 1999); 80% relapse in patients on placebo, and 48% relapse in those on neuroleptics, followed up over two years (Hogarty et al 1979)), and ineffective treatment (5-25% of patients do not respond to anti-psychotic medication, while up to 50% fail to comply with medication treatment plans), makes it a crippling illness for which the cost is high, not only for the sufferers and their families, but also for the health service. Indeed, 1.6% of the mental health care budget in this country is ascribed to the management of schizophrenia. This highlights the need for more effective interventions and clinical management of this disorder (Brenner et al 1990; Lang 1999).

1.1.2 A brief history of the concept of schizophrenia

Interestingly, the manifestation of a condition resembling schizophrenia and anecdotally described as far back as the Greek era of Hippocrates, is not officially recorded as having existed prior to the 18th century (Frey 1999). Only during the 19th century were there concerted attempts to account for and classify this illness (Johnstone 1999). In 1898 Emil Kraepelin expanded the notion of the term 'dementia praecox' to describe the premature mental deterioration he observed in his patients (Johnstone 1999). By combining three distinct disease entities that shared similar features of early onset, poor prognosis and experience of psychotic symptoms (hebephrenia, catatonia and the dementia paranoides), Kraepelin created the new nosological concept of an endogenous independent functional psychosis. The identification of this cluster of signs and symptoms formed the basis of the classification of dementia praecox. Although his definition was limited by the varied prognosis of his patients and a lack of anatomical evidence to indicate an organic basis, Kraepelin believed the

disorder would reveal itself to be rooted in the pathological changes of the brain's anatomy (Johnstone 1999).

By 1911 the definition of this disorder had been further developed and relabelled by the Psychiatrist Eugen Bleuler. He described schizophrenia, or splitting (schizein) of the mind (phren i.e. thought, language and behaviour) from objective reality, as psychological in nature and not marked by early onset or deterioration of function (Heinrichs 2001). Hallucinations and delusions, which were the core features of Kraepelin's dementia, were considered secondary to the four primary aspects of schizophrenia; ambivalence, disturbed associations in thought and language, impaired affect and autism. Indeed, it was the breadth of the predominantly Bleuler influenced American categorisation of schizophrenia, in contrast to the narrower and more Kraepelian inspired classification in Europe, which fuelled the drive for the standardisation of operational definitions of the psychiatric disorders (Davison et al 2003).

1.1.3 Clinical descriptions of schizophrenia

The birth of the Diagnostic and Statistical Manual of Mental Disorders (DSM) in 1952 heralded the beginning of this standardisation and is now a significant tool in the classification of mental disorders. Both the Tenth Revision of the International Classification of Diseases (ICD-10) and DSM-IV define the characteristic impairments and symptoms associated with schizophrenia, differing only in the time period of social and occupational dysfunction required in an individual before a diagnosis of schizophrenia can be made (ICD-10 is one month and DSM-IV is six months) (Mueser and McGurk 2004).

A clinical diagnosis for schizophrenia will be made (after excluding organic brain disorder, substance abuse disorder, or other disorders associated with psychotic symptoms) based on the identification of signs (the explicit behaviours observable by the psychiatrist) and symptoms (the strange and bizarre experiences reported by the patient), two of which must have been present for at least a month, and in the presence of an apparent decline in social and occupational function for an extended duration of time (Frey 1999; Frith 1992). DSM-IV schizophrenia subtypes are distinct in their different

manifestations of diverse symptoms and signs. These types include paranoid (i.e. prominent delusions and/or hallucinations), disorganised (i.e. disorganised, inventive but incoherent speech and behaviour, flat affect, anhedonia, avolition), catatonic (i.e. catatonic immobility or exaggerated and bizarre motor movements), undifferentiated (meets criteria for schizophrenia, but none of the above sub-types) and residual (no longer meets full criteria for schizophrenia, but still showing some signs of illness) (Davison et al 2003).

Schizophrenia can be more broadly characterised by the presence of two types of symptom (positive and negative) and the current notion of schizophrenia symptoms is very similar to that promulgated by Kraepelin and Bleuler nearly a century ago. Delusions, hallucinations and catatonia continue to be considered important aspects of the disorder, while disorganised speech is an amalgamation of Kraepelin's definition of incoherence and Bleuler's concept of loose associations. Negative signs are inclusive of the impaired affect, autism and ambivalence described by Bleuler (Heinrichs 2001). Kurt Schneider's nine first rank symptoms of schizophrenia (only one of which is required for diagnosis) embody the most significant positive features observed in schizophrenia and all include to a certain extent an element of impaired self-monitoring whereby patients misattribute the generation of the experience of emotion, sensation, belief or voices to an external agent (Frith 1992). Schneider's definition of the central schizophrenic features has prevailed in Europe and has significantly influenced diagnostic criteria for schizophrenia (DSM III), including the Present State Examination-CATEGO system categorisation of psychopathology (McGee et al 1996; Wing et al 1974).

Major positive symptoms, which include bizarre behaviour, false beliefs (delusions i.e. of reference) and aberrant perceptual experiences (hallucinations i.e. second and third person auditory hallucinations), are seen most often in the acute stages of the disease process. They may be seen as representative of excesses in normal functioning, may fluctuate in severity over time, and according to some, may be due to hyperdopaminergic activity in the brain, hence responsive to neuroleptic drugs (Addington 2000; Frith 1992). Crow's type 1 syndrome is associated with positive symptoms, has an acute onset, optimistic outcome, and good premorbid function. The more pervasive negative signs (i.e. affective blunting, alogia, apathy and anhedonia) are those which appear to show a detraction

from normal functioning, are associated with impaired cognition and social functioning, and may reflect structural brain abnormalities such as ventricular enlargement (Frith 1992; Johnstone 1999). Crow's type 2 syndrome is characterised by negative, drug resistant symptoms, an insidious onset with poor pre-morbid function and a pessimistic prognosis (Addington 2000). More recently studies have used the dichotomy of deficit (predominantly negative symptomatology) and non-deficit (predominantly positive symptomatology) patients (Carpenter 1992). However, given that most patients display both negative and positive symptoms, a clear-cut distinction between the two types is problematic. Furthermore, the results of factor analytic studies have suggested that the two dimensional model is insufficient and has therefore been challenged by Liddle's three factor model, which splits positive symptoms into the two dimensions of disorganisation (thought disorder) and reality distortion syndrome (florid psychotic symptoms) plus psychomotor poverty (mainly negative symptoms) (Addington 2000; Davison et al 2003).

The diagnosis of schizophrenia is reasonably stable (except just after illness onset) and 21-30% of individuals treated in their first episode of schizophrenia do not relapse within the first five years (Mueser and McGurk 2004). However, the diagnostic process is open to subjectivity and the lack of an established aetiology for schizophrenia makes psychiatric diagnosis difficult and susceptible to error (Frith 1992). Indeed, the variability in its presentation, prognosis, and by reasoning biological basis, continues to obfuscate an understanding of the aetiology of the disorder.

1.2 Cognition in schizophrenia

Although not embodied in clinical descriptions of the disorder, schizophrenia is also characterised by cognitive dysfunction. Historically, Kraepelin and Bleuler considered neuropsychological functioning such as memory to be relatively preserved in schizophrenia, and while Bleuler noted intellectual abilities to be occasionally altered, this was reported to be a consequence of psychological disturbance and not an underlying dementia. Kraepelin ascribed functional decrements in emotional decisions, volitional judgement and motor ability (defined as 'higher intellectual abilities') to the frontal cortex, whilst language and perceptual disturbances were attributed to aberrations in the temporal lobes.

These first postulations on brain disease and functional localisation remain current today (Andreasen et al 1986; Goldberg and Seidman 1991; McKenna et al 2002; Palmer 2000).

'On various grounds it is easy to believe that the frontal cortex, which is especially developed in man, stands in close relation to his higher intellectual abilities...which in our patients invariably suffer profound loss' (Kraepelin as cited in (Goldberg and Seidman 1991).

Over the past fifty years neuropsychological assessment of patients with schizophrenia has provided evidence of both intellectual impairment and deficits across a diverse range of cognitive domains including motor and spatial ability, attention, executive function, language, learning and memory (Bilder 1996; Heinrichs and Zakzanis 1998). Such an array of deficits coincidentally implicates dysfunction in an equally wide range of brain networks including the frontal, temporal and parietal lobes and the cerebellum.

The purpose of the following review is to present and discuss evidence for cognitive deficits across functional domains in schizophrenia and the nature of their developmental course. Furthermore, evidence from follow-back and birth cohort studies allows for a review of general cognitive and intellectual deficits occurring in premorbid schizophrenia, giving further clues as to the timing of development of such deficits and their relationship to the phenotypic expression of the disorder. Due to the magnitude of research investigating neuropsychological deficits in schizophrenia, this review is not exhaustive, but attempts to broadly reflect the general findings of studies in this area. Tables 1A-1D in Appendix 1 detail the main studies concerning neuropsychological function in schizophrenia reviewed below.

1.2.1 Intellectual function

Intelligence testing was originally introduced as a means of aiding schools in the identification of children at the extremes of intellectual ability (Brody 1992). The contemporary intelligence quotient or IQ is therefore a standardised score of a hypothetical general intellectual ability based on the combined level of performance across a range of functions including language, visuo-spatial skills,

abstract thinking, problem solving, non-verbal reasoning, attention and speed of processing (Davison et al 2003; Wechsler 1981). However, it should be noted that although the conceptualisation of intelligence as a unitary phenomenon improves the ability to measure and quantify intellectual ability, aggregated scoring leads to the loss of performance information accrued on individual and functionally distinct sub-tests (Lezak 1995). Intellectual ability is essentially multifactorial and as a derived score used in a clinical capacity can be misleading. Levels of education or previous vocational achievements may be more informative benchmarks against which to compare past with present cognitive ability (Lezak 1995). Furthermore, investigation of individual domains of function may allow for a more complete understanding of the discrete brain networks affected in schizophrenia. Nonetheless, the evidence for 'intellectual dysfunction' in schizophrenia will be considered separately from the other cognitive domains of function (i.e. executive function, attention and memory), but as an indicator of 'general cognitive function', which encompasses all levels of cognitive ability.

1.2.1.1 General cognitive function

Intellectual impairment in schizophrenia is a fairly ubiquitous finding and a proliferation of studies demonstrates significantly lower intelligence test performance in both early and late onset schizophrenia patients when compared to normal controls (Aylward 1984; Nelson et al 1990). Indeed, Payne et al (1960) reviewed 28 studies of over 1,000 schizophrenia patients and reported a deficit of at least 10 points below the general population mean (as cited in (Russell et al 1997)). Heinrichs et al (1998) also reported a considerable effect size of 1.24 for a Wechsler Adult Intelligence Scale-Revised (WAIS-R) measure of general intellectual ability based on 35 studies of schizophrenia patients and controls and an even larger effect size of 1.46 for performance IQ. Furthermore, the WAIS-R effect size was a greater and more reliable estimate than those derived from non-WAIS-R IQ tests (i.e. Shipley, Quick test, National Adult Reading Test (NART); d=0.63) or verbal IQ (d=0.98) (Heinrichs and Zakzanis 1998). This is possibly due to the briefer and less comprehensive nature of the latter tests, and the NART emphasis on verbal knowledge, an aspect of crystallised intelligence, which may be preserved in schizophrenia (O'Carroll et al 1992). However, the variability in performance of schizophrenia patients on tests of general intelligence and the findings of non-

significant differences in general intelligence between schizophrenia patients and controls, suggests the existence of sub groups of patients who are high functioning and do not display the widely reported intellectual deficits associated with the disorder.

1.2.1.2 Preserved intellect and impaired neuropsychological performance in schizophrenia

The evidence for schizophrenia patients who show preserved general intellectual ability in the presence of pervasive neuropsychological deficits implies that schizophrenia may not be characterised by global dysfunction, but by selective deficits in specific cognitive domains (Badcock et al 2004). Elliot et al (1998) reported widespread neuropsychological deficits in 12 schizophrenia patients with preserved intellectual ability (i.e. WAIS IQ greater than 90 points and less than 10 point difference with NART estimated premorbid IQ) relative to 12 matched controls (Elliott et al 1998). Similarly, Badcock et al (2005) identified three distinct groups of schizophrenia patients based on their intellectual performance on the NART (an estimate of premorbid IQ) and the Shipley Institute of Living Scale (from which a reliable estimate of WAIS-R full scale current IQ is derived). Patients with preserved intellect (i.e. less than a 10 point difference between premorbid and current IQ) showed deficits in speed of information processing (i.e. using an inspection time task) equivalent to those in patients with deteriorated (i.e. greater than 10 point decline from premorbid to current) and compromised intellects (i.e. premorbid and current IQ less than 90 points, without evidence of decline). Moreover, although patients with preserved intellect showed superior performance on tests of memory, attention and executive function to the other two groups, they still performed significantly worse than a control group (Badcock et al 2005). Kremen et al (2001) also showed equivalent levels of neuropsychological impairment in schizophrenia patients in groups of both high (95-119 points) and low average IQ (81-94 points) based on an estimate from four sub-tests of WAIS-R. The performance impairment in patients with normal intellectual ability was large relative to that which might be expected for their level of IQ (i.e. in the controls matched for IQ level) (Kremen et al 2001). Finally, Weickert et al (2000) identified average premorbid IQ without decline in 25% of a sample of 117 schizophrenic patients. This group showed similar performance to normal controls, but greater perseveration (Wisconsin Card Sorting Test) and reduced attention (Continuous Performance Test). The consistently intellectually impaired group (25%) showed attention, executive function, memory

and language deficits while the intellectually declining group (51%) showed deficits in the same areas except language processing (i.e. Boston naming test) (Weickert et al 2000).

The importance of preserved general intellectual ability has not yet been established, although it has been postulated that high levels of general intelligence may be a protective factor for the development of schizophrenia by providing greater reserves of cognitive capacity and enabling more efficient strategies for coping with psychosis. This is not reconcilable with the findings of Badcock et al (2005), in that slowed information processing speed in a preserved intellect patient group implies reduced reserves of capacity equivalent to patients with both impaired and deteriorated intellect. Alternatively, impaired and unimpaired general intellectual ability groups could be on different levels of a continuum of disease severity, or more importantly could be representative of aetiologically distinct forms of the disorder (Holthausen et al 2002). Murray et al (1987) have suggested that cognitively impaired patients exhibit indicators of a neurodevelopmental disorder, with early onset and poor prognosis, whereas cognitively intact patients may show less evidence of premorbid deficits or cognitive decline (Murray and Lewis 1987).

1.2.2 Attention

Kraepelin and Bleuler identified 'loose associations' and inadequate maintenance of trains of thought in schizophrenia. This has been cited as the first reportage of an attention deficit in schizophrenia. Researchers since then have assumed impaired information processing to be the underlying causal feature of cognitive impairment in schizophrenia (Neuchterlein et al 1991). Although often described as a mediator in all aspects of cognitive function (i.e. a sensory gate and a capacity for processing), the concept of attention is difficult to define and for this reason has been frequently classified under the umbrella term of executive function.

Alertness or vigilance is understood to represent the ability to maintain a readiness to respond promptly and is typically measured by simple reaction time tasks. Sustained attention is the ability to maintain alertness over longer periods of time and is generally assessed using the Continuous Performance Test (CPT), during which participants are presented with a continuous stream of stimuli

and required to respond to selected target stimuli while ignoring all others (Lezak 1995). Selective attention is the ability to filter and focus on relevant information while suppressing awareness of possible alternatives and is also measured by some versions of CPT, the response suppression condition of the Stroop Colour Word Test and the Trail-making Test (parts A & B) (Lezak 1995). Some aspects of complex attention can be considered as forms of executive control and are therefore included under tests of executive function, for example, divided attention, which involves responding to more than one mental task at a time, and switching of attention, which is the capacity to alternate between modalities, normally measured by the Wisconsin Card Sorting test (WCST) and the Trail-making Test (part B).

1.2.2.1 Alertness and processing speed

In a review of attention and information processing in schizophrenia, Neuchterlein and Dawson (1984) concluded that in tests of simple reaction time, schizophrenia patients (across diagnostic groups) were slowed relative to controls. This general slowing of processing speed has also been reported in other psychiatric groups (i.e. bipolar disorder) and therefore may not be a disease specific deficit. Using early descriptive terms, 'Process' (cf. endogenous) schizophrenia patients were thought to specifically show a 'cross over pattern', such that reaction time to regular preparatory intervals became slower than reaction time to irregular intervals, as irregular intervals increased in time (Neuchterlein and Dawson 1984). Ngan et al (2000) showed that patients with a 'persistent' schizophrenic illness were slower on a reaction time task than those patients with a 'fluctuating' illness and controls, and is provided as evidence of a deficit associated primarily with negative symptoms (i.e. psychomotor poverty) (Ngan 2000). Maier et al (1994) showed drug free schizophrenia patients to perform less well relative to controls and their healthy siblings on a simple reaction time task and displayed both a cross-over and cross-modality effect not apparent in the control group (although healthy siblings showed a cross-over effect which may be a putative vulnerability marker for schizophrenia) (Maier et al 1994).

General slowing of processing has frequently been interpreted as evidence for a limited attentional capacity in schizophrenia, hence responsible for deficits across various cognitive tasks, such as the

effectiveness of maintenance and rehearsal in working memory or verbal fluency (Brebion et al 2000; Vinogradov et al 2003). Nelson et al (1990) showed schizophrenic patients to have slower motor and cognitive speed than controls, with cognitive speed being correlated with negative symptoms. Lussier et al (2001) tested for alertness using a simple reaction time task and showed drug naïve schizophrenia patients to respond more slowly than controls, suggesting that this is not a by-product of anti-psychotic medication (Lussier and Stip 2001). Brebion et al (1999), showed that schizophrenia patients were impaired in maintaining a list in a sequential manner and that processing speed was significantly correlated with the number of items recalled in a superficial and deep encoding task (Brebion et al 1999; Brebion et al 2000). Indeed, after controlling for processing speed (by co-varying for WAIS Digit Symbol performance and Stroop Colour Word Test -naming response time) the differences between patients and controls in both digit and word span lost significance. Elaborating on this result, Brebion et al (1999) suggest that as a result of slowed processing, items will be refreshed less often in Baddeley's hypothetical phonological loop, thus affecting the quality of rehearsal and later recall (Brebion et al 2000). Lussier et al (2001) also tested for online information processing, defined similarly as a measure of Baddeley's hypothetical phonological loop component of working memory, with the serial recall of an increasing number of items. They demonstrated the recall of fewer items by drug naïve patients than by controls for both digits and words. Although included as a measure of attention, the authors present this as evidence for a deficient articulatory loop system of working memory (Lussier and Stip 2001). However, Lezak (1995) asserts that processing speed and attention may be related but conceptually separate phenomena, such that 'underlying many patients' attentional disorders is slowed processing'. Processing speed may therefore only be valuable where it serves as a means of understanding the nature of associated attentional deficits (Lezak 1995).

1.2.2.2 Selective attention

The trail-making task part A involves the joining up of randomly scattered numbers in ascending order and is a basic measure of perceptual motor speed. Part B involves the same task but with the added condition of alternating sets, with letters which have to be joined consecutively after each number. Schizophrenia patients have demonstrated slower performance on both parts of the trail-making task when compared to healthy controls (Saykin et al 1994) or exclusively on part B (Jeste et

al 1995; Palmer 2000), although other studies have shown no such differences (Hoff et al 1992b). In a quantitative review of neuropsychological function in schizophrenia, Heinrichs and Zakzanis (1998) cited effects sizes of 0.95 for trail-making A and 1.07 for the more difficult trail-making B based on the results of 12 and 15 studies respectively, suggesting that task load or difficulty manipulated in one test results in larger effect sizes for the more demanding test aspect. However, the difference in performance between the two aspects of this test was not greater than that for attention measures alone (Heinrichs and Zakzanis 1998).

Heinrichs (2001) additionally reported that in studies comparing patients and controls, the identical pairs CPT version yielded an effect size of 1.21, whereas studies using the degraded stimulus CPT version showed a size of 0.84. The author postulates that due to the variety of CPT versions available, a reliable estimate of performance on this test across studies is difficult to achieve (Heinrichs 2001). Buchanan et al (1997) demonstrated significant differences in performance on the CPT degraded stimulus version between deficit and non-deficit schizophrenia patients and concluded that deficit forms of the disorder could be characterised by impaired visual processing and attention (Buchanan et al 1997). Neuchterlein and Dawson (1991) have conceded that deficits on tests of selective and divided attention in schizophrenia could be interpreted as a consequence of a weak supervisory attentional system rather than a limited capacity attentional system, with 'a difficulty in initiating a predesignated response for each detected target' (Neuchterlein et al 1991). This suggests that the ability to allocate rather than sustain attention may be at the core of this deficit.

1.2.2.3 Control of attention in memory tasks

Researchers have chosen to control for the effects of attention in cognitive performance by co-varying for those tests purporting to measure attention (e.g. Saykin et al (1994), using the CPT vigilance score; Seidman et al, (1998) using WAIS Digit span, block design and vocabulary, Gold et al (1995) using the WMS attention index); by matching groups on measures of attention (e.g. Rushe et al (1999) using the auditory digit span and corsi blocks (visuo-spatial span)); by correlating memory scores with scores on tests of attention (e.g. Binder et al (1998) and Brebion et al (2000)), and by varying the attentional demands of the task (e.g. Gold et al (1992), effortful versus automatic processing) (Binder

et al 1998; Brebion et al 2000; Gold et al 1995; Gold et al 1992a; Rushe et al 1999; Saykin et al 1994; Seidman et al 1998). However, the persistence of impairments (specifically in memory with regards the studies indicated above) in spite of controlling for any differences in attention, suggests that this may be a deficit which overlaps with affected memory processes, but is not exclusively responsible for them (Gold et al 1992a; Rushe et al 1999; Saykin et al 1994; Seidman et al 1998).

1.2.3 Executive Function

Executive function is a modern day construct, which emerged as a means of defining a wide range of elusive higher order skills loosely associated with the frontal lobes. However, the move away from theories of functional localisation and towards those of functional segregation and connectivity has reduced the emphasis on the construct's link specifically to the frontal cortex, allowing for a more contemporary focus on frontal cortical-subcortical circuits (Lezak 1995; Palmer 2000). Lezak (1995) briefly defines executive skills as 'capacities that enable a person to engage successfully in independent, purposive, self serving behaviour' (Lezak 1995).

Baddeley's term 'dysexecutive syndrome' defining the collection of deficits associated with the frontal lobe system, such as perseveration and lack of volition (Baddeley 1990), may contribute in some way to a more comprehensive understanding of those skills which are considered executive in nature (Evans et al 1997). Baddeley's model of working memory incorporated the concept of a central executive responsible for the regulation of both the visuo-spatial sketchpad and the phonological loop (Baddeley 1992). The central executive is equally well described by Norman and Shallice's hypothetical model of the limited capacity Supervisory Attentional System (SAS) (Norman 1986). They asserted that the majority of human behaviour was habitual, schemata driven and cued by the environment. However, for unexpected situations requiring a novel non-habitual response, the SAS must intervene. It is therefore integral in the control of action in instances involving new responses, (i.e. shifting response mode), the inhibition of old responses, planning, strategising and decision-making.

There are considerable overlaps in descriptions of aspects of attention, current conceptions of working memory and executive function. Indeed, performance on a delayed matching to sample memory task and on a test of verbal working memory (sentence span), has been shown to be significantly correlated with performance on aspects of the Wisconsin Card Sorting Test (WCST) in schizophrenia (Hartman et al 2003; Morice and Delahunty 1996), although the lack of a significant correlation between the WCST and working memory performance, as measured by a visuo-spatial working memory task and WAIS digit span forwards and backwards, has also been reported (Stratta et al 1997).

Until the mid 1980's impairment in executive function in schizophrenia was largely ignored. However, with the advent of neuropsychological tests devised to tap functions ascribed to the frontal lobes, interest in frontal functioning was renewed. Such tests considered to be sensitive to frontal lobe lesions have been used with schizophrenia patients in order to demonstrate frontal lobe related deficits, including the Wisconsin Card Sorting Test (WCST), the Tower of London, the Behavioural Assessment of the Dysexecutive Syndrome (BADS), the Cambridge Automated Neuropsychological Test Battery (CANTAB, i.e. Stockings of Cambridge and ID/ED shift), the Hayling Sentence Completion test (HSCT), the Stroop Colour Word Naming Test and verbal fluency. In effect, our current appreciation of what executive function involves has been operationalised through the application of these tests.

1.2.3.1 Cognitive shifting

Cognitive shifting or flexibility is the ability to switch attention between sets, often in adherence to a rule. A failure to switch between sets results in perseveration, which describes the action of being stuck in a category set or mode of responding. This is measured by, for example, the WCST (i.e. perseveration), the BADS (i.e. card rule shift) and CANTAB (i.e. ID/ED shift).

There is a proliferation of studies investigating WCST performance in schizophrenia, which requires the sorting of playing cards that differ along three dimensions of element shape, number and colour. Participants must infer the sorting principle through trial and error, based on the feedback on accuracy after each response. After the completion of a category (10 consecutive correct responses), the

examiner must 'covertly' change the sorting principle. The most common performance scores derived from this test include perseveration number (being stuck in a category or mode of responding) and total categories completed (ability to shift sets or switch attention) (Lezak 1995; Palmer 2000). A large number of these studies have demonstrated poorer performance of schizophrenic patients on the WCST relative to controls (Beatty et al 1993; Bilder et al 2000; Blanchard and Neale 1994; Hoff et al 1992b; Kenny et al 1997; Morice and Delahunty 1996; Nathaniel-James et al 1996; Stratta et al 1997). However, Bellack et al (1990) showed preserved performance in schizophrenics on the WCST, after receiving feedback and rehearsal, which was also demonstrated on a subsequent testing occasion. Saykin et al (1994) also showed abstraction to be the least impaired aspect of cognition in a sample of patients (Bellack et al 1990; Saykin et al 1994). Heinrichs and Zakzanis (1998) showed an effect size of 0.95 for executive function as assessed by the WCST across 43 studies (Heinrichs and Zakzanis 1998), while a recent meta-analysis of 29 studies showed large effect sizes for categories achieved, medium effects sizes for the absolute level of perseveration and small effect sizes for the proportion of perseverative errors (Laws 1999). This pattern of results suggests that patients have difficulty in using feedback and error monitoring to alter their responses, a putative indication of ineffective prefrontal cortex function. However, this deficit may be reversible, given adequate instruction and feedback.

Evans et al (1997) showed both schizophrenia and brain injured patients (mainly anterior frontal/temporal lesions) to be impaired relative to healthy controls on the BADS, which consists of six tests (Rule shift cards, Action program, Key search, Temporal judgement, Zoo map and Modified six elements) and a questionnaire. A subset of the schizophrenia patients showing discrepancies between the NART and WAIS IQ of less than 15 points (and hypothesised as evidence of preserved IQ) were also matched for IQ with a group of controls and performance compared on the BADS. Differences between patients and controls remained evident despite equivalent levels of general intellectual ability (and no correlation with performance on the RBMT) suggesting that executive deficits were in fact independent of intellectual and memory performance (Evans et al 1997). This is in contrast to Laws' (1999) assertion that the greater deficit in WAIS-IQ relative to WCST impairments was indicative of a global deficit, to which executive function was secondary (Laws 1999).

Elliott et al (1995) showed a group of chronic schizophrenic patients to be significantly impaired on a computerised test of attentional set. Deficits were apparent on a 'stuck-in-set' perseveration condition (failure to shift attention from a previously relevant dimension), but not a 'recurrent' perseveration (failure to shift attention to the previously irrelevant condition). Given that working memory demands on both aspects of this task were equivalent, this does not support the view of a working memory impairment being core to executive dysfunction in schizophrenia. Similarly, the same deficit pattern was apparent in a group of patients with preserved intellectual capacity and in the whole patient group independent of poor recognition memory performance. This further suggests that this deficit is not attributable either to memory or intellectual ability impairment, but is indicative of a specific type of perseveration difficulty in schizophrenia, similar to that measured by the WCST (Elliott et al 1995). This finding is supported by a later study showing a lack of correlation between WCST and working memory performance. The authors assert that although constructs such as working memory and attention may be required as part of this task, core executive functions played a greater role in the successful completion of the task, such as goal directed behaviour, planning, strategising and using context to facilitate top down processing of information (Stratta et al 1997). Hutton et al (2002) used a novel computerised decision making task (derivation of a card gambling task), considered sensitive to orbito-frontal dysfunction, to compare chronic schizophrenic patients, first episode schizophrenic patients and controls. Both patient groups were slower in decision making responses and in adjusting betting responses relative to controls, while chronic patients also made fewer optimal adjusted betting responses than first episode patients.

Indeed, although characteristic of schizophrenia, cognitive set shifting may be a feature more prevalent in chronic than first episode patients. Using the CANTAB, attentional set shifting was shown to be more severely impaired in chronic patients than in first episode patients (Hutton et al 1998; Joyce 1999; Saykin et al 1991) and evidence also suggests a deterioration in this domain over 1 year in first episode patients (Joyce 1999). These findings may indicate a change in this area of executive performance over time, which could be related to long term medication, chronicity, duration of illness or neuropathological changes over time (Hutton et al 2002).

1.2.3.2 Planning

Forward planning is an executive function essential to the completion of complex tasks (Morice and Delahunty 1996). The Tower tests and their variants, such as the stockings of Cambridge, emphasise usage of executive functions such as planning and strategy formation abilities in the process of deciding where to move next. Participants are scored on the number of moves required to complete the task, and the time in which it is completed (Lezak 1995). Some studies have shown poorer performance in schizophrenia patients when compared to controls on the Tower tests (Andreasen et al 1992; Morice and Delahunty 1996), whereas others have shown no such differences (Goldberg et al 1990). Performance on the Woodcock-Johnson Test of Fluid Intelligence, also involving concept formation using categorical reasoning, was shown to be unaffected in schizophrenia (Binks and Gold 1998). First episode patients, while showing intact attentional set shifting, show similar deficits to chronic patients in forward planning, as measured by CANTAB (Hutton et al 1998; Joyce 1999).

1.2.3.4 Inhibition of response

Response inhibition is also a form of complex attention, requiring the selection of relevant stimuli while suppressing additionally activated stimuli considered irrelevant. The Stroop Colour Word Test requires the timed naming of the colour of ink words have been printed in, whilst suppressing a response to read the words themselves, which are names of colours. This briefly assesses selective attention and inhibition of response through quantification of time taken and errors made during trials. Perret (1974) showed that lesions of the left frontal lobe impacted negatively on the ability to suppress automatic or habitual response during the Stroop test (Laws 1999). A review of studies addressing Stroop performance differences between schizophrenia patients and controls revealed a slower speed and greater number of errors during the response suppression condition in schizophrenics relative to controls, suggesting that their ability to inhibit response and selectively attend to the stimuli was impaired (Perlstein et al 1998). Heinrichs and Zakzanis (1998) also reported a large effect size of 1.22 based on only 6 studies comparing the Stroop test interference condition performance of schizophrenia patients and controls (Heinrichs and Zakzanis 1998).

1.2.3.5 Verbal Fluency

The Verbal Fluency tests are commonly reported to be associated with the cognitive measures of executive function because they require goal directed behaviour, initiation and a switching between clusters (i.e. between clusters of related words within a category during category fluency). Test performance has also been shown to be improved in Alzheimer's and Parkinson's disease patients through the provision of external cues to guide task related behaviour, while processing speed impacts on the amount of words produced, regardless of effectiveness of set shifting and retrieval (Van Beilen et al 2004).

The letter or phonological fluency test requires participants to generate words beginning with specific letters (usually F, A and S), and may be dependent on the left pre-frontal and inferior parietal cortex, while the semantic or category fluency test requires participants to generate exemplars of specified categories (e.g. four legged animals), and is dependent on the integrity of frontal and temporo-parietal regions (Bokat and Goldberg 2003). Neuroimaging in normal controls has also shown the activation of the dorsolateral prefrontal cortex coincident with the deactivation of the superior temporal gyrus during tests of orthographic fluency (Frith et al 1995). Heinrichs and Zakzanis (1998) showed an effect size of 1.39 for word fluency alone (semantic fluency performance was not reported separately), which after effect sizes on measures of global verbal memory, bilateral motor performance, performance IQ and CPT (all corrected for sample size), was one of the largest effect sizes of 18 measures of cognition, based on 29 studies comparing schizophrenia patients and controls (Heinrichs and Zakzanis 1998).

Although both tests share a similar measure of goal directed behaviour with a planned search and generation of words, semantic fluency differs in that it necessitates a search of the lexicon where words are stored based on their shared semantic as opposed to phonemic properties. Controls have been shown to find the semantic fluency task easier than phonological fluency, possibly due to the greater depth of processing associated with initial encoding of words based on meaning compared to phonology. Indeed, Bokat and Goldberg (2003) assert that this may result in this task being performed automatically (Heinrichs and Zakzanis 1998).

Conversely, schizophrenia patients have consistently demonstrated poorer performance on semantic relative to phonological fluency tests (Bokat and Goldberg 2003). Similarly, early onset first episode adolescent patients have been shown to perform poorly relative to controls on semantic fluency but demonstrate intact phonological fluency (Phillips et al 2004). This has previously been attributed to a depleted semantic store (Chen et al 2000a), a disorganised semantic store (Goldberg et al 1993; Gourovitch et al 1996) or a difficulty in retrieving material from the semantic store (Allen et al 1993). Chance et al (2002) showed early-onset schizophrenic patients to have less effective conceptual boundaries and less logical dimensions to their semantic memories (Phillips et al 2004).

Nonetheless, evidence suggests that the semantic store is not reduced in schizophrenia (Allen et al 1993; Elvevag et al 2002). Allen (1993) showed patients to produce less exemplars across five trials relative to controls, but that the total number of exemplars generated did not differ between groups. Similarly, using a category fluency-switching task, both Van Beilen et al (2004) and Elvevag et al (2002) showed patients to produce fewer words and make more errors, but that the number of items per cluster did not differ between patients and controls (Elvevag et al 2002; Van Beilen et al 2004). Elvevag et al (2002) asserted that the increased reaction time between cluster switches in patients might reflect a general slowness of processing. Similarly, Van Beilen et al (2004) showed psychomotor speed to predict verbal fluency performance in patients, unlike control participant performance, which was predicted by memory and executive functioning. A reduced word production in patients relative to controls could therefore be attributed to a general slowness of processing, which might result in a trade off between the amount of time spent switching between clusters and that spent retrieving words (Van Beilen et al 2004). Other authors have further suggested that the increase in time required to move through related nodes in the semantic network may be due to a failure of spreading activation in associated nodes, although Vinogradov et al (2003) showed an independence of semantic network organisation and psychomotor speed (Vinogradov et al 2003). Conversely, increased time has also been ascribed to the impaired inhibition of the irrelevant exemplars activated (Bokat and Goldberg 2003). In some ways therefore, while semantic fluency deficits could be

considered evidence for an ineffective semantic memory system, they may also be due to both executive deficits and a general slowness of processing impacting on patient performance on this task.

1.2.3.6 Selective deficit of executive function

With respect to attempts at identifying a selective executive function deficit in schizophrenia, Laws (1999) stressed that 50% of those executive function studies reviewed failed to incorporate tests of a non-executive nature. This makes the demonstration of executive dysfunction as a selective deficit unlikely. Additionally, the demonstration of the specificity of a test deemed to be sensitive to the functional domain under scrutiny is vital. The evidence indicating that tests such as the WCST show a specific association with the frontal lobes is weaker than previously thought and while lesion studies provide evidence of a sensitivity of such tests to the frontal cortex, they are by no means specific indicators of frontal dysfunction (Laws 1999; Reitan and Wolfson 1994). Indeed, although frontal activations have been demonstrated in controls during the Tower of London tasks (Andreasen et al 1992; Morris et al 1993; Schall et al 2003) and during the WCST, functional neuroimaging has also shed light on the diversity of activations associated with tasks of executive function. PET and fMRI studies with normal participants administered the WCST, show extensive activations outside of the dorsolateral prefrontal cortex including the orbitopolar cortex, inferior parietal lobule, inferior temporal cortex and cerebellum (Berman et al 1995; Schall et al 2003; Van Horn et al 1996). The tentative nature of inference based on those tests, which are now used to operationally define the behaviour in question, must be kept in mind. Indeed, the diversity of tasks applied which superficially assess the same executive skills, may in fact be recruiting both overlapping and distinct parts of the brain during processing (Laws 1999). Finally, the point is made that not all schizophrenic patients perform poorly on tests of executive function. This is an accepted consequence of the heterogeneity commonly shown in schizophrenia and perhaps strengthens the case for investigation of symptom profiles or indeed single cases, in relation to neuropsychological deficits, due to the unlikelihood of there being a ubiquitous cognitive marker for schizophrenia as a whole (Frith (1999)-commentary on (Laws 1999)).

1.2.4 Memory

1.2.4.1 Introduction to memory in schizophrenia

The literature concerning memory performance in schizophrenia has been quantitatively reviewed in two major papers within the last ten years (Aleman et al 1999; Heinrichs and Zakzanis 1998). Both reviews concluded that memory was a pervasive deficit in schizophrenia, but did not fully address the precise nature of the impairment. Cirillo and Seidman (2003) attempted with more success to qualify this deficit by breaking down the function of memory into encoding, storage and retrieval processes, while at the same time considering extraneous factors such as age, medication, symptoms, attention and intelligence as potential confounds of memory performance in this disorder. Although these additional factors influenced memory performance, they did not fully account for the extent of the deficit demonstrated. They concluded that the memory impairment in schizophrenia could be mainly attributed to acquisition deficits, with forgetting rates less severe than those present in individuals suffering from amnesia (Cirillo and Seidman 2003). A more recent meta-analysis has compared studies of item and associative recognition in schizophrenia and controls, and found greater effect sizes for associative compared to item recognition, implying a deficit in conscious recollection as opposed to recollection supported by familiarity (Achim and Lepage 2003). This may further suggest that the memory 'binding' process, which brings together contextually several aspects of an event and may occur during the information acquisition and later during recollection, could be ineffective in schizophrenia. Based on the reviews mentioned above and an individual investigation of the literature concerning memory in schizophrenia, I will attempt to consolidate these findings and present an overview of those aspects of memory functioning especially impaired in schizophrenia (see Table 1A & 1B in Appendix 1).

1.2.4.2 Non-declarative memory

Implicit memory or non declarative memory reflects the unconscious processes of learning and memory, also referred to as incidental memory and is responsible for experimental priming effects, where the presentation of a word followed by the presentation of fragments of that word or word stem will lead to the production of that word based on the availability of some of the previously presented words' physical characteristics (i.e. word stem completion tasks). This is an effect that is obviously

reliant on the physical attributes of a stimulus and is evident across modalities. It reinforces the idea that activation of a word leaves a form of 'neural residue' and will increase the speed and chance of that word being accessed again among other possibilities (Baddeley 1995). Non associative learning, classical conditioning, habit formation and continuous procedural skills such as riding a bike and discontinuous skills such as typing, are also forms of implicit memory. It is not episodic in nature by virtue of the fact that the memory is not marked by the associated individual learning event or past experience, but by the accumulation of information over time. Under experimental conditions implicit learning would occur without the awareness of the participant, so that future retrieval of that information would be considered incidental, non intentional or automatic. Common motor procedural learning tasks include mirror reading and drawing, pursuit rotor tasks and jigsaw puzzles, while more complex implicit cognitive tasks include for example, problem solving on the tower of Hanoi (Schmand et al 1992) or word stem completion (Kazes et al 1999).

Evidence suggests that implicit memory is generally preserved in schizophrenia despite impaired declarative memory (Bazin and Perruchet 1996; Gras-Vincendon et al 1994; Kazes et al 1999; Kern et al 1997; Lussier and Stip 2001; Perry et al 2000; Schmand et al 1992; Sponheim et al article in press; Stirling et al 1997; Watanabe et al 2002). Kazes et al (1999) also took into consideration the possibility of explicit memory processes impacting on recall of material during word stem completion by estimating and controlling for explicit recall on that task (Kazes et al 1999). The functional memory dissociation in amnesic patients, where explicit memory is impaired but implicit memory remains preserved, is evidence for potentially distinct neural mechanisms supporting these types of processing and further suggests that those brain networks supporting implicit memory are not affected in schizophrenia. However, many aspects of implicit memory (e.g. conditioning) have not been extensively investigated in schizophrenia. More conclusive evidence of preservation across all aspects of memory would be required in order to assert that implicit memory is definitely unaffected.

1.2.4.3 Declarative memory

Explicit or declarative memory is said to reflect the conscious recollection and recognition of past events and factual information and is therefore comprised of both episodic and semantic memories.

When related to experimental memory research, explicit memory often involves the recognition (indicate whether an item is recognised as seen before or not) or recollection (free recall, cued recall) of material previously presented, such as a studied word list. Recognition is probably the easiest form of recollection, because the target or previously seen material is presented to the participant, often combined with similar distractor items. Cued recall is recall aided by some aspect of the target being presented, and free recall offers no cue to the previously presented material. The process of recognition itself can occur under two conditions. Firstly, where the memory for an item is based on familiarity or the feeling of having seen an item before as opposed to being based on explicit recollection of the actual learning episode, or knowing. Indeed, knowing as opposed to familiarity may be reliant upon context information and memory for the source of the learning event.

1.2.4.3.1 Short-term memory

The traditional stage model of memory proposed by Atkinson and Shiffrin (1968) describes the flow of information from a transient sensory store (perceptual system), to be briefly recorded in visual (iconic) and auditory perceptual (echoic) memory, then moving into the limited capacity short-term store (e.g. mentally retaining a new telephone number long enough to make a call), to be either lost/displaced (due to the impact of additional distracting or more relevant information) or (if left long enough) be transferred onto the long term memory store (Atkinson and Shiffrin 1968). Emphasis is therefore placed on the passivity of this store, which sets it apart from theories of verbal working memory (Vallar and Papagno 2002).

Short-term verbal memory tasks typically measure the immediate recall (after a few minutes only) of auditory material such as words and digits. Several studies have postulated that short term verbal memory is preserved in schizophrenia in the presence of impaired verbal working and long term memory systems, similar to the pattern of deficit apparent in amnesic patients (Duffy and O'Carroll 1994; Elvevag et al 2002; Goldberg et al 1993; Kenny et al 1997; McKenna et al 1990; Morice and Delahunty 1996; Riley et al 2000; Schroder et al 1996; Tamlyn et al 1992). This would suggest that the brief storage of verbal material is not affected in schizophrenia, and according to some authors is indicative of an intact phonological store. However, a substantial number of studies have equally

provided evidence of impaired immediate verbal short-term memory in schizophrenia (Beatty et al 1993; Brebion et al 1997a; Chan et al 2000; Hill et al 2003; Moritz et al 2001).

Short-term visual memory tasks measure the temporary storage of aspects of visual material such as colours, contrasts, shapes and contours. Spatial memory on the other hand is defined as memory for the dynamic properties of visual material, such as the movement of an object from one location to another, or an object's rotation in space (Della Sala and Logie 2002). Despite an under investigation of visual memory in schizophrenia, relative to verbal memory, there is consistent evidence for short-term visual memory impairment in schizophrenia (Binks and Gold 1998; Blanchard and Neale 1994; Gold et al 1992a; Tracy et al 2001). However, it has been suggested that visual short-term memory tasks place a greater load on the executive component of short term memory, than on the correspondent store in verbal memory, the phonological loop, which might explain the differences in evidence between modalities (Smith and Jonides 1999).

1.2.4.3.2 Working memory

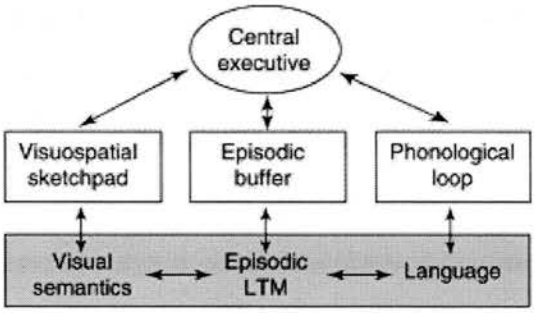
Atkinson and Shiffrin's original model of a passive short term store (Atkinson and Shiffrin 1968), did not fully address why some information might be lost while other material is transferred to the long-term store. The theory of working memory, an active store of which short term memory could be considered a component, differs in its attempt to bridge the gap between short and long term memory, by placing an emphasis on the control of online processing and manipulation of information to facilitate temporary storage as well as information transference to long-term memory (Baddeley 1995; Parkin 1993).

Baddleley and Hitch's theory of working memory comprises an attentional control system or 'central executive' aided by two additional hypothetical systems, the phonological (articulatory) loop and the visuo-spatial sketchpad (Baddeley 1992). The former system is responsible for the allocation of attention and regulation of the latter two systems and is similar in nature to Norman and Shallice's (1986) SAS, as described previously, which helps to implement novel and override habitual actions and is more recently categorised as executive in function. The phonological loop stores a verbal

memory trace and could be equated with more traditional concepts of the verbal short-term memory store. Maintenance of the stored verbal material is facilitated by sub-vocal articulatory rehearsal processes, which revive the memory trace in the loop, thus preventing further decay. The visuo-spatial sketchpad allows for the temporary storage and manipulation (e.g. flipping a mental picture round) of visual and spatial information. Importantly, some authors have asserted that although previously depicted as a gateway between sensory and long-term memory, the working memory system is not impermeable.

Evidence from studies of memory in normal volunteers and brain-injured patients suggests that information can be implicitly learned, bypassing the working memory system. At the same time, input into the working memory system is not raw, as it might be had it been directed straight from the sensory memory system. Information is stored as a whole implying that prior knowledge and experience impacts on the material held within working memory before moving onto a more permanent store. This additionally suggests that visual and verbal processing is not bottom up, but top down, with long term memories activated very early on in sensory processing in order to meaningfully and contextually place incoming sensory information (Della Sala and Logie 2002). More recently Baddleley et al (2000) have added an episodic buffer to their three-part working memory model. The authors suggested a role for the phonological loop in both short-term storage and long-term phonological learning (e.g. vocabulary development in children). The shaded areas in figure 1.1 represent 'crystallized' knowledge systems involved in the acquisition of long-term knowledge (e.g. language and semantic knowledge), while the unshaded areas of the figure represent 'fluid' abilities (e.g. attention and temporary storage), unaffected by direct learning (Baddeley et al 2000). This additional buffer is proposed as a temporary storage space for representations such as feature combinations, which are retrieved from or entered into long-term memory. This therefore allows for the brief holding of both 'top down' and 'bottom up' information (Baddeley 2000).

Figure 1.1:Baddeley's four-component model of working memory



trends in Cognitive Sciences (Baddeley 2000)

Digit span backwards, letter, word and sentence span tasks, have typically been used to assess the function of verbal working memory in schizophrenia, although these tests also occasionally appear in lists of attention, executive function or verbal short term memory tasks. Heinrichs and Zakzanis (1998) showed an effect size of 0.92 for digit span (a score composed of WAIS forwards digit span and Oltman's span with a distraction). While digit span forwards requires the simple holding of an increasing number of digits in short term memory before recall (or rehearsal in the articulatory loop), digit span in reverse places an additional load on the short term memory system by requiring the manipulation of incoming information (i.e. reversal of digits) while attempting to maintain and then recall, and would therefore call into play aspects of working memory (Heinrichs and Zakzanis 1998).

Several studies have shown impaired verbal working memory in schizophrenia patients, as assessed by backwards digit span (Brebion et al 1997b; Conklin et al 2000; Goldberg et al 1993; Stirling et al 1997; Stone et al 1998; Stratta et al 1997). Morice and Delahunty (1996) found no such differences on either digit or word span forwards or digit span backwards, but did however show differences on both alphabet (recall of strings of words in alphabetical order) and sentence span (dual task of sentence verification and recall of last word of each sentence) (Morice and Delahunty 1996). The authors suggest that intact verbal short-term but impaired verbal working memory (as measured by sentence span) could be suggestive of an intact short-term store or articulatory loop and a deficit in the central executive/attentional control aspect of working memory.

Tests of visuo-spatial working memory include the CANTAB spatial working memory task, which requires the systematic visual search for tokens by touching on-screen boxes. Tokens hidden in on-screen boxes are found by touching the screen. However, once a box has been searched it should not be returned to again. Load is increased by increasing the number of boxes presented (Elliott et al 1998; Hutton et al 1996; Hutton et al 1998). Elliot et al (1998) reported only a trend for significance in a group of patients matched with a control group for IQ, while Hutton et al (1998) showed impairment only at the most extreme levels of task difficulty in schizophrenia patients. This similarly suggests that working memory is affected by increases in load and difficulty, again indicating a defective executive control system (Glahn et al 2003; Keefe et al 1995).

Delayed response tasks were originally devised by Goldman and Rakic for the measurement of the visuo-spatial component of working memory in non-human primates, although they have since been 'borrowed' and applied in a clinical domain (Goldman-Rakic and Selemon 1997). At a basic level they require the recall of one of two spatial locations across a delay period. A more complex version requires the recall of one of an increasing number of possible spatial locations and often with delays filled with distractions. Studies show that where the delay duration is manipulated, recall deficits in schizophrenia patients do not worsen as a function of increasing time, suggesting that it is perhaps not maintenance but encoding processes which are impaired (Hartman et al 2003). Hartman et al (2003) assessed the amount of time required by patients to encode stimuli in a delayed matching to sample task, with varying lengths of delay time till recall. Patients required more time to encode (i.e. view) stimuli in order to perform to the same level of accuracy as controls. However, after equating groups for differences in encoding speed, there was no increase in loss of information with increasing delay periods (6 seconds, distraction filled period). The authors suggest that the initial encoding of stimuli and not the maintenance or storage of that information over time is impaired (Hartman et al 2003).

1.2.4.3.3 Long term episodic memory

Within declarative memory, episodic memory refers to the long-term memory for personal experiences, bringing together both the encoding and retrieval of events (Baddeley 1995). It is based on the perceptions and sensations experienced by an individual and hence it is constantly changing to

accommodate the encoding of new experiences and events. Pertinent to this sub component is its sensitivity to processing depth and strategy, such as organisation of memories and attention. These factors contribute to the encoding, eventual storage, and accessibility of information. Most tests of verbal episodic recall involve the learning and delayed recall (free and cued) or recognition of word lists (e.g. RAVLT, CVLT, HVLT, AVLT) and narratives (e.g. RBMT story recall, WMS-R logical stories). The recall of complex figures (e.g. WMS-R Visual Reproductions and Rey-Osterrieth Complex Figure Test) and faces (e.g. Warrington's Recognition Memory Test-for Faces) are consistently used measures of visual-spatial memory in schizophrenia research. However, an array of additionally available tests, assumed to measure visuo-spatial memory, has often been used, and may not reflect the integrity of comparative areas of brain function. A further complication is the verbalisability of some visual stimuli, such that many measures may in fact be testing recall in the verbal as opposed to visual domain (Wood et al 2002).

1.2.4.3.3.1 Recall

Schizophrenia patients show poor levels of recall when compared to controls on tests of verbal memory in both list (Beatty et al 1993; Calev et al 1983; Chan et al 2000; Elvevag et al 2000; Harris et al 1997; Hill et al 2003; Holthausen et al 2003; Kenny et al 1997; Moritz et al 2001; Nathaniel-James et al 1996; Paulsen et al 1995; Sonntag et al 2003; Van Oostrom et al 2003) and story recall tests (Abbruzzese and Scarone 1993; Bilder et al 2000; Blanchard and Neale 1994; Clare et al 1993; Harvey et al 1986a; Mohamed et al 1999; Rushe et al 1999; Saykin et al 1991; Saykin et al 1994; Seidman et al 2002b). Heinrichs and Zakzanis (1998) reported effects sizes of 1.53 for global verbal memory based on 3 studies (i.e. total word list recall, total story recall, total memory quotients, total immediate and sum recall) and 1.11 for selective verbal memory based on 9 studies (i.e. delayed free recall of word lists, percentage of words retained, number of intrusions, word recognition).

Evidence also suggests that non-verbal memory impairments are also apparent in schizophrenia (Beatty et al 1993; Bilder 1996; Blanchard and Neale 1994; Mohamed et al 1999; Saykin et al 1991; Saykin et al 1994), in some cases to an equivalent degree as those shown in verbal memory (Gold et al 1992a; Gold et al 1992b; McKenna et al 1990; Tracy et al 2001; Wood et al 2002). Several studies

show no significant differences between patients and controls on non-verbal recall (Binder et al 1998; Bryson et al 2001; Buchanan et al 1997). Although Buchanan et al (1997) showed no differences between patients and controls on face recognition, deficit patients showed worse performance than non-deficit patients on the same task (Buchanan et al 1997). Similarly, Wood et al (2002) showed first episode patients to be less impaired on a visual paired associate task than chronic patients, although equivalent in performance on a visual recognition task. Authors suggest that in spite of evidence to suggest stable cognitive impairment in schizophrenia, visual associative memory specifically, which recruits right hippocampal areas, may be degenerative with the course of the illness (Wood et al 2002). Others studies still, have shown greater impairments in verbal relative to non-verbal memory (Holthausen et al 2003; Rushe et al 1999; Saykin et al 1991; Saykin et al 1994; Seidman et al 2002b). This however, may not be a true difference, and Saykin et al (1991 & 1994) as well as Holtahuasen et al (2003) assert that task difficulty differences may be responsible for a more prominent and apparent impairment in verbal rather than non-verbal measures.

Tracy et al (2001) demonstrated deficits in both non-verbal and verbal memory using the Biber Figure Learning Test (BFLT) and CVLT. Interestingly, performance on the CVLT was significantly better in patients than performance on the BFLT. The authors suggest that meaningful verbal material may be more easily encoded than meaningless visuo-spatial material. Indeed, while recognition was slightly better than recall for verbal stimuli, both recall and recognition were equally impaired for non-verbal material, indicating that poor encoding may be fundamental to the non-verbal memory deficit in this group, whereas retrieval processes in part were responsible for verbal memory deficits in the same patients. The authors postulated therefore that an episodic memory deficit across modalities may be apparent in schizophrenia (Tracy et al 2001).

Heinrichs and Zakzanis (1998) reported an effect size of 1.42 for non-verbal memory (i.e. WMS-R Visual Reproductions, Warrington's Recognition Memory test for Faces and RCFT) based on 16 studies, similar to that cited for verbal memory. However, a large standard deviation for the non-verbal memory effect size (SD=1.98 after correction for sample size) suggests a large dispersion of effect sizes around the mean. This implies a heterogeneity of effects across studies for non-verbal

memory in schizophrenia and the possibility of both impaired and intact non-verbal memory in patient sub-groups (Heinrichs and Zakzanis 1998). This may be partly due to the differences in tests used to measure non-verbal memory. Indeed, if declarative memory deficits in schizophrenia were characterised by poor encoding and retrieval, rather than material specific stimuli, then both verbal and non-verbal memory deficits would be expected.

1.2.4.3.3.2 Storage

Some early studies of schizophrenic patients have shown a deficit in recall of information but a relative preservation of recognition of the same material (Beatty et al 1993; Nathaniel-James et al 1996; Rushe et al 1999; Schwartz et al 1991). This lead some theorists to suggest that storage processes are unaffected in schizophrenia and that the retrieval difficulty may be due to inadequate executive control. However, evidence has also supported the existence of both recall and recognition deficits in schizophrenia (Calev 1984a; Calev 1984b; Calev et al 1983; Elvevag et al 2000; Gold et al 1992a; Moritz et al 2001; Paulsen et al 1995; Schroder et al 1996). Tracy et al (2001), showed impaired recall and recognition despite intact maintenance and storage of material in patients relative to controls, and further suggested that retrieval deficits may be due to inadequate encoding (Tracy et al 2001). Earlier findings of intact recognition may therefore have been a consequence of tasks not effectively matched for difficulty, especially when performance on cued recall and recognition are equivalent, but still below performance of controls (Calev 1984b; Harris et al 1997).

Cirillo and Seidman (2002) asserted that retention scores on story recall in schizophrenic patients were about 74% relative to controls' average retention score of 85%, based on a sample of 362 patients and 216 controls. Similarly, evidence for impaired delayed relative to immediate word recall implies a poorer retention of information over time, and in some cases has been presented as evidence for a memory impairment likened to an amnesic syndrome in schizophrenia (Beatty et al 1993; Clare et al 1993; Elvevag et al 2002; Kenny et al 1997; McKenna et al 1990; Tamlyn et al 1992).

However, despite qualitatively lower retention, not all studies have reported significant differences between groups in forgetting rates (Goldberg et al 1993; Harris et al 1996; Mohamed et al 1999;

Paulsen et al 1995; Van Oostrom et al 2003) and while impoverished relative to controls, patients still retain more information after a delay than Alzheimer's and Huntington's disease patients (Cirillo and Seidman 2003; Van Oostrom et al 2003) and equivalent amounts to temporal lobe epilepsy patients, suggesting that this may be only a mild deficit in the decay of stored information (Seidman et al 1998).

1.2.4.3.3.3 Encoding

Numerous studies have reported differences in information acquisition organisation during memory tests in schizophrenic patients compared to controls (Brebion et al 1997a; Calev 1984a; Chan et al 2000; Egeland et al 2003; Elvevag et al 2000; Gold et al 1992a; Harris et al 1997; Harvey et al 1986a; Harvey et al 1986b; Hill et al 2003; Holthausen et al 2003; Iddon et al 1998; Maher et al 1995; Manschrek et al 1997; Nathaniel-James et al 1996; Paulsen et al 1995; Tracy et al 2001; Van Oostrom et al 2003). Most of these studies report poor spontaneous usage of available semantic cues to facilitate non-verbal (Tracy et al 2001) and verbal recall of both word lists (Brebion et al 1997a; Calev 1984a; Chan et al 2000; Gold et al 1992a; Harris et al 1997; Hill et al 2003; Holthausen et al 2003; Iddon et al 1998; Manschrek et al 1997; Paulsen et al 1995; Van Oostrom et al 2003) and prose (Harvey et al 1986a). This inefficient usage of semantic strategy is still apparent in spite of the overt provision of cues (Calev et al 1983; Chan et al 2000; Gold et al 1992a; Manschrek et al 1997; Stone et al 1998), although some studies have found performance to be normalised or improved with assistance in applying strategies, context and organisation at encoding (Bazin and Perruchet 1996; Chan et al 2000; Hill et al 2003; Koh and Marusarz 1980; Ragland et al 2003). Additionally, in some patients' organisation of material there is evidence of poor semantic clustering, a preference for serial over and above semantic clustering, an idiosyncratic form of information organisation during recall, intrusion errors during free recall and increased false alarms (Brebion et al 1997a; Iddon et al 1998; Nathaniel-James et al 1996). Elvevag et al (2004) showed schizophrenic patients to be worse than controls on word recognition, but invulnerable to the effects of interference from a previously learned list. This suggests that patients had acquired and stored the information differently from controls (Elvevag et al 2004). Moritz et al (2001) showed both schizophrenic and depressive patients to be no more effected by retroactive and proactive interference than controls, while Tracy et al (2001) showed patients to be

less impaired on a measure of proactive interference than on other aspects of memory performance (Moritz et al 2001; Tracy et al 2001). Kareken et al (1996) attributed invulnerability to proactive interference to poor semantic clustering in their patient group, such that a lack of encoding based on conceptual features, apparent in controls, would mean less interference from a list of conceptually similar words. These differences suggest inadequate executive control, which would normally enable effective strategising of material to be newly encoded, and goes some way to explaining subsequent poor retrieval in schizophrenics compared to controls (Kareken et al 1996).

1.2.4.3.3.4 Recognition

Recognition memory is generally tested through tasks which re-present previously studied or encoded information, thus making it the most aided form of recall. As described previously, evidence suggests that recognition memory is generally less impaired in schizophrenia than recall (Beatty et al 1993; Nathaniel-James et al 1996; Rushe et al 1999; Schwartz et al 1991), although this may be due to the greater difficulty of free recall tasks. Indeed, the evidence for improved recall given external cues suggests that impairment may be partly due to an access rather than a storage problem.

Item and associative recognition tasks are commonly used to test familiarity and recollection respectively. Item recognition refers to the previously described forced choice recognition task, whereas associative recognition re-presents items which will all be familiar but which require recognition of the relationships between items (either old or new), in order to make an accurate choice (Achim and Lepage 2003). Common associative recognition tasks include memory for the original pairing of a target item with its source, paired associate memory and memory for a target item with the temporal order of its original presentation (Achim and Lepage 2003). In a recent meta-analysis of twenty three studies of recognition in schizophrenia, the effect size for item recognition ($d=0.40$) was less than that for associative recognition ($d=0.48$) (Achim and Lepage 2003). However, without a subjective indication of the recollection strategy used in recognition tasks it is difficult to gauge whether or not responses are based on feelings of familiarity or overt recollection of the information presented.

1.2.4.3.3.5 Remember/Know judgements

The Remember/Know paradigm was initially devised by Tulving, and requires participants to subjectively qualify the type of judgment made following a recognition response and whether or not it was a 'Remember judgement' (i.e. the event is actually recollected) or a 'Know' judgement (i.e. the item is associated with a feeling of familiarity, but in the absence of recollection). However, this method is often criticised for its fallibility due to the subjective nature of the reporting and the possibility that responses are based on familiarity and confidence, rather than familiarity and recollection. The supposition that defective encoding in schizophrenics may lead to poor retrieval is not a new one. Given that schizophrenics have been shown to have deficits in explicit verbal memory, but intact implicit memory, some researchers have used this to demonstrate that only memory that requires conscious awareness is affected in this group (Danion et al 1999; Huron et al 1995).

Drakeford et al (2002) showed patients to have more 'know' responses and fewer 'remember' responses than either depressed patients or controls during word recognition, Danion et al (2003) showed patients to have fewer 'remember' responses than controls, and Lecompte et al (2000) showed the same pattern for picture recognition (Danion et al 2003a; Drakeford et al 2002). Huron et al (2002) showed no differences between patients and controls in guessing and familiarity based responses, but significantly poorer conscious recollection based responses during a word recognition test, while exhibiting equivalent levels of impairment in both true and false recognition, but only during 'remember' based recognition responses (Huron and Danion 2002). Sonntag et al (2003) demonstrated similar degrees of directed forgetting of words to controls, but only for words that were recognised based on familiarity, the opposite pattern to that seen in controls (Huron et al 2003; Sonntag et al 2003). Huron et al (1995) asked schizophrenics and controls to make a recognition decision about previously presented high (common) and low (rare) frequency words, qualified by whether this recall was based on a conscious recollection of the study episode or on a feeling of familiarity, without conscious recollection of having seen the word previously. Schizophrenics recognised significantly less words and made significantly less responses based on conscious recollection than controls. Furthermore, schizophrenics did not show the word frequency effect seen in the control group, which is the more confident recall of low frequency words relative to high frequency words. The authors

suggest that this effect in healthy controls is due to the deeper processing associated with words, which are less common or have not been encountered before. Indeed, the absence of this effect in the patients may be indicative of a lack of elaborative processing and hence recognition based only on familiarity (Huron et al 1995). This theory is supported by a similar study by Danion et al (1999), who suggest that a lower level of recognition responses based on conscious recollection, or autonoetic awareness, is due to inefficient 'relational binding', the bringing together of different aspects of an event into a cohesive representation (Danion et al 1999). Several other authors have since postulated that impaired context memory may be a core deficit in schizophrenia (Bazin et al 2000; Rizzo et al 1996a; Rizzo et al 1996b).

1.2.4.3.3.6 Context Memory

Context memory differs from 'content' memory, the latter being memory for an episode itself, and the former being memory for features related but extrinsic to the episode, such as source, spatial and temporal location. Braver et al (1999) describe context as 'any task-relevant information that is internally represented in such a form that it can bias processing in the pathways responsible for task performance'. In such a way context representations are actively maintained online and used to influence further processing i.e. goals, task instructions and word meanings, especially in situations of competitive response selection (Braver et al 1999). This closely resembles the most recent working memory model outlined by Baddeley et al (2000), incorporating an episodic buffer for the transient holding of external information incoming to or retrieved from long term memory, which may influence current processing (Baddeley 2000).

Source memory is typically measured by testing participants' recognition and recall for the source of objects or items previously self generated or generated by an experimenter and has been shown to be impaired in schizophrenia when compared to controls (Keefe et al 2002; Stirling et al 1997; Waters et al 2003). Indeed, Rankin and O'Carroll (1995) attributed this aspect of memory to an impaired reality monitoring, leading to difficulty in distinguishing between externally and internally generated information (Burglen et al 2004). Keefe et al (2002) showed patients to perform worse relative to controls in the identification of the source of pictures and words generated by themselves, but

equivalent in performance to controls in identification of material generated by others. Misattribution of the source of self-generated material, to an external agent, was more prevalent in those patients with hallucinations and thought insertion compared to patients without. This is presented as evidence for a relationship between Schneiderian symptoms and defective autonoetic awareness in schizophrenia (Keefe et al 2002). Conversely, in a memory for action test, Stirling et al (1997) showed patients' impaired immediate and delayed recall and memory for source to be related to the experience of negative symptoms (Stirling et al 1997). Vinogradov et al (1997) also showed patients to be impaired on memory for source, despite intact recognition memory, which was related to an executive dysfunction, mediated by low IQ. In addition, patients showed increased errors in the identification of the source of items, which had been self-generated as well as items that were novel (never presented before), which was also associated with low IQ. Although low IQ and poor executive function suggests that executive control may be core to source memory, patients with normal IQ still showed poorer memory for source than controls. The authors suggest that if an item were only familiar, but not fully recollected, individuals would be expected to identify the source of that item as external rather than internal (Vinogradov et al 1996).

Memory for the temporal order of events is typically measured using recency discrimination tasks and has been demonstrated as deficient in schizophrenics relative to controls (Rizzo et al 1996a; Schwartz et al 1991; Stone et al 1998; Waters et al 2003). Rizzo et al (1996) showed schizophrenic patients to have preserved picture recognition and recall but impaired memory for when pictures were learned (Rizzo et al 1996a). Schwartz et al (1991) showed poor recency discrimination in patients, which was inversely correlated with perseverative errors on the WCST, but not related to recognition memory. This suggests that presupposed frontally mediated deficits on the WCST are related to those on recency discrimination and authors describe it as reflective of difficulties in effortful processing in schizophrenia (Schwartz et al 1991). Waters et al (2003) demonstrated both source and temporal order memory impairments in patients compared to controls in a test of object pair recognition and context memory. Controls who showed poor recognition accuracy for object pairs, conversely showed intact source and temporal memory, unlike patients who showed deficits in all areas. This is

presented as further evidence for dysfunction in the combining of contextual cues in memory in schizophrenia (Waters et al 2003).

Burglen et al (2004) used a similar temporal order memory paradigm to that of Rizzo (1996b) with a shorter stimuli presentation time, and a shorter delay period without distraction, in order to test working memory for intentionally encoded objects and locations (both separately and combined). Although both controls and patients showed poorer performance for combined over separate memories for objects and locations, patients showed significantly worse performance overall. Moreover, patients showed a disproportionate impairment for combined memory relative to controls, even in a subset of patients who had equivalent separate feature memory performance to controls (Burglen et al 2004). This was a similar conclusion to that of Sullivan et al (1997), but at odds with Gold et al (2003) who found comparative performance in patients and controls on memory for separate and combined visual and orientation features in a working memory task (Burglen et al 2004; Rushe et al 1999). These differences may be due to measures used in the individual studies, and while Burglen presented objects and locations both separately and together, the features of Gold (2003) were always presented bound together (Burglen et al 2004). Other studies have also failed to show differences between patients and controls in memory for temporal order (Rushe et al 1999). Rushe et al (1999) used a similar paradigm to that of Sullivan et al (1997), but with a shorter inter stimulus interval between visual word presentations. It is conceivable therefore that automatic processing, considered intact in schizophrenia, allowed for effective encoding of temporal order in this instance (Rushe et al 1999). The Elvevag et al (2000) finding of differences in temporal order memory between patients and controls disappeared after controlling for the overall level of recall (Elvevag et al 2000). Other authors have asserted that memory for temporal order encoding is due to automatic processing (Schacter et al (1987) as cited in Rushe et al 1999), although depending on the demands of the task effortful processing may be needed in order to process temporal information (Schwartz et al 1991).

1.2.4.3.3.7 Semantic memory

Semantic memory refers to long term memory for facts, language, rules, abstract concepts and general knowledge about the world, also encompassing both encoding and retrieval of such information. Semantic memories are noted to be context free, fixed and based on understanding. Semantic encoding involves a more complex and hence deeper form of procuring information, than shallow or episodic encoding, because it is based less on the appearance of the item presented and more on association and meaning in connection with that item. Though initially considered to be separate and distinct systems, it is now accepted that the two are inextricably linked. Semantic memories may originate as episodic memories, but the learning experiences or events associated with them are no longer retrievable individually, therefore the information is no longer defined by the experience from which it was yielded. Furthermore, evidence from amnesia literature suggests that without an intact episodic memory it is difficult for individuals to formulate new semantic memories, though access to previous semantic memories is still intact (Baddeley 1995).

A proliferation of studies suggest that semantic memory organisation is disrupted in schizophrenia (Aloia et al 1998; Bacon et al 2001; Clare et al 1993; Duffy and O'Carroll 1994; Kareken et al 1996; McKay et al 1996; Tamlyn et al 1992). Several authors have shown defective remote or autobiographical memory in schizophrenia (Calev et al 1987; Danion et al 2003b; Tamlyn et al 1992), particularly around the period of illness onset (Feinstein et al 1998), suggesting an acquisition deficit specifically associated with psychosis development. Other studies have shown a semantic memory deficit in schizophrenic patients using the Collins and Collins Silly Sentences Task and the Speed of Comprehension and Language Processing task, which require the verification of a series of statements (e.g. dragonflies have wings, the prime minister has feathers or rats have teeth). Patients have demonstrated longer times to verify sentences and more errors than controls (Clare et al 1993; Duffy and O'Carroll 1994; Tamlyn et al 1992). This is not necessarily attributable to processing speed however, because in the comparison with Korsakoff patients, schizophrenic patients showed equivalent processing speed performance as measured by the verbal fluency test and the WAIS Digit Symbol task (Duffy and O'Carroll 1994). Other investigations reported similar deficits in category judgement or sorting tasks, requiring the timely assignation of words or pictures to relevant categories

(Clare et al 1993; Green et al 2004; McKay et al 1996; McKenna et al 1994) or during category searches (Gurd et al 1997), while deficits in semantic fluency, discussed earlier, have been posited as evidence of semantic network disorganisation. Green et al (2004) asked participants to sort pictures into categories and then group them according to their over-inclusions (items from more than one category grouped together) or under-inclusions (one or more items of the same category grouped separately) prior to a category based deductive reasoning task. The authors reported that both controls and patients under-included, but only patients over-included. Removal of items from their correct categories may be due to a low level of perceived semantic similarity. However, although semantic relationships drive deductive reasoning, patients still made effective judgements, suggesting that given adequate context patients can perform the task normally (Green et al 2004). Over inclusive thinking in schizophrenia is not a recent finding and was investigated extensively by Payne and others (1973) (McKenna et al 1994). They further suggested it to be a feature specific to acute rather than chronic schizophrenia patients, above all in those with formal thought disorder (McKenna et al 1994).

Another study suggests that over-activation of connected words without the constraint of context may cause semantic memory impairments in schizophrenia. Nestor et al (1998) investigated word list recall, using words of varying associative strengths (connectivity), and in varying hypothetical sizes of network (number of associates), such that words could fall into one of four possible categories (high connectivity-small network, high connectivity-large network, low connectivity-large network, low connectivity-small network). Patients showed poorer overall recall than controls. Moreover, while controls showed the expected better recall for high-small, then low-small, high-large and low-large words, patients showed enhanced recall for highly connected and poor recall for lowly connected words irrespective of network size. This suggests that semantic networks are activated differently in schizophrenia and may be driven by strongly connected words regardless of the number of associates (Nestor et al 1998).

Semantic network dysfunction in schizophrenia is also supported by evidence from semantic priming tests. The semantic priming effect can be seen in tasks where a target word (e.g. black) is recognised faster if it follows the presentation of a semantically related prime (e.g. white) than it would following

a non-semantically related prime (i.e. round). Several studies have suggested that this priming effect is enhanced (faster) in patients than in controls due to lack of inhibition and increased semantic network activation in schizophrenia (Aloia et al 1998; Chenery et al 2004; Moritz et al 2002; Moritz et al 2001; Passerieux et al 2003; Spitzer M et al 1993a; Spitzer M et al 1993b). Maher and Spitzer's model also suggests that major thought disorder and therefore the associative intrusions apparent in schizophrenic patients' speech, may be due to the excessive activation /hyper-priming of semantic networks early on in processing and prior to conscious attentional control. The model of spreading activation is an attractive one, and suggests that information is stored in single nodes in networks of related concepts, such that when one node is activated all other close nodes in the same network will be activated too, spreading and weakening the further the association. Both Spitzer et al (1993) and Moritz et al (2002) showed thought disordered patients to activate further and more indirect associations faster than controls and non thought disordered patients in a lexical decision task (Spitzer M et al 1993a; Spitzer M et al 1993b), and Passerieux et al (1997) demonstrated greater priming for related than unrelated pairs in non thought disordered patients and controls, but not in thought disordered patients. Aloia et al (1998) showed the same pattern of priming for more highly associated pairs in both patients and controls, but at a more enhanced level in patients, while Chenerey et al (2004) also showed enhanced priming in schizophrenic patients at shorter time intervals and on pairs of low relatedness relative to controls (Aloia et al 1998; Chenery et al 2004). There is however no established biological evidence to suggest that this is the case, and an alternative theory asserts that executive processes are affected in thought disorder to create this semantic memory deficit (Siekmeirer and Hoffman 2002) (Salisbury et al 2002). Indeed, Barch et al (1996) demonstrated similar levels of priming in both patients and controls for times less than 950 milliseconds (Barch et al 1996). This negative finding has been described elsewhere, but like Barch et al (1996), such experiments have used a word pronunciation task, which can be completed without semantic processing, unlike the former experiments employing lexical decision tasks (Siekmeirer and Hoffman 2002).

1.2.4.4 Summary of memory deficits in schizophrenia

Neuropsychological abilities affected in schizophrenia are wide ranging (Heinrichs and Zakzanis 1998). Indeed, in a meta-analysis of neuropsychological assessment performance in patients with schizophrenia compared to controls in 204 studies, Heinrichs and Zakzanis (1998) showed effect sizes for global verbal memory (d =1.53) to be greater than those for intellectual ability (d= 1.24) or executive function (d = 0.95). However, the authors did not conclude that this was indicative of a differential memory deficit and there is as yet no substantial evidence to conclusively assert a selective deficit in any one domain relative to all others in schizophrenia (Heinrichs and Zakzanis 1998).

However, there does appear to be a growing body of evidence depicting such a pattern. McKenna et al (1990) demonstrated nearly 50% of their patient sample to be severely impaired on the Rivermead Behavioural Memory Test (RBMT) compared to only 19% of the same group falling into the mild or severely demented category on the mini-mental state examination (McKenna et al 1990). Similarly, Gold (1992) administered the Wechsler Adult Intelligence Scale-Revised (WAIS-R) and the Wechsler Memory Scale-Revised (WMS-R), both of which are standardised and significantly correlated in healthy normal participants. A group of schizophrenic patients showed a higher pre-morbid than current intellectual ability score, while both scores of intellectual ability were greater than the general memory index score in the same group (Gold et al 1992a). These findings suggest a greater impairment in tests of general memory than on other tests of global intellectual function in schizophrenia patients.

Strict guidelines established by Chapman and Chapman (1978 and 1989), indicate that several factors must be considered before a selective deficit can be verified. First, impairment in one domain must exceed in severity impairments apparent in other affected functional domains, also known as the 'weak' form of a differential deficit. Secondly, this severity will be greater in those domain tasks relative to tasks of equivalent difficulty in other affected functional domains, or the 'strong' version of a differential deficit. This poses a problem for a number of studies which have either failed to include measurements across functional domains or which have administered tasks of varying difficulty

(Chapman and Chapman 1989). Moreover, the involvement of attention and executive functions in all tasks makes it difficult to assert that tests are assessing pure and undiluted cognitive functions. This overlap may give the impression of selective impairments, which in fact are several deficient functions assessed by one task (Heinrichs and Zakzanis 1998). Additional confounding factors such as age, gender, medication, chronicity and intelligence may have an extraneous influence on memory performance, and therefore should also be controlled where possible, in order that specific deficits cannot be attributed to differences between groups in these areas (Cirillo and Seidman 2003).

Chapman and Chapman (1989) suggest that comparability across different neuropsychological tests is achievable without psychometrically matching tasks. Using the regression equation of task B on task A in control participants, one can compute for each observed score on task A the predicted score for task B, in order to address the question 'to what extent is performance on task B deviant, given the subject's score on task A?' This therefore considers performance on task B relative to and in spite of performance on task A and has the additional advantage of accounting for the correlation between the two tasks (Chapman and Chapman 1989).

Saykin (1991and 1994) used standardised residual scores (based on the control group mean and standard deviation) by converting raw scores to standardised residual scores (z transformations) which were adjusted for potential confounds such as age, sex and executive functioning and compared performance between un-medicated schizophrenic patients and controls in a wide ranging neuropsychological test battery. Using this method, patients scored nearly three standard deviations below controls on tests of memory compared to one or two standard deviations below controls on tests in other areas of cognitive ability. The same authors, using a larger sample of first-episode medication-naïve patients and previously medicated schizophrenic patients, later demonstrated a specific deficit in verbal but not visual memory relative to all other cognitive domains of function. Binks and Gold (1998) replicated this finding in a study of 30 schizophrenic patients using a broad range of neuropsychological tests, which also conformed to the requirements of Chapman and Chapman (1978)(Binks and Gold 1998; Saykin et al 1991; Saykin et al 1994).

However, these results should be acknowledged with caution. Chapman and Chapman assert that the standardised residual score method allows for comparisons between unmatched tasks A and B, and will remove specific extraneous variance associated with task B. Nonetheless, in groups where there is robust evidence of a generalised neuropsychological deficit, such as schizophrenia, the effects of the generalised deficit cannot be removed (i.e. low scores on task B could be due to both a specific and a generalised deficit on task B). They therefore stress that this method may be more beneficial in groups such as relatives of schizophrenics who will display a less severe generalised deficit across neuropsychological tests (Chapman and Chapman 1989). Blanchard and Neale (1994) reiterate this point and show that using the same method, non-medicated schizophrenic patients performed less well relative to controls across all neuropsychological tests, supporting the existence of a more generalised cognitive deficit (Blanchard and Neale 1994).

In summary, schizophrenia patients show pervasive deficits in declarative memory, extending to encoding, recognition, and recall processes. This suggests a basic impairment in the acquisition and retrieval of information, which cannot be attributed to attentional deificits, or to failed material storage. Furthermore, lack of spontaneous semantic clustering, poor context memory, and the improvement in recall performance in some patients following aid in the organisation of information, suggests that recall deficits may be partly explained by poor encoding processing in this group. Access may therefore be compounded by the quality of processing exerted on acquired information.

1.3 Development of cognitive deficits in schizophrenia

1.3.1 Stability of cognitive function in schizophrenia

1.3.1.1 Longitudinal studies

Cognitive deficits have been identified in first episode schizophrenic patients (Albus et al 1997; Albus et al 2002; Bilder et al 2000; Censits et al 1997; Gold et al 1999; Hill et al 2004; Holthausen et al 2003; Hutton et al 1998; Joyce et al 2002; Kravariti et al 2003; Mohamed et al 1999; Riley et al 2000; Saykin et al 1994) and medication naïve schizophrenic patients (Hill et al 2003; Saykin et al 1991), suggesting that deficits outlined previously may be present to a certain extent independently of medication status or illness duration. However, while it is acknowledged that cognitive deficits exist

early in the course of schizophrenia, the stability of such deficits throughout the illness is still unclear. This has significant implications for the understanding of the aetiology of the disorder, because decline in function throughout the course of the illness might suggest a neurodegenerative process, whereas stability would indicate a neurodevelopmental condition. Research has therefore focused on distinguishing between 'stable vulnerability factors' (i.e. cognitive deficits which remain stable during florid periods and periods in remission), and 'episode components' or 'state dependent factors' (i.e. cognitive deficits which improve or normalise during periods in remission). Stable vulnerability factors may be reflective of structural abnormalities and may be present in relatives of schizophrenics, making them possible trait indicators, or intermediate phenotypes for the disorder. State factors will however be reflective of the underlying neurophysiological disturbance associated with psychosis (Rund 1998)(see Table 1C in Appendix 1).

Longitudinal follow-up studies enable the investigation of cognitive performance from first episode schizophrenia to several years later. In this way any cognitive performance change and its relationship with symptomatology and medication can be assessed. However, although the age of onset, years of illness and medication status of patient samples are generally provided, it is unlikely that all patients across studies are manifesting the same type of symptoms, with the same severity and in the same stage of illness. This should therefore be considered in light of findings reported.

A number of studies have reported improvements in cognitive performance of schizophrenic patients over time (Addington 2000; Albus et al 2002; Censits et al 1997; Gold et al 1999; Hoff et al 1992a; Hoff et al 1999; Landro 1994; Nopoulos et al 1994; Sweeney et al 1991). Addington et al (1991) noted an improvement over 6 months in the cognitive performance of 38 acutely ill schizophrenic patients, which was correlated with positive symptoms improvement. However, deficits on the WCST and word fluency persisted throughout periods of remission (Addington and Addington 1991; Addington et al 1991). Albus (2002) showed improvement in visuo-motor processing/attention (Trial-making B, Stroop test, and Digit symbol) in both controls and first episode schizophrenics and in verbal learning (CVLT 1-5) in first episode patients between initial hospitalisation and follow up 2 years later. Symptoms had no effect on neuropsychological performance and although visuo-motor

processing/attention was influenced by medication status, verbal learning may be state related, while deficits on semantic memory (WMS-R Logical memory) remained stable throughout (Albus 2002). Between discharge from hospital following clinical recovery and again 1 year later, Sweeney et al (1991) demonstrated an increase, but not normalisation, in psychomotor (Digit symbol and Finger tapping) and verbal recognition memory scores (RAVLT) in acute schizophrenia patients, although the latter result could be reflective of practice effects on the RAVLT (Sweeney et al 1991). However, Nopoulos et al (1994) reported improvements in complex attention (Trial-making B and Stroop response set shifting) correlated with psychotic symptom improvement and stable deficits in memory (RAVLT 1-5 and delayed recall, WMS-R Logical memory, WMS-R Paired associates) in patients between time of hospitalisation and 1 to 2 years later (Nopoulos et al 1994). Hoff et al (1999) showed 42 first episode schizophrenia patients in the first 2 to 5 years of illness to perform consistently less well relative to controls, while a remittance of psychotic symptoms (but no change in negative symptoms) was positively correlated with cognitive performance, except in verbal memory, where they failed to show any improvement (Hoff et al 1999). Similarly, Censits et al (1997) showed no differences in cognitive function between never medicated first episode patients and previously treated patients, suggesting no impact of medication on performance over time. A general improvement in cognitive function in patients was associated with improved symptomatology, however 10 of the 15 neuropsychological variables positively correlated with negative symptoms, above all anhedonia, suggesting that negative and not positive symptom amelioration effected neuropsychological change. Gold (1999) showed more extensive improvement in both performance and general IQ, but stability of function in verbal IQ only and also showed this to be related to negative rather than positive symptoms. Finally, Morrison et al (2000) compared patient performance on NART IQ, a measure of verbal intellectual ability, at baseline and 7 years later and revealed no change. However, although mean change in score over time was only 1.4, 2 of the 45 patients assessed did show a dramatic score increase from –16 to +18 over this period (Morrison et al 2000).

Several longitudinal studies have also shown stable cognitive deficits over time (Heaton et al 2001; Hughes et al 2002; Hyde et al 1994). Heaton et al (2001) showed stable neuropsychological performance deficits between schizophrenia patients and controls over short (1.6 years) and long (5

years) periods. Small improvements in first episode patients' motor function were attributed to practice effects paralleling those in the control group. However, a lack of chronically institutionalised schizophrenia patients makes these results less generalisable. Hughes et al (2002) showed the relationship between improvements in symptoms and neuropsychological performance to be non-causal, and as such patients showed only stable neuropsychological deficits over time (Hughes et al 2002). Russell and others (1997) demonstrated lower premorbid IQ scores (WISC-R) in patients assessed at a mean age of thirteen, up to nineteen years before illness onset. Although demonstrating significantly poorer scores relative to controls, patients showed no difference between their current IQ scores (WAIS-R) and premorbid scores (WISC-R) nearly two decades earlier, suggesting a stable intellectual ability over time and throughout the course of their illness. However, it should be noted that 13 of the 34 patients followed up, were diagnosed as schizophrenic in childhood, of which 9 completed their baseline IQ test at the same time or shortly after this diagnosis (Russell et al 1997).

Stirling et al (2003) did demonstrate cognitive decline in 3 out of 9 subtests (WAIS-R Object assembly, picture completion and recognition memory for faces) in a 10-year longitudinal study of a mixture of first episode schizophrenics and schizoaffective disorder patients. Without a comparison group it is difficult to be sure of the importance of evidence of decline in these patients, especially over such an extended period of time (10-12 years) (i.e. although average age at onset was 26.4 years, a 32 year old at onset would be 44 at follow-up, an age at which age-related decline cannot be ruled out). Persistent negative symptoms predicted poor functional outcome but were not related to neuropsychological performance. Furthermore, although there were significant deficits in onset performance on several tests, these remained stable over time. The authors suggest a pattern of long-term deterioration in fronto-parietal networks (Stirling et al 2003).

1.3.1.2 Cross sectional studies

Several studies have explored differences in neuropsychological performance across age groups in schizophrenia (Bilder et al 1992; Fucetola et al 2000; Heaton et al 1994; Hyde et al 1994; Mockler et al 1997). Heaton et al (1994) showed three age groups of schizophrenic patients (85 early onset young schizophrenics, 36 early onset old schizophrenics, 22 late onset schizophrenics) to perform

significantly differently on neuropsychological tests from both controls and Alzheimer's patients, but not from one another. Mockler et al (1997) reported a similar result investigating performance across five and then two age cohorts. There was no decline in any age group between premorbid and current IQ, nor were there any differences in general neuropsychological performance between groups which could be considered age related (Mockler et al 1997). Although Fucetola et al (2000) showed an age related decline in cognitive performance similar to that apparent in a control group, decline in an aspect of executive function (i.e. abstraction as measured by WCST) was found to be greater in patients than in controls (Fucetola et al 2000).

1.3.2 Summary of stability of cognitive function in schizophrenia

These studies on the whole suggest a lack of cognitive deterioration through the course of the schizophrenic illness, coupled in some instances with slight improvements in varied cognitive domains due to a remittance of psychotic symptoms (Addington and Addington 1991; Addington et al 1991; Nopoulos et al 1994), negative symptoms (Censits et al 1997; Gold et al 1999) or unaffected by symptoms at all (Albus et al 2002; Hughes et al 2002). There is a lack of consistency of medication application across studies, with some patients medicated at follow up but not at baseline (Censits et al 1997; Gold et al 1999) and at least one study where patients were not medicated at all among those on medication at both assessments (Nopoulos et al 1994). This makes it difficult to extrapolate what aspects of perceived improvement are due to medication (which admittedly will vary in type and dosage across and within patient samples), symptomatology change and/or practice effects, and in the latter especially so given the varied follow-up periods across studies. The inclusion of a comparison group at baseline and follow-up is crucial in order to compare any apparent deterioration with performance in a control group, i.e. Albus et al (2002) noted that due to an improvement in visual memory over time in the control group, the patient group showed an apparent deterioration over time (Albus et al 2002). Some of these difficulties are removed from the cross sectional studies of age related changes in neuropsychological performance, whose findings tend to support the notion of stability of function demonstrated by longitudinal investigations in schizophrenic patients.

1.3.2.1 Cognitive deficits and relationship to functional outcome

Cognitive deficits have often been described as epiphenomenona, that is, attributable to the effects of the negative symptoms (lack of motivation, anhedonia, avolition) or positive symptoms (hallucination and delusion interference) of the disorder. However, several studies have reported improvements in symptomatology of patients on medication, in the absence of coincidental improvements in cognitive function, suggesting that psychotic symptoms and neuropsychological function may be relatively independent of one another (i.e. Goldberg et al (1993b) as cited in (O'Carroll 2000). Studies of functional outcome in schizophrenia have also shown aspects of cognitive ability to be predictive of outcome in patients i.e. verbal memory is predictive of all functional outcomes and vigilance abilities predict competence in social problem solving and skill acquisition (Green 1996). General cognitive measures have been shown to predict occupational ability and outcome on anti-psychotic medication (i.e. clozapine) (Meltzer et al 1996), while a later meta-analytic study by Green et al (2000) revealed considerable effect sizes demonstrating a significant relationship between neurocognitive measures and functional outcome (i.e. measures of immediate and secondary memory, card sorting and vigilance) (Green et al 2000).

1.3.3 Premorbid general intellectual ability in schizophrenia

Several investigators have hypothesised that a deterioration in intellectual and cognitive ability may occur before the onset of psychosis, or at least before definitive signs of overt psychosis manifest themselves. However, comparisons between premorbid or prodromal and current intellectual ability in schizophrenia patients can be difficult, above all when measurements shortly prior to illness onset may not be available, or if available, not directly comparable with current standardised measures of general intellect (see Table 1D in Appendix 1).

1.3.3.1 Measures of premorbid and current intellectual ability

The NART, which requires the ability to pronounce irregular words (i.e. campanile, drachm), is a widely used test of premorbid ability in schizophrenia and has been shown to account for 66% of the IQ variance in full scale WAIS. The results of factor analytic studies show it to load considerably higher on the 'g' factor of general intelligence than 9 of 11 WAIS sub-tests (Crawford et al 1992).

Evidence also supports NART as a stable measure of intellectual ability in acutely ill, unmedicated schizophrenia patients, which is unaffected by psychotic symptoms (O'Carroll et al 1992). Crawford et al (1992) showed no significant differences between community residing schizophrenia patients and controls on this test. However, long stay schizophrenia patients were significantly lower in scores on both NART and WAIS IQ. This could suggest an illness related reduction in scores on the NART in chronic schizophrenia patients, but is also suggested as representative of a difference in premorbid IQ predating illness onset (Crawford et al 1992). Both O'Carroll et al (1992) and Crawford (1992) showed patients to score lower on the WAIS than on the NART, which authors posit as suggestive of a decline from premorbid to current intellectual function. Some studies have therefore adopted this test as a valid measure of premorbid function, based on its reported resistance to cerebral dysfunction and dependence on acquired knowledge about words (O'Carroll et al 1992).

The usage of NART to estimate premorbid levels of function has however been challenged. A comparison between NART IQ, WAIS-R IQ and IQ measured premorbidly in childhood, in 24 adult schizophrenia patients, showed no change between premorbid and current IQ levels (as measured by WAIS-R), but significant differences between both measures when compared with NART. The authors suggest this difference is especially prominent in groups where IQ deviates from the average (Russell et al 2000). Indeed, Nelson (1990) advises against using the NART in extremes of scoring on this test, such that those at ceiling level will tend to incline lower towards the mean, whereas those at base levels will incline higher towards the mean (Nelson et al 1990). The lowest achievable estimated score of intelligence on this test is 84 points, a fact that Russell et al (1998-letter to editor) stress is likely to give the appearance of 'premorbid' intellectual ability within normal limits (Russell and Murray 1998). NART may in fact be both over and under estimate (e.g. in younger patients) premorbid function in schizophrenia patients, particularly when it is a test reliant on acquired knowledge and educational achievement. Any interruptions in schooling, as is common in early onset conditions, could prevent patients reaching a higher score, which would have been predicted based on performance in other domains of function (Russell and Murray 1998).

A further difficulty is also evident (despite an overlap in variance between the two), in the type of abilities the NART and WAIS are actually measuring. Lezak (1995) reports higher correlations of the NART with WAIS verbal IQ (VSIQ) than with performance IQ (PSIQ) or full scale IQ (FSIQ) (Lezak 1995). In the 1960's, Catell's concept of crystallised intelligence was operationally defined by tests measuring the influence of education and acculturation on intellectual performance (i.e. verbal ability and vocabulary). Conversely, fluid intelligence was operationally defined by tests measuring a biological capacity to accrue knowledge, such as inductive and spatial reasoning (Brody 1992). Catell argued that because of the assumed biological basis of fluid intelligence, it was the factor most vulnerable to prenatal insult, brain damage and age related decline, whereas crystallised intelligence would remain fairly intact (Brody 1992). These forms of intellectual measurement are often referred to as 'hold' and 'no hold' tests, where 'hold' tests are considered insensitive to forms of brain damage and 'no hold' tests are not (Lezak 1995). Several studies have shown preserved functioning on measures of crystallised intelligence in schizophrenia, such as tests of language and vocabulary (Binks and Gold 1998; Saykin et al 1994), while WAIS-R vocabulary has been touted as a better estimate of premorbid intelligence than that measured by NART. On the other hand, full scale WAIS-R IQ incorporates many different sub tests, broadly classed as measures of verbal and performance IQ. WAIS-R IQ is therefore a more robust indicator of fluid intelligence and is sensitive to any subtle changes in specific cognitive ability conducive with the development of brain abnormalities in localised areas.

Longitudinal, prospective and retrospective study designs are often limited by those measures used premorbidly to assess intellectual function in individuals who later develop schizophrenia. For this reason, many studies rely on standardised psychometric tests or standard school assessments to indicate levels of performance in their samples. It must be noted therefore that the different forms of test measurements used will often confound generalised conclusions based on findings across these studies.

1.3.3.2 Follow-back studies

The possibility that premorbid intellectual function is compromised in individuals who later develop schizophrenia has been extensively explored using follow-back studies, which take a present cohort of schizophrenic patients and compare current cognitive performance with scores on tests of intellectual and cognitive function acquired premorbidly. One of the earliest follow-back studies compared premorbid IQ at age 7 to 8 years old (Kulhman Cleveland IQ test) between 36 adult schizophrenia patients with 36 of their adult siblings and 35 adult controls and 35 of their adult siblings, having matched all patients and controls for IQ. A significant difference in IQ at this age was present between the patients and their unaffected siblings, a difference not extended to the matched controls and their siblings (Lane and Albee 1964). Ambelas et al (1992) compared premorbid IQ scores from childhood (10 to 15 years old) between 18 males who later became adult schizophrenia patients and 18 male controls, all seen in childhood at a child guidance centre. Controls had higher IQ, speech and language scores than those individuals who went on to develop schizophrenia by the age of 27 (Ambelas 1992). Similarly Isohanni et al (1998) investigated hospital treated psychiatric disorders and past school performance in 11017 adults of a Finnish Birth Cohort and showed low school marks at age 16 to be predictive of non-psychotic disorders, whereas being in an inappropriate class at age 14 predicted future hospital treated disorders (Isohanni et al 1998). Russell et al (2000) compared a childhood measure of IQ in 24 adult schizophrenia patients with current measures of WAIS-R and NART IQ, and found no difference between IQ scores (Russell et al 2000). Finally, Jones et al (1994) compared premorbid childhood IQ between 50 adult schizophrenia patients and 50 adults with affective disorder, both having been seen in childhood at a child psychiatric clinic and found those who were schizophrenic to have a lower premorbid IQ score than the affective disorder patients (Jones et al 1994a).

Premorbid general intellectual decline may also be apparent at a significant point in development, in individuals who go on to develop schizophrenia. Ang et al (2004) similarly compared 30 first episode male schizophrenia patients and 30 male controls (all in the military service and with a mean age of 20 years), on standardised school exam scores (GCE and PLSE) at two periods between the ages of 12 and 16 years old. Although both groups showed a general reduction in mathematics performance

between exams at age 12 to exams at age 16, the drop between scores in mathematics was significantly greater in those who went on to develop schizophrenia between 3 and 8 years later (Ang and Tan 2004). Fuller et al (2002) compared 57 male and 13 female adult schizophrenia patients on premorbid standardised school assessment scores (Iowa tests of educational ability, covering 6 domains of function including reading, vocabulary, comprehension, language and maths) at ages 9, 13 and 16. Although school scores in this group were non-significantly below the state average at both 9 and 13 years old, there was an improvement in performance on some tests between ages. However, there was a statistically significant drop in scores between the ages of 13 and 16 years old, to significantly below the state average and specifically on tests of language (on which no improvement had been demonstrated at any point) (Fuller et al 2002).

Finally, the possibility that separate symptom clusters may have discrete yet overlapping aetiologies should also be considered. Guerra et al (2002) took a different approach to follow-back investigation and explored, using principal component analysis and multiple regression, the possible predictors of specific symptom clusters, rather than of schizophrenia as a disorder. Interestingly, family history of schizophrenia was identified as a predictor for delusions and hallucinations and paranoia, family history of bipolar disorder was a predictor for negative symptoms and disorganisation, while obstetric complications were predictive of paranoia. Delusions, hallucinations, and mania were predicted by good premorbid intellectual function, whereas negative symptoms were predicted by early first psychiatric admission and disorganisation by low premorbid intelligence. Paranoia, delusions, and hallucinations were also predicted by poor adolescent school functioning. Negative symptoms, delusions and hallucinations and paranoia all had a developmental origin, although these were manifested as different childhood difficulties (Guerra et al 2002).

1.3.3.3 Birth and conscript cohort studies

Birth cohort studies have prospectively investigated a diverse range of psychosocial variables and their possible relationships with the development of schizophrenia in a proportion of their sample and benefit from the substantial size of their sample and the amount of data acquired over time. Jones et al (1994) showed schizophrenia to be associated with low IQ in childhood in a British National Birth

Cohort study, while Cannon et al (2000) reported a similar finding using a birth cohort to identify adult schizophrenic patients, their unaffected siblings and controls who had previously undergone cognitive assessment at ages 4 and 7 years old. Although patients and their siblings performed significantly less well than controls on tests at 4 and 7 years old, there were no differences between patients and their siblings, suggesting that function at this stage may be reflective of a trait deficit (Cannon et al 2000a; Jones et al 1994a). Crow et al (1995) also showed that children who go on to develop schizophrenia have poorer reading and mathematical ability at the age of 7 and are slower in achieving developmental milestones relative to equivalent aged control children and children who later develop affective psychosis or neuroticism (Crow et al 1995).

Prospective conscript cohort studies are additionally advantageous in that most males eligible for service between 16 and 17 years old will be assessed with standard psychometric tests at entry to the military service and at regular points thereafter. This reduces the labour intensiveness associated with birth cohorts, which must follow a sample from birth through the putative period of risk, thus requiring monitoring over a longer period of time and suffering from high rates of attrition in the process. Caspi et al (2003) compared performance of 44 adult schizophrenic patients, between a first psychometric assessment (when all were 16-17 year old Israeli draft board conscripts and during which time, and for 2 years afterwards, none had any psychotic symptoms), and a second psychometric assessment between 2 and 14 years afterwards (prior to discharge following a first episode schizophrenia). Although there were no changes in conscript performance between the two assessment points, comparison with an age matched control group revealed poorer performance of the patients both premorbidly and following first episode psychosis, as well as a deterioration relative to controls on a test of abstract reasoning, mental speed and concentration (Caspi et al 2003). Like Jones et al (1994), David et al (1997), in an investigation of 50, 000 18 year old male Swedish army conscripts (195 of which developed schizophrenia and 192 of which developed a non-psychotic disorder), showed low IQ (specifically in verbal and mechanical knowledge) to be associated linearly with an increased risk for schizophrenia, while the effect was similar, but less linear for those who later developed non-psychotic disorders (David et al 1997). In the same way, Gunnell et al (2002)

showed poor verbal and performance intelligence test scores in 18-year-old Swedish conscripts to be associated with psychosis development 5 years later (Gunnell et al 2002).

1.3.4 Summary of the differences between premorbid and current general intellectual ability in schizophrenia

In spite of large participant numbers in both cases, there is poor statistical power due to the low rate of eventual schizophrenia development in these samples. Moreover, studies are weakened by low attrition and outdated or overly general methods of assessment, especially longitudinal designs. However, despite this, findings from follow back and cohort studies seem to consistently suggest that low general intellectual ability from an early age, in individuals who develop schizophrenia in adulthood, may be considered a risk factor for schizophrenia (Cannon et al 2000a; David et al 1997). However, this is not a discrete risk factor given that low IQ is also present in individuals who later develop affective and non-psychotic disorders (David et al 1997; Guerra et al 2002; Isohanni et al 1998). In addition, the declines in intellectual function which have also been reported occurring in early adolescence (12-16 years old), suggest that if not pre-existing and deteriorating further, then cognitive deterioration in those who later develop schizophrenia may occur at a significant developmental stage pre adulthood (Ang and Tan 2004; Fuller et al 2002).

It is therefore encouraging that cognitive indicators of risk for the later development of schizophrenia may be present a considerable time before onset. With this in mind, researchers have increasingly focused on the investigation of groups of individuals who are currently well, but at an enhanced risk for development of the disorder, as a means of identifying those factors, which may exclusively predict schizophrenia onset.

1.4 Genetic liability to schizophrenia

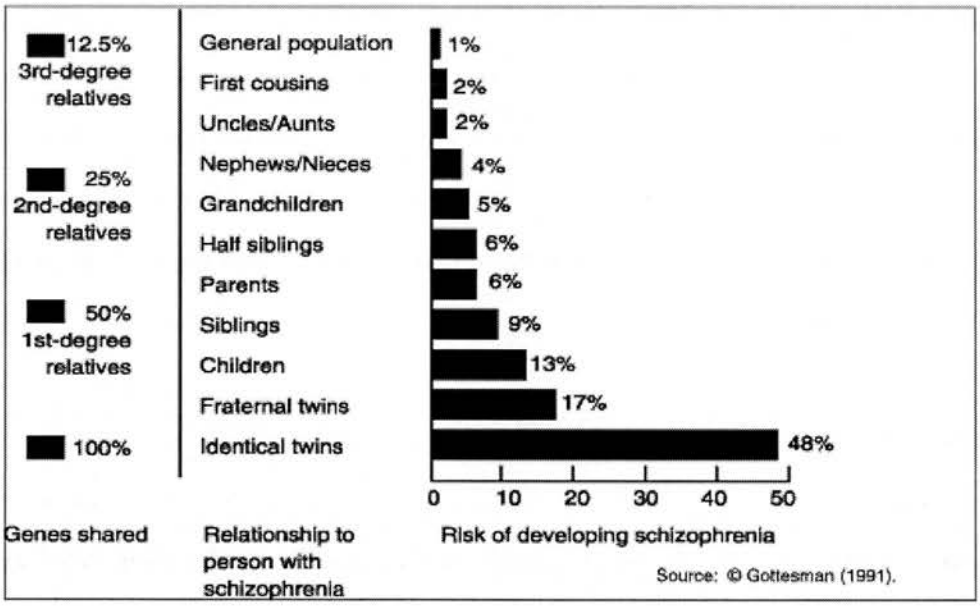
1.4.1 Genetic liability

Although there is a risk of 1 in 100 that a member of the general population will develop schizophrenia, this likelihood is approximately 10% in individuals with a first degree relative with the disorder. Moreover, family, twin and adoption studies have revealed the risk of psychosis to increase

as a function of the number and proximity of relatives affected, such that risk is about 46% when both a parent and a sibling manifest the disorder, and about 50% for the unaffected member of a pair of monozygotic twins (Gottesman 1991)(see figure 1.2). While it is notable both that schizophrenia is not a Mendelian condition and that a significant proportion of schizophrenic patients do not have genetically related affected relatives, nonetheless genetic predisposition is the most robust risk factor for schizophrenia to date (Kendler and Diehl 1993).

The development of schizophrenia is now conceptualised as occurring along two continua (Cannon et al 2003). The first being the genetic-environmental continuum, where the interaction between genetic and non-genetic influences increases the risk for manifestation of the schizophrenia phenotype, and the second, the environmental or maturational continuum, impacting throughout the developmental stages of life. Because the genotype alone is not sufficient for the development of schizophrenia, deficits present in unaffected relatives are considered 'vulnerability' or 'trait' deficits, while those associated with the overt phenotypic expression of schizophrenia could be considered 'disease-related' or 'state-related' deficits (Cannon et al 2003).

Figure 1.2 Relative risk for schizophrenia (Gottesman 1991)



Genetic studies of schizophrenia have attempted to identify relationships between genes and familial or population based schizophrenia. Linkage studies have investigated associations between specific genetic loci and the incidence of schizophrenia in multiple families, segregation analyses have examined transmission through disease phenotypes in nuclear families and pedigrees, and association studies have compared the frequency of specific alleles in non genetically related affected individuals and matched controls (Kendler and Diehl 1993; Weinberger et al 2001). The inconsistent results which have previously emerged may be due to the weak predictive relationship between the phenotype and genotype, the limitations of restrictive diagnostic classifications, and the heterogeneity and symptom overlap in psychiatric disorders (Sivagnansundaram et al 2003). Nonetheless, more recently, a number of linkages to chromosomal regions have been shown across studies (i.e. loci 8p and 22q), and several candidate genes have been proposed, all of which act upon brain synaptic connectivity through their varying influence over the transmission of the excitatory neurotransmitter glutamate at N-methyl-D-aspartate (NMDA) receptors (i.e. G72, D-amino acid oxidase (DAAO), Neuregulin (NRG1), Regulator of G-protein signalling (RGS4), Dysbindin (DTNBP1), Proline dehydrogenase (PRODH), and Catechol-O-methyltranferase (COMT)). Given the apparent genetic complexity of the disorder, it makes it more likely a product of several 'susceptibility' genes, some of which may also be contenders for the underlying genetic components to other psychiatric conditions, such as bipolar disorder. In fact, Gottesman and Shields initially postulated polymorphism as a model for the genetic underpinnings of schizophrenia in their liability/threshold model as early as 1967. This assumes that liability for the disorder is distributed normally in the population, and will be manifested through the additive effects of multiple genes and the environment. The enhanced genetic liability in relatives of schizophrenics increases their chances of exceeding a hypothetical threshold for the manifestation of the illness (McGuffin et al 1995).

Becker (2004) outlines a similar hypothetical model for complex genetic disorders such as schizophrenia, called the Common Variants/Multiple Disease Hypothesis of Complex Genetic Disorders. Comorbidity is well known in disorders such as schizophrenia and bipolar disorder, while schizoaffective disorder is also common in families with incidences of both schizophrenia and/or affective disorder. Becker suggests that this overlap of clinical characteristics is due to multiple

interacting genetic loci contributing small effects in an additive manner to several disorders, and that when combined with external environmental influences such as stress, pollution, diet and developmental stages, the specific disorder may manifest itself (Becker 2004). These models propose that multiple disease producing alleles occur at high frequency within the general population and explain both the observation of increasing risk with an increasing number of affected relatives and the persistence of such disease in the population, despite the negative impact on reproductive fitness (Becker 2004; McGuffin et al 1995).

However, the potential multitude of gene interactions fundamental to schizophrenia, will also give rise to a proliferation of complex phenotypes. This highlights the need for a simplification in the search for susceptibility genes, by focusing on different families in which the disorder aggregates or in distinct clinical sub-types of the disorder, which may reflect separate aetiologies and separate susceptibility genes (Kendler et al 1997; Weinberger et al 2001). In this way it is hoped that more specific phenotypes will provide clues to its genetic underpinnings.

Susceptibility genes may impact directly on the intermediate phenotypic expression of the disorder. Weinberger et al (2001) asserts that this relationship makes intermediate phenotypes powerful indicators of genetic vulnerability in families. An intermediate phenotype can take many forms, be it neuropsychological, neurophysiological, biochemical, neuroanatomical or endocrine (Gottesman and Gould 2003). Gottesman and Gould defined an endophenotype for a disease as 'a measurable component unseen by the unaided eye along the pathway between disease and distal genotype'. However, in order to be a reliable and useful endophenotype, it must fulfil certain criteria. Firstly, it must have specificity for the disorder under study and be an enduring stable trait throughout the course of the illness, whilst being relatively invulnerable to state related effects. It must also be heritable, co-segregate in families with the illness and be present and stable in unaffected relatives with the disorder to a greater extent than in the normal population (Gottesman and Gould 2003; Heinrichs 2001).

1.4.2 Family and High Risk studies

1.4.2.1 Family studies

Investigation of individuals at an enhanced genetic risk for the disorder has allowed for the elucidation of any underlying cognitive trait abnormalities of schizophrenia. These assessments are freed from some of the more difficult confounds such as stage of illness, symptom types and medication effects, due to the fact that none of the sample are actually ill (and are unlikely to become ill if over the age of 45). Indeed, cognitive impairments in this group, based on a comparison with a matched control group, are inherently subtle and performance would not generally be classified as sub-normal. This makes differences in performance between groups even more compelling. Impairments found in unaffected relatives of schizophrenics, relative to healthy controls, which are both stable and milder than but consistent with impairments found in schizophrenia, may qualify as 'vulnerability' deficits, or reflections of a predisposition to the disorder. However, importantly, cognitive deficits associated with schizophrenia could also be considered intermediate phenotypes for the disorder, given that impairments are generally more severe in patients with schizophrenia, than in unaffected relatives.

1.4.2.2 High Risk studies

Without measuring neuropsychological performance in relatives of schizophrenics over time, it is difficult to assess how far cognitive deficits reflect an increased risk for the development of schizophrenia. Secondly, it is unclear whether development of psychotic symptoms interferes with or is associated with further reductions in performance and to what extent changes could be viewed as predictors of future psychosis. Prospective high-risk studies have attempted to resolve these issues by monitoring the cognitive function of young people at high risk of schizophrenia, by virtue of their close blood relationship to schizophrenics, over an extended period. In such a way the development of the illness in some participants can be investigated in relation to potential cognitive indicators (Cornblatt and Obuchowski 1997; Ott et al 1998).

High-risk groups (defined as groups of people who have a greater statistical chance of developing schizophrenia relative to the general population) have traditionally been selected based on genetic relatedness, a more robust risk factor than any previously described environmental factors (Cornblatt

and Obuchowski 1997; McGuffin et al 1995). The majority of high-risk projects recruited the offspring of schizophrenics, with a risk for development of 10% with one affected parent. However, this criterion precludes generalisation to the population as a whole, because findings will be based on a familial form of schizophrenia. Moreover, while this method allows for follow up, most early investigations have had to span at least 20 years in order to monitor performance of schizophrenic offspring through the period in which they are most likely to develop schizophrenia, leading to high rates of attrition. This is further confounded by the relatively small number of participants who do eventually develop schizophrenia, thus it has been crucial for initial samples to be large enough to withstand both high rates of attrition and low rates of transition to psychosis (Cornblatt and Obuchowski 1997; Niemi et al 2003).

In spite of these difficulties, high-risk studies have provided an interesting insight into the development of high-risk children over time. The recent comprehensive review of Niemi et al (2003), details the findings of childhood developmental abnormalities from high risk studies (i.e. those at genetically enhanced risk for development of the disorder)*(i.e. New York Infant Study (1952)*(established to test pandysmaturation hypothesis) *Copenhagen High Risk Study (1962), Edinburgh High Risk Study (1994), Israeli High Risk Study (1964), Minnesota HR study (1968), Rochester Longitudinal Study (1970)* (data collection began during affected mother's pregnancy), *New York High Risk Study (1971), Stony Brook High Risk Project (1971), University of Rochester Child and Infant Study (1972), Jerusalem Infant Development Study (1973)* (data collection began during affected mother's pregnancy), *Swedish High Risk Study (1973)* (data collection began during affected mother's pregnancy), *Helsinki High Risk Study (1974), Emory University High-Study (1981) Boston National Collaborative Perinatal Project (1959)* (data collection began during affected mother's pregnancy), and *St Louis Risk Research Project (1966)* (Niemi et al 2003). Niemi et al (2003) concluded that children at high-risk for schizophrenia (between the ages of 0 and 12) showed greater developmental abnormalities relative to control children (i.e. poor psychomotor development, and impaired coordination, balance and gross motor skills). In addition, they report the presence of lower intellectual, memory and attentional function and more maladaptive emotional and social behaviour in high-risk children when compared to controls (Niemi et al 2003). These findings support evidence

from the follow back, conscript and cohort studies, which also show correlations between delayed motor development (Jones et al 1994b), and poor general intellectual ability, in children who later develop schizophrenia (Crow et al 1995; David et al 1997; Kremen et al 1998a). Several of the original high-risk studies have since followed participants over an adequate period of time to allow for investigation of adult clinical outcome (*Copenhagen High Risk Study (1962), Finish Adoption Study (1962), Israeli High Risk Study (1964), Jerusalem Infant Development Study (1973), New York Infant Study (1952), New York High Risk Study (1971), Swedish High Risk Study (1973), St Louis Risk Research Project).* Results from these follow-up studies provide evidence of factors which are predictive of future schizophrenia development such as poor cognitive, social and emotional function, and greater prevalence of neurotic and psychotic symptoms (Niemi et al 2003).

However, in addition to the noted methodological limitations of traditional high-risk models, clinical and neuropsychological measures incorporated into studies, which began 20 or so years ago, are often inappropriate or outdated by the time participants reach their age of maximum risk for the disorder. A wider range of measures, as well as a shorter follow up period and more enriched sample of high-risk participants is therefore required to improve understanding of both trait deficits and any state related factors which are prevalent in the pre-psychotic phase. Ultra high-risk or close-in strategy models have since been developed to increase the rate of sample participants eventually developing psychosis, and decrease the follow up period preceding this development. This is facilitated by the selection of help seeking participants close to the age of maximum risk for development of the disorder. In this way participants are generally experiencing changes in mental functioning, are most probably symptomatic (attenuated or intermittent psychotic symptoms), and in some cases may also have close relatives already affected by a schizophrenia related disorder (McGorry et al 2003). The advantages of this model include the early identification of young people who may quickly develop a psychotic disorder, and in some cases early intervention which may ameliorate its development (Lieberman et al 2001; Wolkin and Rusinek 2003). However, if functional changes are occurring at an earlier stage, then crucial information regarding the development of the disorder may be available even before clinical manifestations of psychosis and is more likely to be gleaned from individuals who have not yet sought help.

1.5 Cognition in unaffected relatives of schizophrenics

1.5.1 Attention

Erlenmeyer-Kimling and Cornblatt (1992) (New York High-Risk Project) have asserted that global attention is a consistent deficit in offspring of schizophrenics, and a potential behavioural marker for later schizophrenia development (Erlenmeyer-Kimling and Cornblatt 1992; Erlenmeyer-Kimling et al 2000). High-risk studies therefore provided initial evidence of sustained attention deficits in relatives of schizophrenics (Mirsky et al 1995; Neuchterlein and Dawson 1984). Sustained attention is considered the ability to maintain alertness over extended periods of time and is generally assessed using the Continuous Performance Test (CPT), during which participants are presented with a continuous stream of stimuli (i.e. letters, numbers and shapes) and required to respond to selected target stimuli while ignoring all others (Lezak 1995). Some studies have reported poorer CPT performance in relatives compared to controls using the verbal aspect of task (i.e. numbers) (Chen et al 1998; Egan et al 2000), poorer performance on the more difficult aspects of CPT (i.e. blurred single target version) (Maier et al 1992) or on distraction/degraded stimulus conditions (Egan et al 2000; Saoud et al 2000; Wittorf et al 2004), worse performance on the verbal over spatial CPT stimuli (i.e. shapes) (Appels et al 2003), spatial over verbal stimuli (Laurent et al 2000; Laurent et al 1999), both (Franke et al 1994), or no differences at all on either verbal, spatial or auditory stimuli (Cosway et al 2002; Faraone et al 1995; Kremen et al 1998b). However, methodological differences across studies, such as non randomised stimuli presentation (Appels et al 2003), studies controlling for IQ differences where others do not (Cosway et al 2002; Laurent et al 1999) and inconsistent usage of different test versions, has lead to difficulties in generalising results. A recent meta-analysis showed a small to moderate effect size of 0.35 for CPT, based on 11 studies of unaffected biological relatives and controls, although a significant Q statistic (27.6, $p<0.01$) indicated considerable heterogeneity across investigations (Sitskoorn et al 2004a). Heinrichs (2000) reported a similar lack of homogeneity in CPT results in schizophrenia patients, possibly also attributable to the wide variety of types and formats of CPT applied (Heinrichs 2001).

The trail-making test is often included in studies of neuropsychological performance as a test of attention and executive function. Part A involves the joining up of randomly scattered numbers and is a measure of perceptual motor speed, while Part B involves the added condition of alternating sets, with letters to be joined consecutively after each number. While a number of studies have reported significant differences between groups on both aspects of the trail-making test (Gochman et al 2004; Ismail et al 2000; Wittorf et al 2004), some report differences only on trails B (Egan et al 2001; Keefe et al 1994; Laurent et al 2000; Laurent et al 1999) and others no significant differences on either aspect (Appels et al 2003; Dollfus et al 2002; Goldberg et al 1995; Zalla 2004). Trails B appears to be impaired in relatives compared to controls, even after controlling for the contribution of perceptual motor speed. This aspect of trail-making may therefore be more appropriately viewed as a measure of alternating sets, and therefore a test of executive function (Keefe et al 1994; Laurent et al 2000). Sitskoorn et al (2004) reported an effect size of 0.38 for trail-making A and a considerably larger effect size of 0.51 for trail-making B (time on part B and part B-part A), based on the meta-analysis of 10 and 12 studies respectively (Sitskoorn et al 2004a).

Unfortunately, the trend for aggregating neuropsychological performance scores has lead to an obfuscation of the true levels of deficit in the domain of attention. Although Kremen et al (1994) identified three separate factors, which could be considered components of attention, not all studies, have aggregated tests specific to these factors. These include Perceptual motor speed (Stroop test, digit symbol, digit cancellation tests and the trail-making test), Mental control/encoding (WAIS digit span, arithmetic and mental control sub-tests), and Sustained Attention (CPT, dichotic listening) (Kremen et al 1994). Faraone et al (1995) and Kremen et al (1998) showed significant differences between relatives and controls in sustained attention after controlling for age, gender, and IQ. However, given the non-significant difference in auditory CPT, this will have been mainly attributable to poor performance on the dichotic listening test (Faraone et al 1995; Kremen et al 1998b). Neither of the two groups showed significant differences between unaffected relatives and controls on perceptual motor speed or mental control/encoding (Faraone et al 1995; Kremen et al 1998b). Similarly, Mirsky et al (1992) showed no differences between groups on the latter factor (Mirsky et al 1992, as cited in (Kremen et al 1994)). Cannon et al (1994) showed controls to perform significantly

better than both schizophrenic probands and relatives of schizophrenics on their aggregate score of attention, which included WAIS Digit span, trail-making A, WAIS Digit symbol, Stroop test and CPT vigilance/ distractibility test (Cannon et al 1994). Differently again, Krabbendam et al (2001), identified working memory ability (WAIS Digit span and modified trail-making/concept shifting test), and speed (Stroop test and digit symbol substitution test) as two of four factors emerging from a principle components factor analysis. Multiple regression analysis showed them to be significant predictors of family group membership (Krabbendam et al 2001). This pattern of findings suggests that some aspects of attention, as defined by combined performance on various tests, may be impaired in the unaffected relatives of schizophrenia patients. However, aggregated scoring may mask true levels of dysfunction. Moreover, some tests selected as measures of attention, such as digit span, may be better described as measures of verbal short term or working memory.

1.5.2 Executive function

A number of family studies have also shown deficits in relatives of schizophrenics on tests of executive function, such as the Stroop test, which requires the timed inhibition of the response to name the colour word presented and instead name the colour of ink in which the word is printed (Cannon et al 1994; Dollfus et al 2002; Faraone et al 1995; Kremen et al 1994; Rybakowski and Borkowska 2002; Zalla 2004). However, several family studies have also shown non significant differences between groups for this test (Byrne et al 2003; Goldberg et al 1995; Kremen et al 1998b; Laurent et al 2000). Sitskoorn et al (2004) reported a small effect size of 0.28 for the Stroop test, based on the meta-analysis of 8 family studies (Sitskoorn et al 2004a).

Less robust differences are also apparent on the Wisconsin Card Sorting Test (WCST), which measures conceptual shifting (categories) and getting stuck in a previous mode of responding (perseveration)(Appels et al 2003; Condray et al 1992; Dollfus et al 2002; Goldberg et al 1995; Ismail et al 2000; Keefe et al 1994; Kremen et al 1998b; Laurent et al 1999; Saoud et al 2000; Wittorf et al 2004; Zalla 2004) with only a few exceptions (Egan et al 2001; Faraone et al 1995; Franke et al 1992; Rybakowski and Borkowska 2002; Toomey et al 1998)(Mirsky 1992 et al as cited in (Kremen et al 1994). Kremen et al (1992) suggest that increased WCST perseverative response but preserved or

less impaired non-perseverative response (i.e. categories) in healthy siblings relative to controls (i.e. Kremen 1992, Egan et al 2001, Toomey et al 1998) highlights a dichotomy between trait and state deficits on this test. However, this test is also shown to be associated with age, so it's worthiness as a cognitive indicator of vulnerability may be limited (Franke et al 1992). Sitskoorn et al (2004) showed an effect size of 0.29 for WCST performance between relatives of schizophrenics and controls (Sitskoorn et al 2004a).

The small effect size for the WCST and Stroop, and considerable effect size for trails B, reported by Sitskoorn et al (2004), suggest differences in the aspects of function being directly measured by each task (Sitskoorn et al 2004a). The former result is surprising in some respects, given the wide application of WCST in assessment of patients, with consistent deficits demonstrated in perseveration and categories achieved. However, there is evidence of preserved WCST performance with feedback in schizophrenia (Bellack et al 1990) and abstraction performance was demonstrated as the least impaired of a number of cognitive functions in patients (Saykin et al 1994). Similarly, Faraone et al (1995) showed relatives' performance to improve over time on the WCST, after showing a mild deficit at baseline. This suggests that conceptual shifting and inhibition of irrelevant response may be features of the illness itself, more than trait deficits in unaffected relatives, whereas the set-alternation measured by trails B may be a more promising indicator of genetic vulnerability.

1.5.3 Spatial working memory

Spatial working memory deficits have also been identified in relatives of schizophrenia patients. Oculo-motor delayed response tasks require the online maintenance of the spatial position of a previously presented target across a brief delay period, before guiding eye movements (saccades) to the position of the previously presented item. Sensori-motor control tasks normally differ only in the removal of the delay period following target presentation. Memory guided anti-saccadic eye movement tasks additionally require an inhibition of response, by requesting that patients do not glance in the direction of the previously presented stimulus until cued. Glahn et al (2002) showed a negative relationship between genetic loading for schizophrenia and performance on a spatial delayed response task in twins discordant for the disorder and controls. The number of spatial locations was

varied parametrically, while encoding time and button pressing was held constant across trials. Interestingly, the magnitude of difference between groups was not influenced by set size (i.e. 1 or 5 locations to be remembered), suggesting that a fundamental disruption occurred at the encoding stage (i.e. iconic to working memory visuo-spatial sketchpad) or disruption during the maintenance of location information. McDowell et al (2001) showed an increase in the number of saccades generated during the delay period in relatives compared to controls (Glahn et al 2003; McDowell et al 2001). During an oculo-motor delayed response task, Park et al (1995) showed increased reaction times during memory saccades, and a larger number of errors in both relatives and patients compared to controls, which may have reflected difficulties in maintaining a spatial representation in memory over the short delay period (Park et al 1995). Ross et al (1998) did not replicate the finding of increased reaction times, and additionally showed poorer accuracy in the relatives of schizophrenics 'least likely to be carriers of genetic risk for schizophrenia' than those with a positive family history for the disorder. Conversely, those with a positive family history and patients exhibited more impaired response inhibition than controls (Ross et al 1998). Finally, Myles-Worsley et al (2002) reported no differences in a sensori-motor control task, but less accuracy and increased response times during a delayed response task in relatives, which were less than in patients, but greater than in controls. More interestingly, this was apparent in families on a remote Micronesion island in the Pacific, where schizophrenia clusters in multi-generational families and prevalence is double that in the rest of the world. Given that this parallels the deficit apparent in Caucasian families, this result further supports the observation that schizophrenia is phenomenologically similar throughout the world, irrespective of culture and ethnicity. The ability to maintain spatial representations in working memory and inhibit response may be important indicators of dorsolateral prefrontal lobe integrity (Myles-Worsley et al 2004; Myles-Worsley and Park 2002).

1.5.4 Summary

These results suggest that unaffected biological relatives of schizophrenics do show similar impairments to patients on some aspects of executive function (i.e. set-alternation and perseveration) and visuo-spatial working memory (i.e. information acquisition and maintenance), but less consistent results in the domain of attention challenge our ability to make inferences about attention performance

in relatives. These results further imply a possible deficiency in prefrontal areas responsible for response monitoring and maintenance. However, given that cognitive functions are supported by a diversity of regional brain responses and therefore cannot be localised to isolated brain regions, it is more likely a reflection of an impaired fronto-brain network, possibly implicating the anterior cingulate, temporal and parietal lobes and cerebellum, as apparent in schizophrenia.

1.6 Declarative memory and intelligence in unaffected adult relatives of schizophrenics: A Systematic Review

Although neuropsychological impairments in schizophrenia are diverse (Bilder 1996; Heinrichs and Zakzanis 1998), deficits in the domains of executive function and memory are now considered especially prominent (Aleman et al 1999; Cirillo and Seidman 2003; McKenna et al 1990; Saykin et al 1991; Saykin et al 1994). Moreover, although verbal memory impairment in schizophrenia has not been established as a differential deficit, several studies have reported larger effect sizes for verbal memory than for other cognitive functions (Saykin et al 1991; Saykin et al 1994; Toulopoulou et al 2003a; Toulopoulou et al 2003b). Interestingly, this has been additionally shown in unaffected relatives of schizophrenic patients (Sitskoorn et al 2004a). Verbal memory could therefore be considered a core deficit of the disorder and for this reason my thesis will concentrate fundamentally on this aspect of function in relatives of schizophrenics.

The purpose of this review is to systematically and quantitatively review the literature investigating declarative verbal and non verbal memory performance in healthy, non-psychotic, first degree relatives of schizophrenic patients, when compared with normal controls, in order to clarify the nature and magnitude of the memory impairment. In addition, effect sizes are also derived for measures of intellectual function acquired in the included studies, as a means of qualitatively comparing relative global intellectual performance with memory ability.

Heinrichs and Zakzanis (1998) organised measures of memory into one of two categories. Global memory, which included summed trial recall and general learning indices (d =1.53), and selective memory, which included specific scores such as intrusion rate, forgetting, recognition and recall on specific trials (d =1.11). Aleman et al (1999) more discretely calculated separate effect sizes for verbal and non-verbal cued and free recall and recognition, and digit span backwards and forwards. Finally, Sitskoorn et al (2004) combined scores on three tests of verbal memory-the Rivermead Behavioural Memory Test (RBMT), the California Verbal Learning Test (CVLT) and the Wechsler Memory Test (WMS) to derive one effect size for verbal memory in relatives of schizophrenics compared to controls. In this quantitative review, we sought to refine these estimates for specific

declarative memory tests. We have therefore looked at performance on individual tests of short and long-term declarative episodic and semantic memory, which have been used consistently throughout the literature to compare relatives of schizophrenic patients with controls. Finally, where possible, we have qualitatively compared effect sizes to those reported in reviews of memory in schizophrenia (Aleman et al 1999; Cirillo and Seidman 2003; Heinrichs and Zakzanis 1998).

In many studies where large batteries of varied neuropsychological tests have been administered, researchers have grouped tests into functional domains according to the common factor they may be measuring, either through subjective selection, or based on cluster analytic studies, in order to reduce the number of statistical tests carried out, or in the hope that identification of selective cognitive deficits will be strengthened (Kremen et al 1994). However, methods of classification are not always consistent across studies, clouding further the conclusions drawn from neuropsychological assessments. For this reason aggregated scores cannot be included in the quantitative analysis. However, a general qualitative overview of the relevant literature not meeting the criteria for inclusion in the quantitative analysis is also provided.

1.6.1 Methods

1.6.1.1 Criteria for inclusion

Case control and cohort studies published between 1965 and 2004 were considered for inclusion where neuropsychological assessments were performed on a sample of no less than 10 non-psychotic first or first & second degree relatives of schizophrenic patients and 10 healthy non-psychiatric control participants. Studies examining participants under the age of sixteen were not included. This was based on similar factors to those outlined by Kremen et al (1994)(Kremen et al 1994). Aside from not yet being within the maximum risk age period for development of the disorder, and therefore a group comprised of both pre-schizophrenics and those who will never develop the disorder, children will also have been at a different developmental stage from adults at the time of testing. This means that the structure and function of the frontal lobes will be immature in children relative to controls. Both groups will have different life and educational experiences, and some test formats will be less familiar to and less appropriate for children than for adults, thus restricting comparisons between groups. It

was also necessary that studies had used at least one of the memory tests listed in table 1.1 (for ease of discussion, these tests have been classified under short and long term episodic and semantic memory for both verbal and visual information), ensuring that only measures of memory derived from the same groups of tests were included in the analysis. Only studies providing sample numbers, test means and standard deviations for each group were included in the analysis. Where standard deviations were not provided, these were imputed from the largest standard deviation from all studies measuring performance on the same scale. Where studies listed limited statistical values (i.e. F or t), we attempted to reconstruct the original summary data in accordance with established methods.

Table 1.1: Neuropsychological tests used across included studies

Immediate memoy	Stories: WMS- Logical Memory test/RBMT Story recall Words: CVLT/AVLT trial 1 recall Digits: WAIS-R or WMS-R Digit span forwards and backwards (working memory) Figures: Visual WMS-R Visual Reproductions
Delayed memory	Stories: WMS- Logical memory test/RBMT Story recall (delayed)/Heaton story learning test Figures: Visual WMS-R Visual reproductions (delayed)
Verbal Learning	Words: Total recall over five trials CVLT/AVLT, paired associate learning
Semantic retrieval	Verbal phonological fluency (cued with letters) Verbal category fluency (cued with category exemplars)
IQ	NART (verbal), WAIS-R (general)

WAIS-R Wechsler Adult Intelligence Scale-Revised; WMS-R Wechsler Memory Scale-Revised; CVLT- California Verbal Learning Test, NART- National Adult Reading Test, RAVLT- Rey Auditory Verbal Learning Test, AVLT- Auditory Verbal Learning Test, RBMT- Rivermead Behavioural Memory Test

1.6.1.2 Search

Relevant studies were identified from the databases Medline (using Science Direct interface, http://www.sciencedirect.com/), Psycinfo (using the Bath Information Database interface, http://www.bids.ac.uk/) and the Science Citation Index (using ISI Web of Knowledge http://wok.mimas.ac.uk/) for 1965-2004. This was followed by a hand search of the journal Schizophrenia Research and a search of the reference sections of chosen articles for additional studies of relevance. Search terms included:

(1) Schizophrenia and genetic liability and memory

(2) Schizophrenia and relatives and memory

(3) Schizophrenia and family and memory

(4) Schizophrenia and family and neuropsychology

(5) Schizophrenia and genetic liability and neuropsychology

(6) Schizophrenia and relatives and neuropsychology

Table 1.2: Tabulation of search results 1965-2004

Search words	**Abstract databases**				
	Medline (60-04)	Psycinfo (67-04)	Science Citation (60-04)	Schizophrenia Research	Total
Schizophrenia and family and memory	1253	90	100	16	1459
Schizophrenia and genetic liability and memory	8	5	15	2	30
Schizophrenia and relatives and memory	1626	64	140	44	1874
Schizophrenia and family and neuropsychology	344	61	17	6	428
Schizophrenia and genetic liability and neuropsychology	12	4	4	1	21
Schizophrenia and relatives and neuropsychology	551	44	32	11	638
	3794	268	308	80	4450

A total of 4450 articles were identified from the search of abstract databases with a considerable overlap in the potential articles produced from each search, on each database (see table 1.2). Studies were initially rejected or selected based on a reading of the abstracts. Selected studies were then acquired in full text.

1.6.2 Analysis

All studies listing independent means (interval scale data) and standard deviations for each group (or exact t values) were included in the meta-analysis. The analysis was computed with the meta-analysis statistics package STATA (www.stata.com) using fixed and random effects models. The standardised mean difference was calculated for each study. This is the difference between the experimental group mean and the control group mean divided by the pooled standard deviation (i.e. the root mean square of the two standard deviations). The sampling variance d effect size was corrected for biased estimation in small sample sizes using Hedge's correction (Hedges & Olkin 1985). The pooled effect size from all studies was estimated using two methods. Fixed effects estimates were calculated by weighting each study by the inverse of its sampling variance. This model assumes no between study variation in effect size and only one common effect in all studies. Studies were also analysed using a random effects model, which allows for variation between studies in terms of the true effect size. Between studies variance was incorporated into the model using a product-moment estimate. Cohen classified effect sizes of 0.2 to 0.4 as small, 0.5 to 0.7 as medium, and 0.8 and above as large (Cohen 1988). Individual study estimates were plotted alongside the pooled estimate using a forest plot, and only forest plots following random effects analysis have been presented (see figures 1.3-1.15).

The assumption of homogeneity was tested using Cohen's Q statistic, which compares the variance of a set of effect sizes with the variance expected by sampling error (Chi-square distribution, Q statistic, 2 tailed probability) (Shadish and Haddock 1994, p266 as referenced by (Alferes 2003)). In addition, the I squared statistic provides a measure of the degree of inconsistency in results by giving the percentage of total variation across studies attributable to heterogeneity rather than chance, and is considered a more sensitive indicator of heterogeneity than the Q statistic (Higgins et al 2003). Higgins et al (2003) tentatively describe values of 25%, 50%, and 75% as indications of low, moderate, and high heterogeneity respectively. Where a test shows significant heterogeneity across studies, Galbraith plots present the standardised mean differences of individual studies plotted along with the overall 95% confidence intervals for that test. Publication bias, which describes the tendency for publication or non-publication of research results based on the nature and direction of results, was also tested using Egger's weighted regression test (see table 1.3b).

1.6.3 Results

The 61 studies selected were acquired in full text and 27 relevant studies, comprising 1109 relatives of schizophrenics and 878 controls, met our inclusion criteria for review. 2 studies from each of 3 research groups were included in the final selection (Byrne et al 2003; Byrne et al 1999; Faraone et al 2000; Goldberg et al 1995; Goldberg et al 1993; Seidman et al 2002a) This enabled the extraction of data not available from a research group's most recent paper (with the exception of Faraone et al (2000), and Seidman (2002), where data was taken where possible from the larger of the two studies i.e. Faraone et al (2000)). These details are included within table 1E (Appendix 1), which lists all studies included in the meta-analysis. The results of the meta-analysis are shown in table 1.3a. An additional table 1F (Appendix 1) lists those studies included in a qualitative review of the literature, but excluded from the quantitative analysis due to non fulfilment of inclusion criteria.

Table 1.3a: Results of meta-analysis

Memory task	No. studies K	Rels N	Controls N	d (fixed effects mean weighted effect size)	d (random effects mean weighted effect size)	t	P (One tailed)	95% CIs	Chi-Squared
Trial 1 list recall	3	201	66	0.65	0.65	4.4	<0.001	0.36-0.95	0
Immed. story recall	12	759	489	0.55	0.55	8.5	<0.001	0.42-0.65	10.1
Delayed story recall	9	587	368	0.51	0.51	6.7	<0.001	0.36-0.66	6.5
NART/WRAT	8	544	306	0.37	0.49	2.9	0.003	0.16-0.81	26.8 *
CVLT 1-5 total	6	496	187	0.43	0.44	4.5	<0.001	0.25-0.63	5.7
Verbal letter fluency	11	672	365	0.41	0.42	4.5	<0.001	0.24-0.60	15.7
Paired associates	4	227	189	0.41	0.41	3.8	<0.001	0.19-0.62	2.3
Immed. visual recall	8	583	358	0.44	0.41	2.8	0.005	0.12-0.69	12.4
Verbal cat. fluency	9	611	290	0.36	0.39	3.8	<0.001	0.19-0.59	13.5
Digit Span BW	9	370	299	0.35	0.35	3.9	<0.001	0.17-0.52	8.6
WAIS-R IQ	11	708	433	0.32	0.35	2.8	0.006	0.10-0.59	32.5 *
Digit Span FW	12	502	414	0.32	0.32	4.4	<0.001	0.17-0.46	11.1
Delayed visual recall	7	546	321	0.30	0.31	3.7	<0.001	0.18-0.61	9.6

* P < 0.001

Table 1.3b: Results of Egger's test of publication bias

Memory task	Publication Bias	
	t	p
Trial 1 list recall	-1.40	0.39
Immed. story recall	-0.29	0.78
Delayed story recall	-0.66	0.53
NART/WRAT	-2.16	**0.007**
CVLT 1-5 total	-0.66	0.54
Verbal letter fluency	-0.61	0.56
Paired associates	-0.55	0.64
Immed. visual recall	-0.69	0.51
Verbal cat. fluency	-1.5	0.17
Digit Span BW	-0.96	0.37
WAIS-R IQ	-0.50	0.63
Digit Span FW	-1.1	0.31
Delayed visual recall	-0.53	0.62

1.6.3.1 Verbal Immediate Memory: Digit Span

Although digit span is often included in the functional domains of attention, executive function, mental control and working memory, we have added it to our analysis as a measure of verbal immediate memory. WAIS Digit span requires the repeating back of a string of digits of increasing size forwards in the forwards condition and then backwards in the backwards condition. The importance of separating scoring for individual measures of span is apparent when it is considered that different processes may be differentially responsible for the two aspects of the task. Backward span is thought to measure verbal working memory through the maintenance and manipulation of items in the hypothetical visuo-spatial sketchpad (i.e. reversal of digits) and phonological loop (i.e. articulatory rehearsal). Forward span is more likely a measure of the limited capacity verbal immediate memory system through the articulatory rehearsal of digits within the phonological loop.

Most studies that have combined scores for forwards and backwards digit span have not shown differences in performance between relatives of schizophrenics and controls, with the exception of two investigations (Goldberg et al 1995)(Mirsky et al 1988-as cited in (Kremen et al 1994)). Moreover, studies using aggregated scores have often included digit span as an additional test of attention, with mixed results (Cannon et al 1994; Faraone et al 1995; Harris et al 1996; Krabbendam et al 2001; Kremen et al 1998b). Comparing aspects of digit span separately, several studies have shown significant differences between groups on both (Conklin et al 2000; Laurent et al 1999). Appels et al (2003), found a significant difference between parents of schizophrenics and controls on forwards and a trend for significance on backwards digit span. Shedlack et al (1997) showed a significant effect of family membership (between controls and schizophrenic families) in both forwards and backwards span, while Franke et al (1999) found a significant difference between groups on forwards recurring span (Appels et al 2003; Franke et al 1993; Shedlack et al 1997). However, a number of studies have found no significant differences between groups on either test (Byrne et al 2003; Chen et al 2000b; Docherty and Gordinier 1999; Franke et al 1993; Gochman et al 2004; Goldberg et al 1993; Ismail et al 2000; Keri et al 2001; Wittorf et al 2004).

Following the quantitative analysis, results showed effect sizes for both forward (d=0.32, 95% Confidence Interval=0.18-0.46) and backward digit span (d=0.35, 95% Confidence Intervals=0.17-0.53) to fall within Cohen's small effect size range, based on 12 and 9 studies respectively. This corresponds approximately to a non-overlap in the distributions of controls and unaffected relatives of between 21.3 and 27.4% (see figures 1.3 and 1.4).

Figure 1.3 Forest plot of individual and pooled estimates of standardised mean difference between relatives of schizophrenics and controls in forward digit span

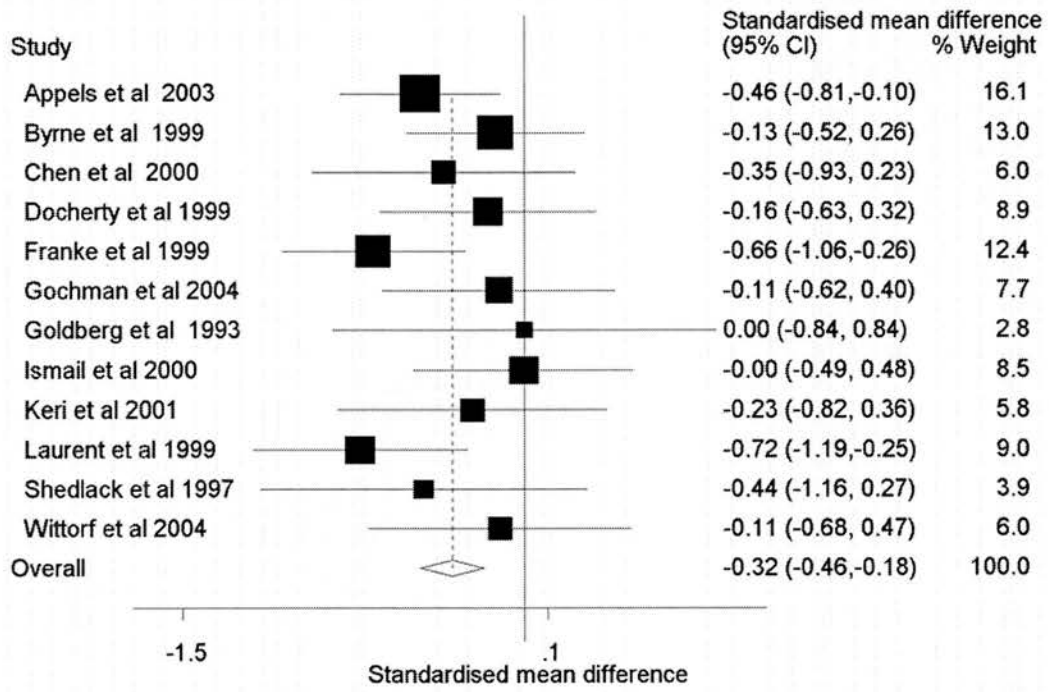
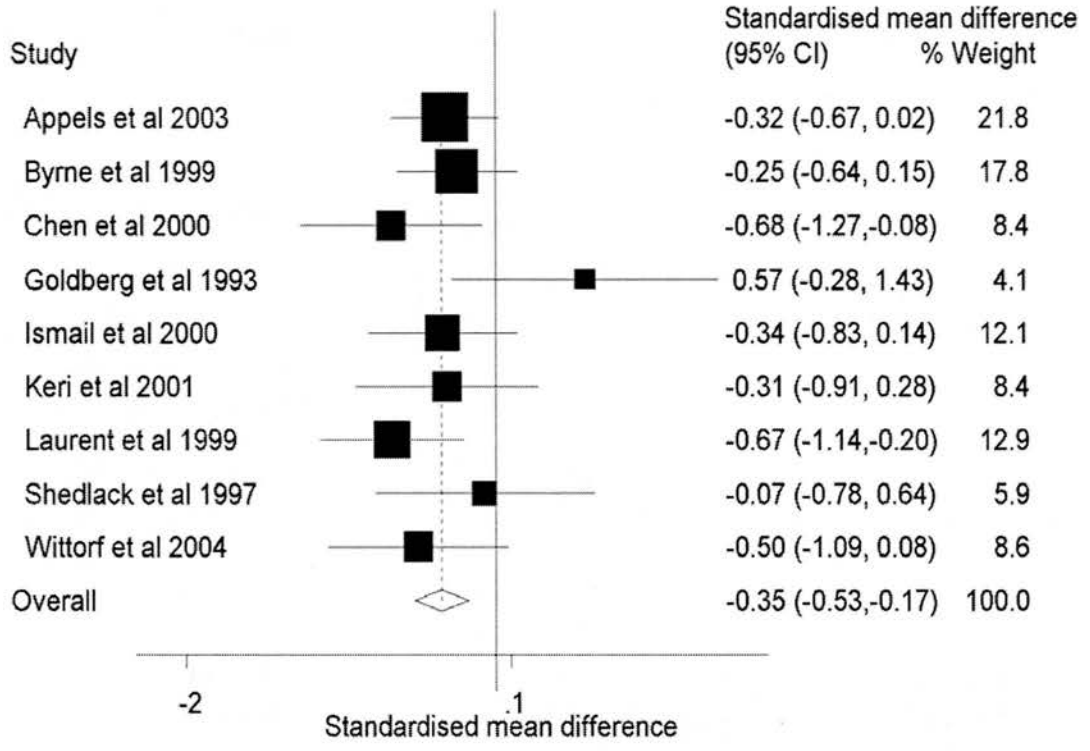


Figure 1.4 Forest plot of individual and pooled estimates of standardised mean difference between relatives of schizophrenics and controls in backward digit span



The Q statistic for both forward and backward digit span was not significant (chi-squared = 11.1 (d.f. = 11) p = 0.44; chi-squared = 8.6 (d.f. = 8) p = 0.37) and I-squared showed only 0.6% (forward digit span) and 6.9% (backward digit span) of variation in the standard mean difference to be attributable to heterogeneity. Although small, the percentage of variation in backwards digit span attributable to heterogeneity may be influenced by the small study of Goldberg et al (1995), which shows the opposite direction of effect from all other studies (i.e. relatives performed slightly better than controls on backwards digit span). This result is difficult to explain with respect to the findings from the other studies. However, it is possible that the large number of relatives to controls in this study will have reduced statistical power to detect a significant difference on this test.

Sitskoorn et al (2004) also reported a small effect size of 0.35 for combined WAIS-R Digit Span, based on a meta-analysis of 10 studies comparing relatives of schizophrenics and controls (Sitskoorn et al 2004a). In a meta-analytic comparison of schizophrenic patients and controls, Heinrichs and

Zakzanis (1998) showed an effect size of 0.62 for combined digit span, while Aleman et al (1999) showed effect sizes of 0.71 (95% CI: 0.56-0.86) and 0.82 (95% CI: 0.49-1.16) for forwards and backwards span respectively (Aleman et al 1999; Heinrichs and Zakzanis 1998). Although the effects sizes between patients and controls are almost double those between relatives and controls, they are comparable in that both demonstrate non-significantly greater effects for backwards relative to forwards span. It is also clear that the confidence intervals for digit span forwards in patients relative to controls do not overlap with those in relatives compared to controls, suggestive of a possible disease specific/phenotypic deficit. Given the importance of attention on aspects of memory function, were attention solely responsible for deficits on this task, then the backward span effect size would have appeared significantly greater than that for forward span (Aleman et al 1999). This supports inclusion of this task in measures of memory over and above measures of attention.

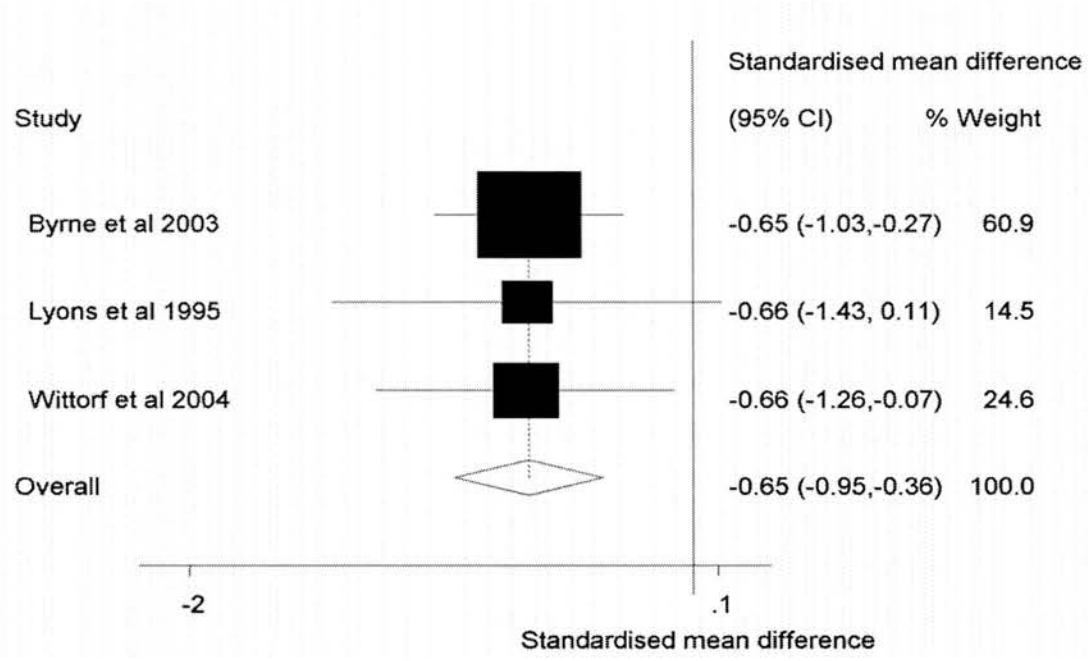
1.6.3.2 Verbal Immediate Memory: List recall trial 1

Verbal learning and memory is most consistently measured using auditory verbal learning tests such as the Rey Auditory Verbal Learning Test (RAVLT) or the California Verbal Learning Test (CVLT). The CVLT involves dictation by an experimenter of a list of 16 words (presented as a shopping list of items) to be freely recalled immediately across 5 trials, with 1 trial of interference, immediate and delayed cued recall, free recall and recognition. This test differs from the RAVLT in that it contains one extra item. It also allows for measurement of strategic encoding processes because items can be grouped into specific implicit categories, thus facilitating encoding and later recall. For the purpose of this review, trial 1 of the AVLT will be included as a measure of immediate word list recall. This is because this trial is presented prior to additional repetitions and without the semantic structure which would normally enhance learning of material (Lezak 1995).

Immediate recall of trial 1, like digit span forward, is a basic assessment of the integrity of the phonological store. On the first immediate recall trial of the CVLT Asarnow et al (2002), and Lyons et al (1995) found no significant differences between relatives of schizophrenics and controls, although the former study included relatives under the age of sixteen, and therefore is not directly comparable (Asarnow et al 2002; Lyons et al 1995). Conversely, Byrne et al (2003) and Wittorf et al

(2004) found a significant difference between relatives of schizophrenics and controls on trial 1 of the AVLT (Byrne et al 2003; Wittorf et al 2004). The increased difficulty associated with immediate serial recall without the option of semantic categorisation, even at the first stage of recall, may explain the difference in results between these studies. However, the results of the meta-analysis for immediate trial 1 recall do suggest that short-term low load verbal memory is impaired in relatives of schizophrenics when compared to controls, with an effect size in the moderate range (d= 0.65, 95% confidence interval = 0.36-0.95). This suggests a hypothetical non-overlap in distributions of approximately 38.2 to 43.0%. (see figure 1.5).

Figure 1.5 Forest plot of individual and pooled estimates of standardised mean difference between relatives of schizophrenics and controls in trial 1 immediate word list recall



The Q statistic was not significant (chi-squared = 0 (d.f. = 2) p = 0.99) and I squared showed 0% variation attributable to heterogeneity (note: this is additionally reflected in the identical results from

both fixed and random effects models). Given that this result is based on only three studies, it should be considered tentatively.

Aleman et al (1999) reported an effect size of 1.27 for immediate free verbal recall in a comparison between patients and controls, the largest reported effect size in a meta-analysis of 17 different aspects of memory measurement in schizophrenia (Aleman et al 1999). Although this deficit is considerably greater in the disorder itself, the effect size here is the second largest of all thirteen measures in relatives of schizophrenics.

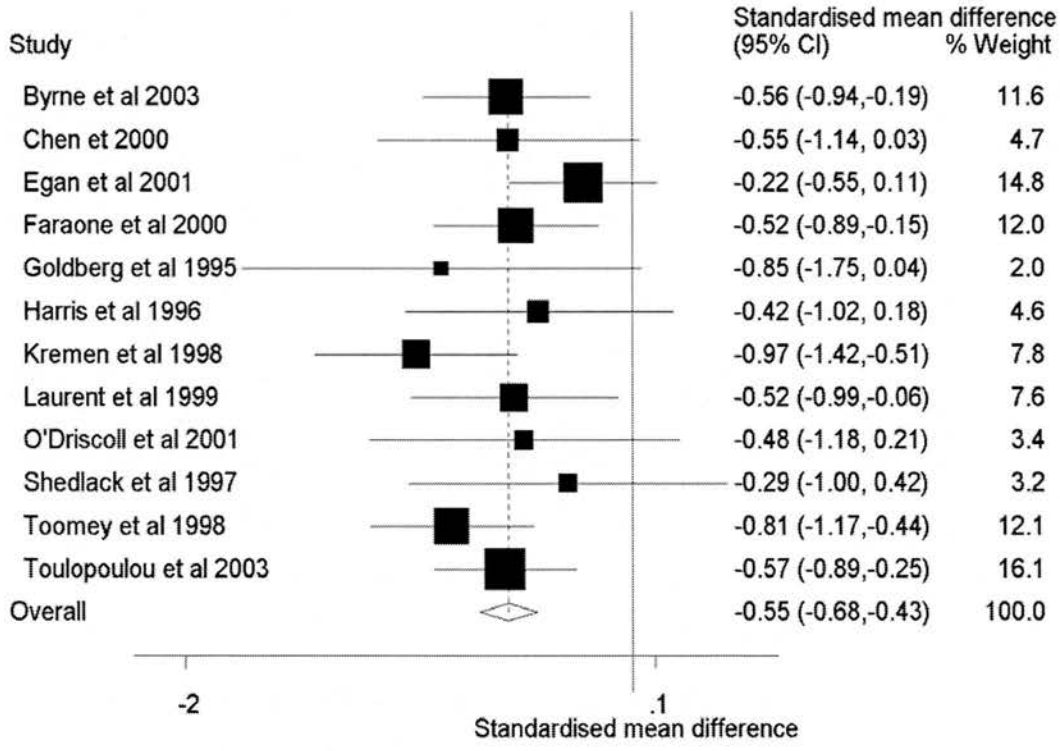
1.6.3.3 Verbal Immediate Memory: Story Recall

Story recall is commonly assessed using the Logical Memory subtest of the WMS or the prose recall aspect of the Rivermead Behavioural Memory Test (RBMT) (although Harris et al (1996) used Heaton's Story Learning Test). Following the experimenter's reading of a story, participants are required to immediately recite back the story verbatim and are scored on the number of correct words or 'ideas' recalled. After a delay of 20-30 minutes, normally filled with a non-verbal task, participants are required to freely recall as many words/ideas from the original story. This particular test may place demands on context and associative processing during encoding, in order for the ideas of the story to be correctly recalled, and may therefore be more difficult than standard verbal list recall tasks.

Several studies have found relatives of schizophrenics to perform worse than controls on immediate story recall (Faraone et al 1995; Faraone et al 1999; Goldberg et al 1995; Kremen et al 1998b; Toomey et al 1998; Toulopoulou et al 2003a; Toulopoulou et al 2003b). Faraone et al (2000) found a significant difference between relatives from multiplex families and controls on the WMS-R immediate story recall, while Byrne et al (2003) found high-risk participants to score significantly lower than controls on the immediate story recall aspect of the RBMT (Byrne et al 2003; Faraone et al 2000). However, others have also found a lack of significant differences between groups on this test (Chen et al 2000b; Egan et al 2001; Goldberg et al 1995; Harris et al 1996; Laurent et al 1999; O'Driscoll et al 2001; Shedlack et al 1997). In spite of the mixed results for this aspect of memory recall, the results of the meta-analysis showed the effect size to be in the medium range (d=0.55, 95%

Confidence Intervals=0.42-0.68) suggesting a hypothetical non-overlap in distributions of between 33 and 38.2 %. The Q statistic was not significant (chi-squared = 10.1, d.f. =11, p=0.52), and I squared indicated that 0 % of variation in the standard mean difference was attributable to heterogeneity (see figure 1.6).

Figure 1.6 Forest plot of individual and pooled estimates of standardised mean difference between relatives of schizophrenics and controls in immediate story recall

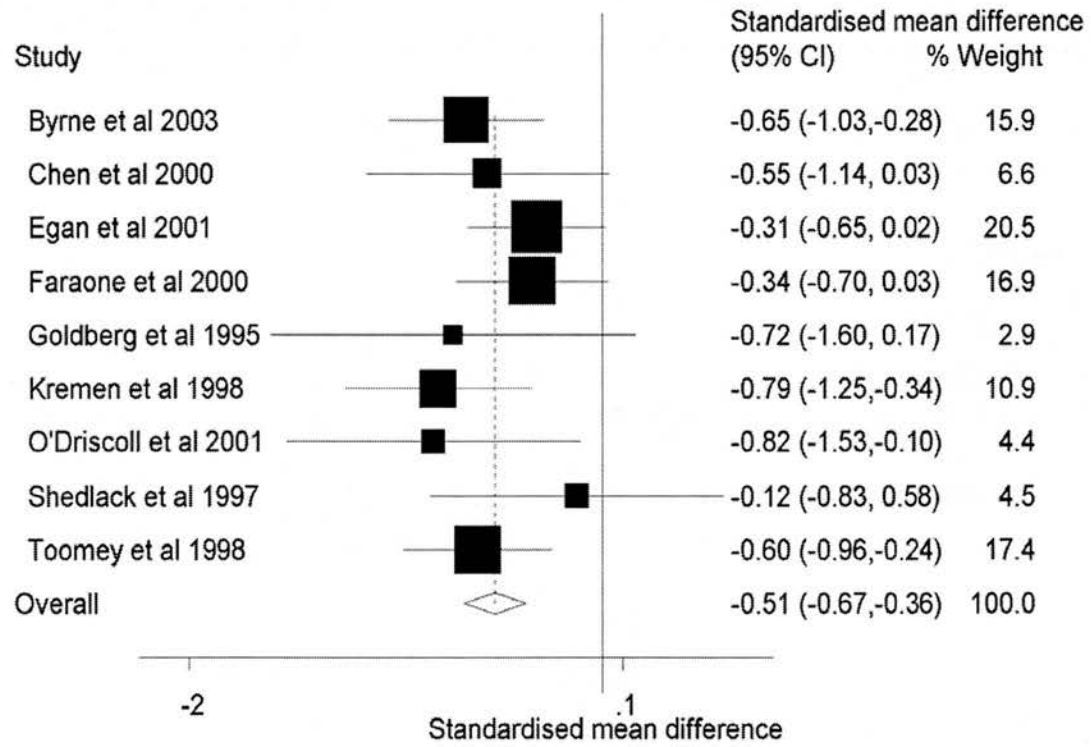


1.6.3.4 Verbal Delayed Memory: Story Recall

Several studies have found relatives of schizophrenics to perform worse than controls on delayed story recall (Byrne et al 2003; Faraone et al 1995; Faraone et al 1999; Kremen et al 1998b; O'Driscoll et al 2001; Seidman et al 2002a; Toomey et al 1998), while others have not (Chen et al 2000b; Egan et al 2001; Faraone et al 2000; Goldberg et al 1995; Laurent et al 1999; Shedlack et al 1997). Effect sizes for the 9 studies in this domain were however in the medium range, as with immediate story recall (d=0.51, 95% Confidence Intervals=0.36-0.66). This implies an approximate non-overlap in distributions of 33%. Furthermore, the Q statistic was not significant (chi-squared = 6.5 (d.f. = 8) p =

0.58), and I-squared was equal to 0%, implying relative homogeneity across studies included (see figure 1.7). While Shedlack et al (1997) appears to show the smallest standardised mean difference between groups, the small sample numbers ensure that this has little impact (4.5% weight) on the overall effect size for delayed story recall.

Figure 1.7 Forest plot of individual and pooled estimates of standardised mean difference between relatives of schizophrenics and controls in delayed story recall

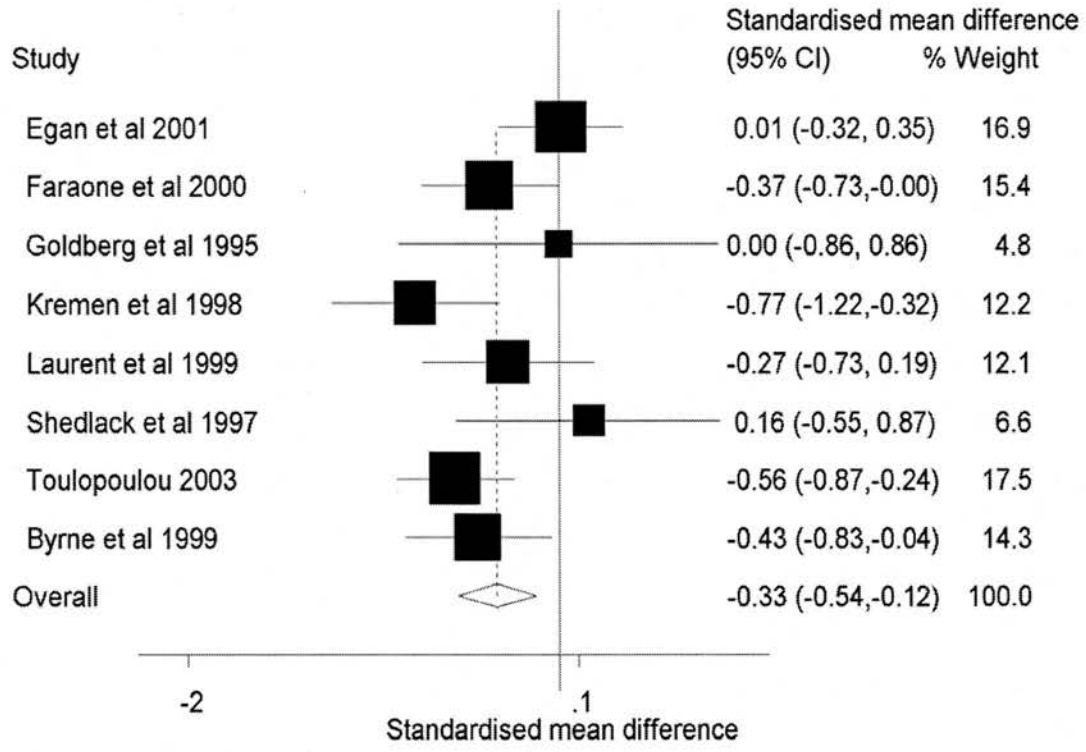


1.6.3.5 Visual Immediate Memory

Visual memory recall has been measured in most studies using the Visual Reproductions subtest of the Wechsler Memory Scale. This involves the copying from memory of a drawing/figure presented at the start of the test and recall of the picture is after a few minutes and again after a delay of approximately 20-30 minutes. Although supposedly a test of visual memory ability, some evidence suggests it may be less sensitive to right hemisphere function than other tests of visual memory, possibly due to the verbalisability of the figures (Lezak 1995). A number of studies have reported a significant difference (Faraone et al 2000; Toulopoulou et al 2003b) (multiplex family relatives only in Faraone 2000), or nearly significant difference between relatives and controls (Byrne et al 1999;

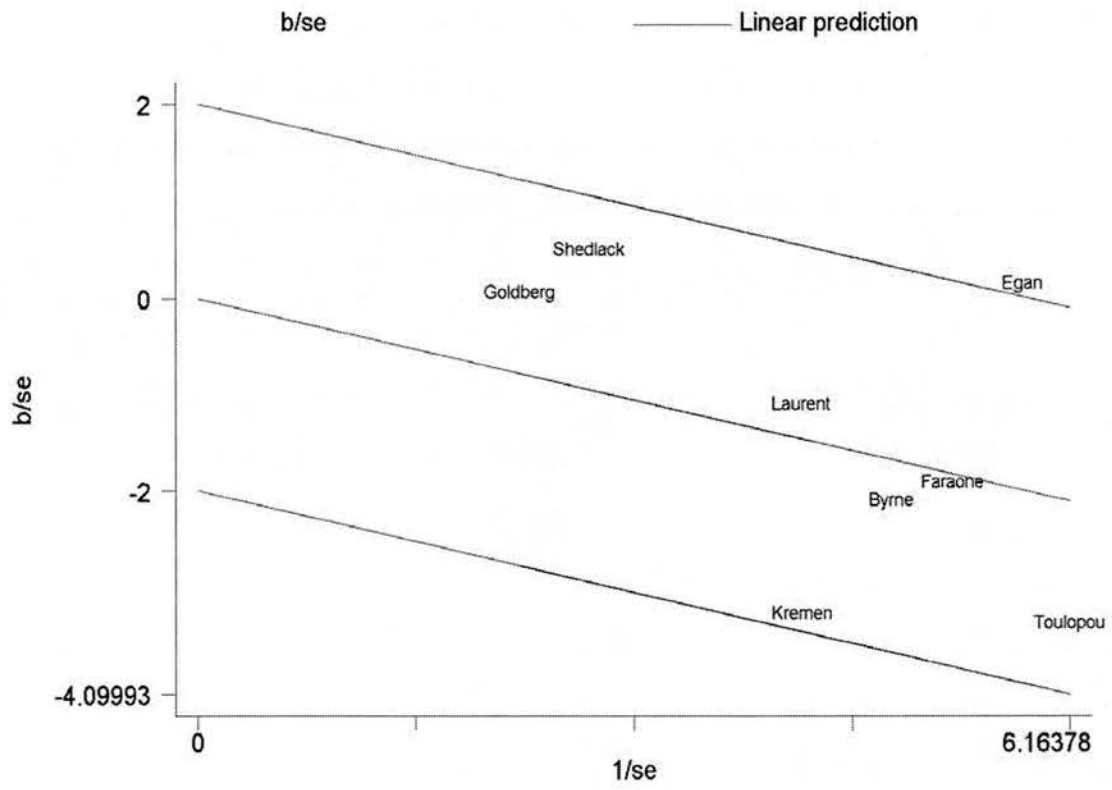
Kremen et al 1998b) and others no such differences (Egan et al 2001; Goldberg et al 1995; Laurent et al 1999; Shedlack et al 1997). The results of the meta-analysis showed the effect size to be in the moderate range for immediate visual recall (d=0.33, 95% Confidence Intervals=0.12-0.54), a non-overlap in distributions of approximately 21.3%. The Q statistic was not quite significant (chi-squared = 12.4 (d.f. = 7) p = 0.09), although I squared showed 43.8% variability to be due to heterogeneity (see figure 1.8(a)).

Figure 1.8 (a) Forest plot of individual and pooled estimates of standardised mean difference between relatives of schizophrenics and controls in immediate visual recall



Egan et al (2001) have the largest sample numbers, account for 16.9% of the overall standardised mean difference and show large variability (standard deviations) for group means in the this test. The Galbraith plot shows that Egan et al (2001) lie just outside the 95% confidence intervals for this test, and may be the main contributor to heterogeneity across studies included (see figure 1.8 (b)).

Figure 1.8 (b) Galbraith plot for studies of immediate visual recall



Aleman et al 1999, reported a smaller effect size for immediate non-verbal relative to verbal memory (d=1.00), and while Heinrichs and Zakzanis (1998) did not split immediate from delayed non-verbal memory, the effect size was smaller than that reported for global verbal memory. Furthermore, as in our results, the results of non-verbal memory assessment across studies was reportedly more heterogeneous than those for verbal memory (Heinrichs and Zakzanis 1998).

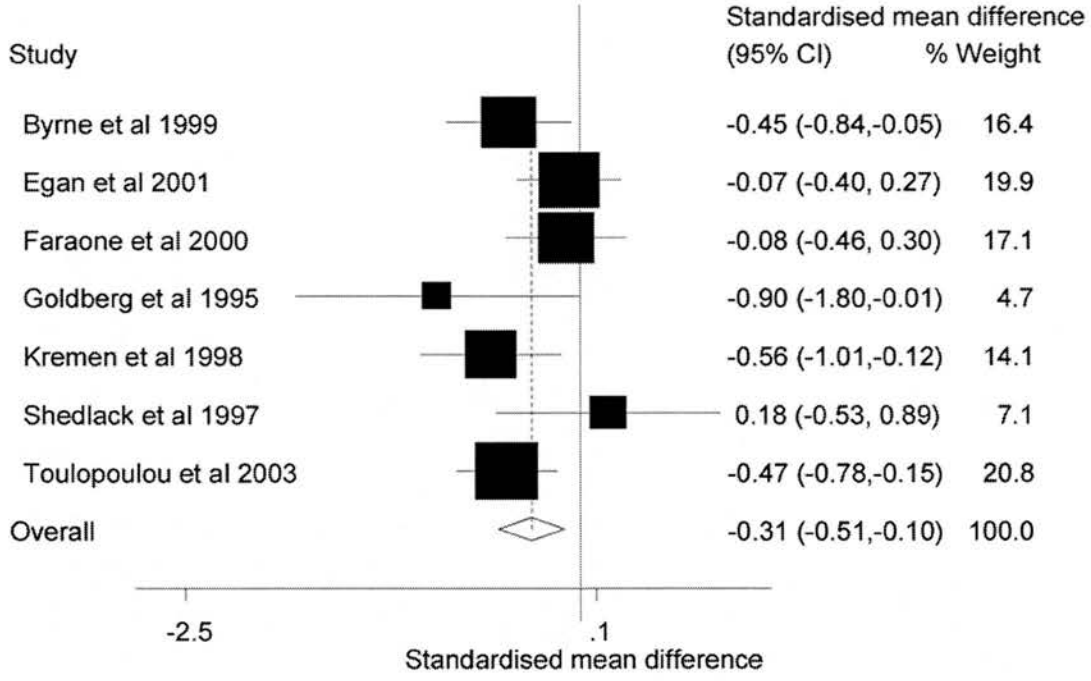
1.6.3.6 Visual Delayed Memory

While some studies have shown differences on non-verbal delayed recall (Byrne et al 1999; Kremen et al 1998b), albeit at trend level (Goldberg et al 1995), several others have not (Egan et al 2001; Faraone et al 2000; Shedlack et al 1997). Wittorf showed significantly poorer performance at baseline in relatives compared to controls on the delayed aspect of the Rey Complex Figure Test (RCFT), although significant improvement was apparent on this test at follow up testing a year later.

The results showed effect sizes for this domain to be in the small range (d=0.31, 95% Confidence Intervals=0.10-0.51), which suggests approximately 27.4% non-overlap in distributions. The Q

statistic was not significant (chi-squared = 9.58 (d.f. = 6) p = 0.14), although I squared indicated that 37.4% of variability in the mean difference was due to non-homogeneity (figure 1.9).

Figure 1.9 Forest plot of individual and pooled estimates of standardised mean difference between relatives of schizophrenics and controls in delayed visual recall



It is conceivable that the heterogeneity in the sample means for the visual recall test in Egan et al (2000) may be responsible for overall heterogeneity once again. Galbraith plots show Egan et al (2000) as a borderline outlier of the upper limit of 95% confidence intervals for this test. While Shedlack et al (1997) also show the opposite direction of effect to the other studies, the small study sample size means this study's impact on the overall standardised mean difference is minimal (7.4%).

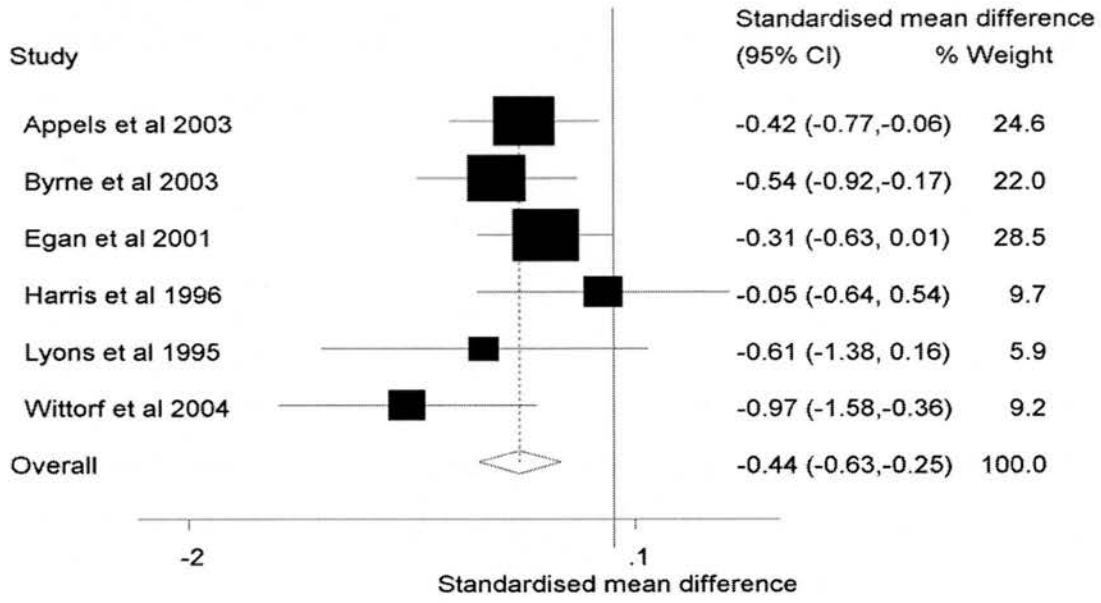
1.6.3.7 Verbal Learning: Total recall across 5 trials

The CVLT and RAVLT both combine the total number of words recalled across the first five trials to give a score of verbal learning (i.e. total recall trials 1-5). For the complete CVLT, Staal et al (2000), found no significant differences between controls and siblings of schizophrenics, while Wittorf et al (2004) showed relatives to perform significantly less well than controls across all aspects of the

RAVLT task (Staal et al 2000a; Wittorf et al 2004). Cannon et al (1994) aggregated performance scores on the logical memory test, the CVLT, and paired associate learning and found significant differences between relative and control groups (Cannon et al 1994). Appels et al (2003), Egan et al (2000), and Lyons et al (1995) showed relatives to recall significantly less than controls over 5 trials of the CVLT, while Byrne et al (1999) showed the same result over 5 trials of RAVLT (Byrne et al 1999). However, Harris et al (1996) found no significant difference between parents of schizophrenics and controls on verbal learning over 5 trials (Appels et al 2003; Egan et al 2000; Harris et al 1996; Lyons et al 1995).

The effect size for verbal list learning across 5 trials was shown to be in the moderate range (d=0.44, 95% Confidence Intervals=0.25-0.63), suggesting a hypothetical non-overlap in distributions of between 27.4 and 33%. The Q statistic was not significant (chi-squared = 5.7 (d.f. = 5) p = 0.3) and the low proportion of variation in the standardised mean difference attributable to heterogeneity, suggests homogeneity across studies (I-squared = 11.7%) (see figure 1.10).

Figure 1.10 Forest plot of individual and pooled estimates of standardised mean difference between relatives of schizophrenics and controls in total verbal list learning (trials 1-5)



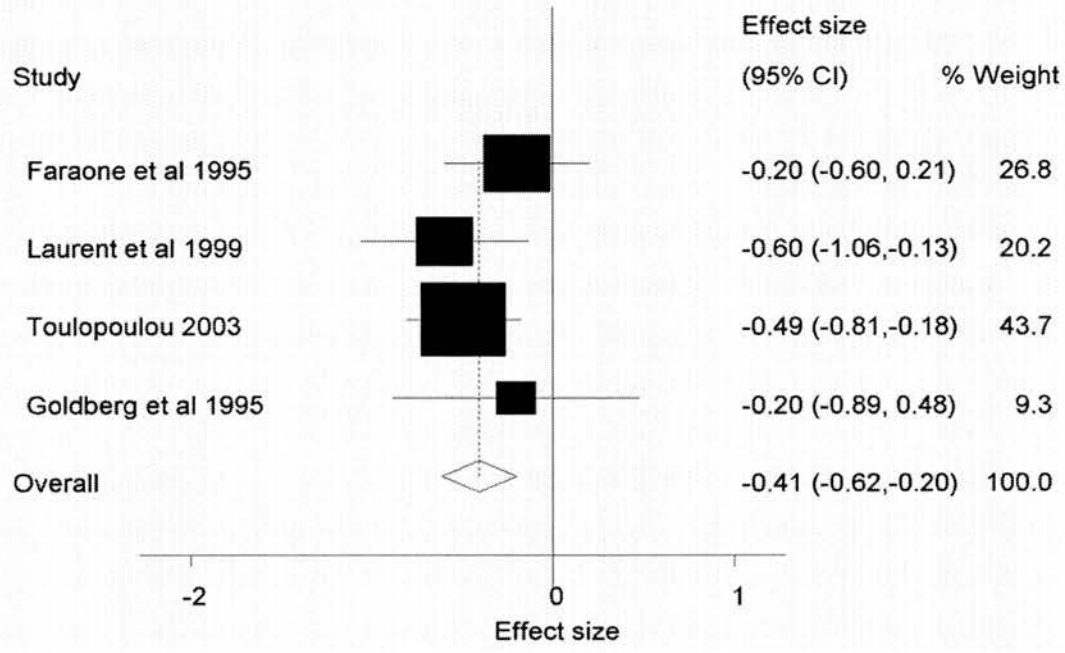
The larger standardised mean differences between groups in Lyons et al (1995) and Wittorf et al (2004) may be due to their smaller sample sizes. Harris et al (1996) used a sample of parents of schizophrenic probands, which resulted in a mixture of both positive and negative history parents. It is likely therefore that performance of negative history parents may have reduced the extent of differences between positive history parents and controls.

1.6.3.8 Verbal Learning: Paired Word Association

The paired word associates test is a test of verbal learning in which participants are asked to learn pairs of words and then later recall these words when presented with only one part of the original pair. Goldberg et al (1995) and Faraone et al (1995) found no difference in performance between relatives and controls on verbal paired associate learning. This is in contrast to the significant difference found between relatives and controls in two other studies (Laurent et al 1999; Toulopoulou et al 2003b). The effect size for verbal paired associates based on four studies was in the moderate range (d=0.41, 95% Confidence Intervals=0.20-0.62), corresponding to approximately a 27.4% non-overlap in

distributions, and not shown to be heterogeneous (chi-squared = 2.3 (d.f. = 3) p = 0.5, and I-squared = 0.0%) (see figure 1.11).

Figure 1.11 Forest plot of individual and pooled estimates of standardised mean difference between relatives of schizophrenics and controls in verbal paired associate learning



1.6.3.9 Semantic memory retrieval

The Verbal Fluency tests are commonly reported to be associated with the cognitive measure of executive function because they require goal directed behaviour, initiation and a switching between clusters. The required self-initiated search of the inner lexicon in order to retrieve and then generate words beginning with a specific letter or in a specific exemplar category also makes it a test of semantic memory organisation and integrity. Several studies show relatives of schizophrenics to perform significantly worse than controls on both aspects of the verbal fluency task (Chen et al 2000b; Dollfus et al 2002; Keefe et al 1994; Laurent et al 1999; Roxborough et al 1993; Zalla 2004), although Appels et al (2003) combined both scores (Appels et al 2003). Egan et al (2001) demonstrated significant differences between relatives and controls for phonological fluency, but not for the verbal fluency for animals (Egan et al 2001), while Byrne et al (2003) demonstrated the opposite effect (Byrne et al 2003). Goldberg (1995) showed no differences between groups on phonological fluency

(Goldberg et al 1995), while both Ismail et al and Wittorf et al did (Ismail et al 2000; Wittorf et al 2004).

Based on meta-analysis of 12 studies of verbal fluency for letters, the effect size was in the small range (0.42, 95% confidence intervals 0.24-0.60), corresponding to an approximate non-overlap in distributions of between 21.3 and 27.4%. The Q statistic was not significant (chi-squared = 15.73 (d.f. = 11) p = 0.15), and I-squared was equal to 30% (see figure 1.12). Based on 9 studies of verbal fluency for categories, effect sizes were in the small to medium range (0.39, 95% confidence intervals 0.19-0.59) respectively, corresponding to a non-overlap in distributions of 27.4%. However, the Q statistic was nearing significance (chi-squared = 13.53 (d.f. = 8) p = 0.09), and I-squared showed 40.9% of the variance to be attributable to heterogeneity (see figure 1.13). The Galbraith plot shows all studies to lie within the limits of the 95% confidence intervals for this test. Heterogeneity may perhaps be attributable to the lack of difference between relatives and controls in the study of Laurent et al (1999), which contributes a weight of about 12% to the overall effect size.

Figure 1.12 Forest plot of individual and pooled estimates of standardised mean difference between relatives of schizophrenics and controls in verbal fluency for letters

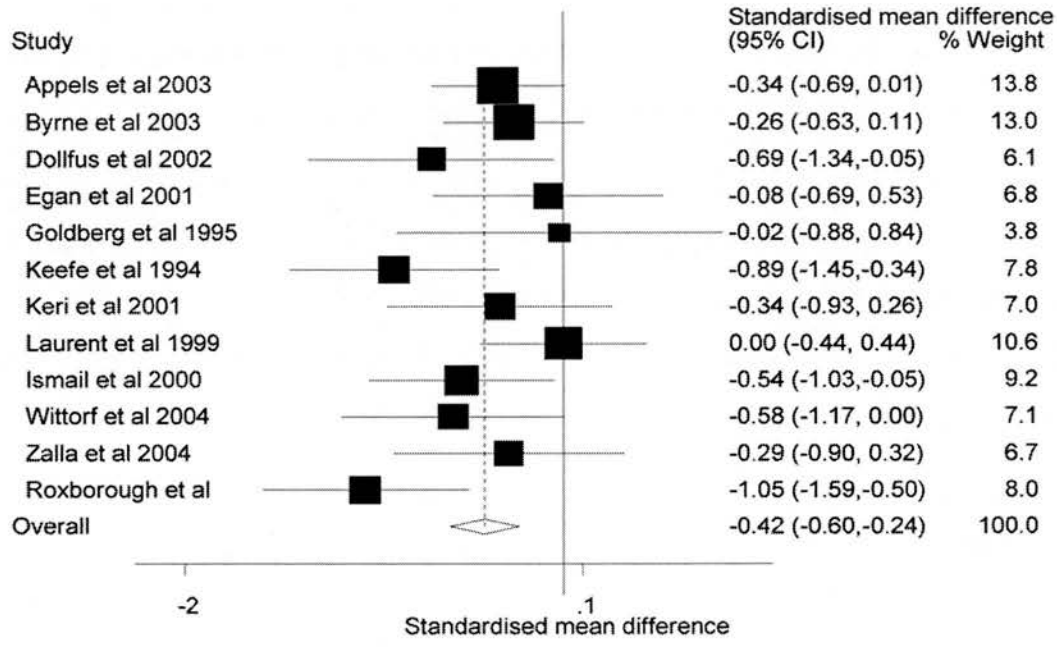


Figure 1.13(a) Forest plot of individual and pooled estimates of standardised mean difference between relatives of schizophrenics and controls in verbal fluency for category exemplars

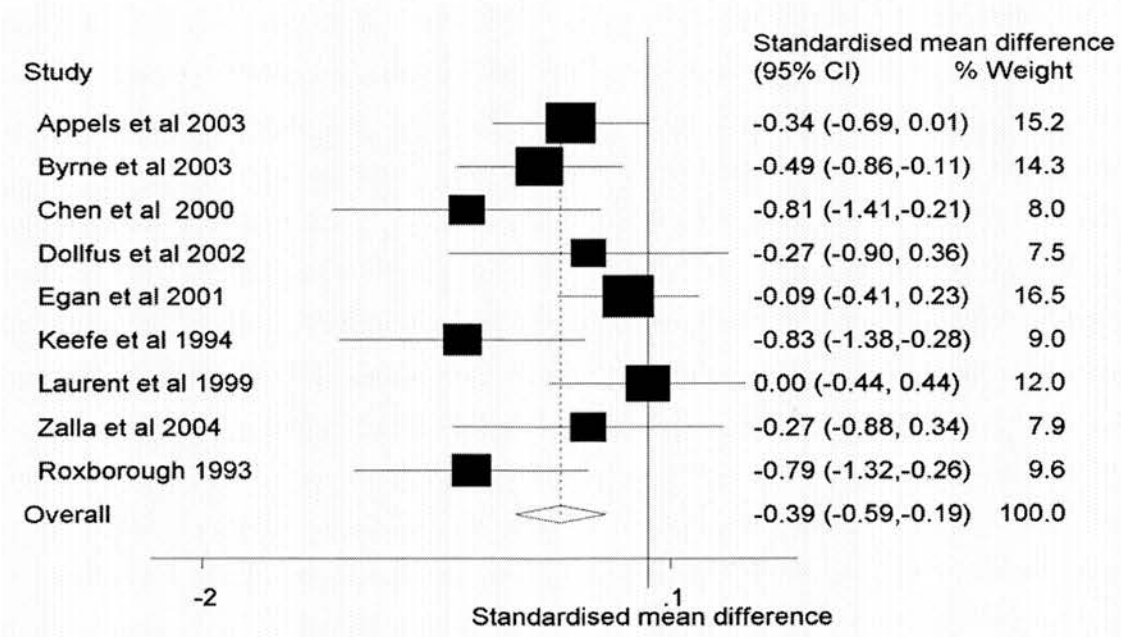
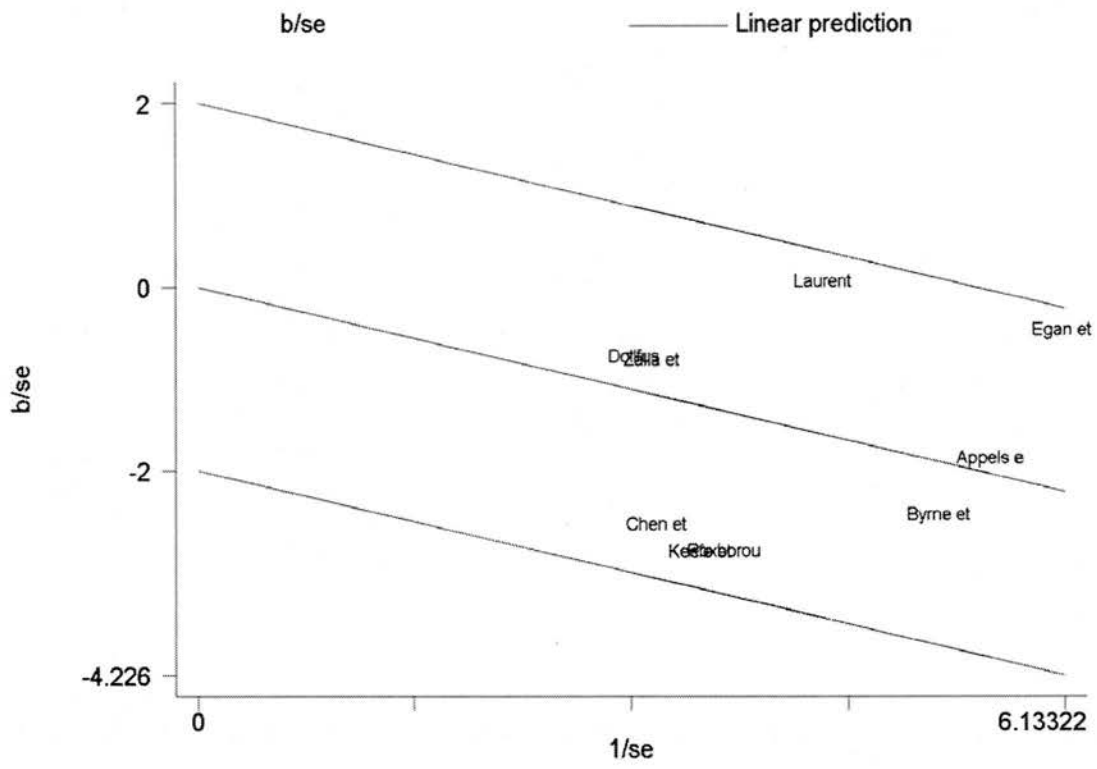


Figure 1.13 (b) Galbraith plot of studies of verbal category fluency

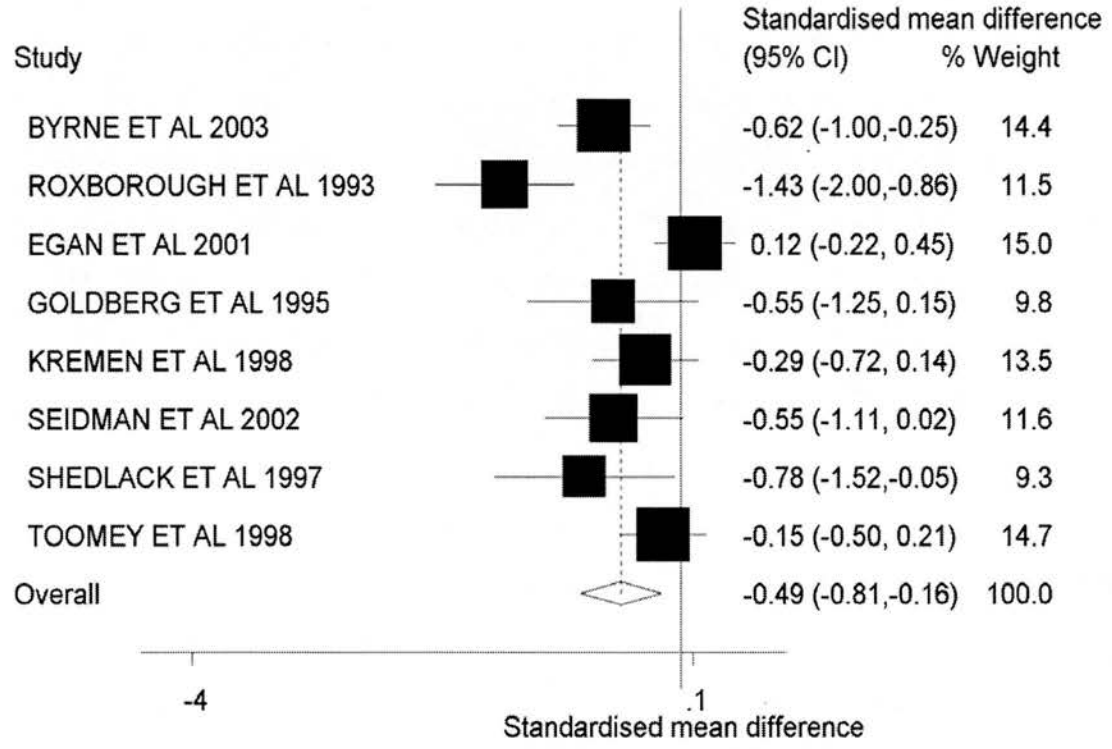


1.6.3.10 General Intelligence

Verbal IQ

Verbal intelligence tests in schizophrenia have often been used as indicators of premorbid ability because of their presumed measurement of crystallised intelligence, or knowledge based on acquired learning, considered less vulnerable to the effects of brain damage than tests of fluid intelligence. These tests are more closely related to educational levels, because ability on the NART, WRAT-Reading and WAIS vocabulary is circumscribed to a certain extent by the level of reading ability and schooling. The effect size for scores on NART or WRAT-Reading were in the moderate range, based on 8 studies in relatives of schizophrenics compared to controls (0.48, 95% confidence intervals 0.16-0.81). This suggests a non-overlap in distributions of about 33% (figure 1.14).

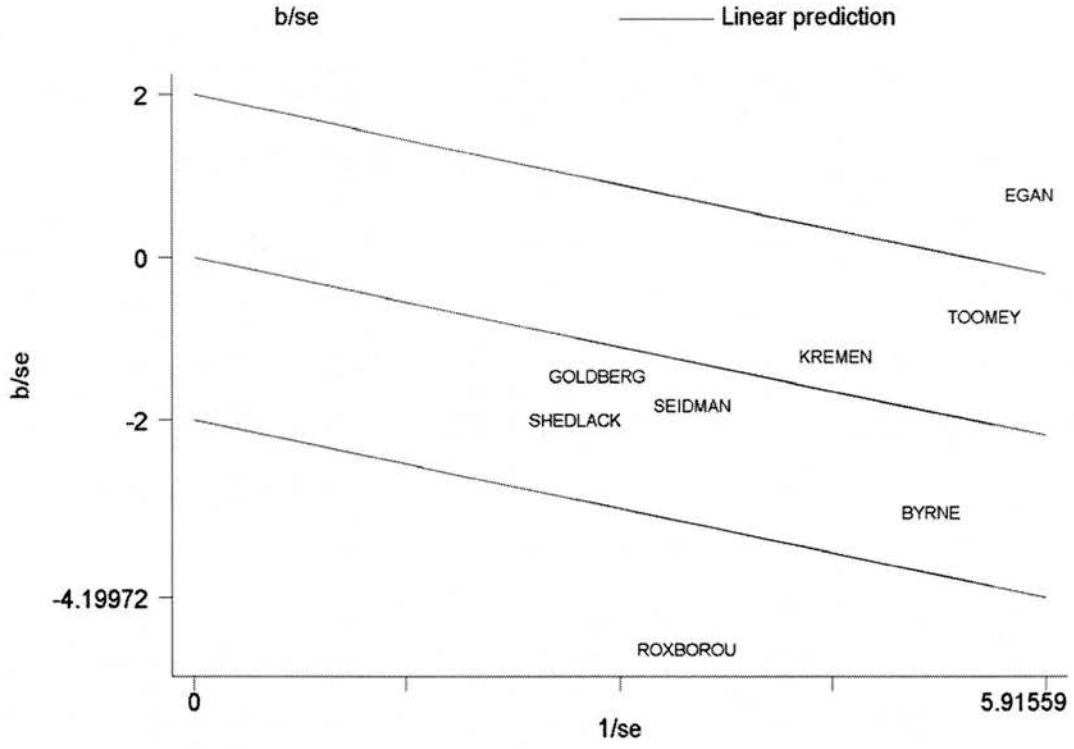
Figure 1.14(a) Forest plot of individual and pooled estimates of standardised mean difference between relatives of schizophrenics and controls in verbal IQ



However, the Q statistic was significant (chi-squared = 26.8 (d.f. = 7), $p < 0.001$) and I squared showed 73.9% of variation in the standardised mean difference to be attributable to heterogeneity. From the Galbraith plot it is clear that Egan et al (2000) lie outside the upper limits of the 95% confidence intervals for this test, while Roxborough et al (1993) lie outside the lower limits of the confidence intervals for this test. Egan et al (2001) also show an effect in a different direction from the other studies for this test, due to their relatives achieving a marginally higher IQ score than the controls. However, the basis for this difference is unclear, given that all but two studies also used WRAT reading as the measure of verbal IQ. The control group were matched to the relatives for age, gender, educational achievement, and WAIS IQ, and were recruited from the National Institute of Mental health Volunteer Centre. However, the number of relatives far outweighed the number of controls, with an additional over representation of females in both groups. Only Roxborough et al (1993) and Byrne et al (2003) used the NART. The age of the relative sample in Byrne et al (2003) was between 16 and 25 years on entry to the study. It is possible that the reliance of this test on educational attainment could have lead to an underestimation of the actual level of performance in this

group. Alternatively, a sub-group of participants in this sample who were experiencing transient psychotic symptoms and who would subsequently develop schizophrenia may have contributed to the substantially lower group mean on this test relative to controls. Roxborough et al (1993) used an older 'relative' sample, so that an underestimation of IQ ability would be less likely. Without details of educational level relative to controls, it is difficult to assert this conclusively. It is additionally possible however, that the IQ of the control group might have been slightly above average, given that the control sample was selected from staff and students within the hospital. A test for publication bias showed a trend for significance ($t = -2.16$, $p = 0.07$). However, this is likely to be influenced by the fact that IQ effect sizes were only derived from those studies investigating memory, which were included in the meta-analysis. A more thorough search and inclusion of all studies of verbal IQ in relatives of schizophrenics would probably rectify this bias.

Figure 1.14(b): Galbraith plot of studies of verbal IQ

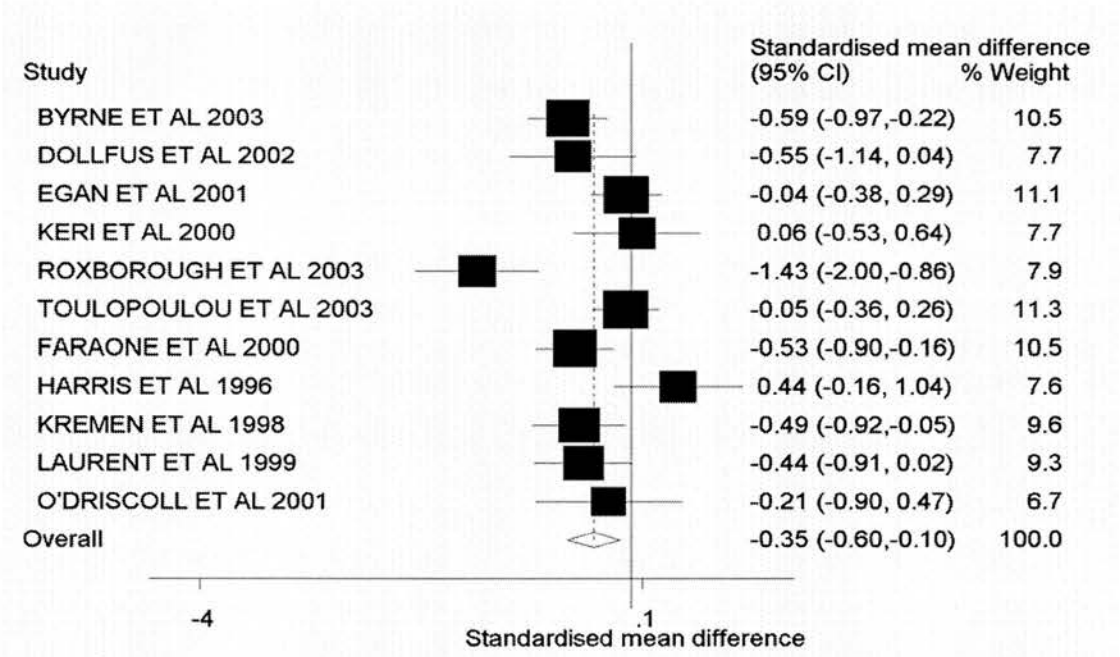


WAIS-R IQ

The WAIS-R full scale IQ (or short form) combines measures of performance and verbal IQ to provide a score of general intellectual function. This is also considered a measure of fluid intelligence

because performance is dictated by the biological capacity for learning. Our meta-analysis showed that based on 11 studies the effect size was less than that for verbal IQ and in the small to moderate range (0.34, 95% confidence intervals 0.10-0.59), corresponding to a non-overlap in distributions of between 21.3 and 27.4%. The Q statistic was highly significant (chi-squared = 32.5, (d.f. = 10), $p<0.001$), and I squared showed 69.3% of variation in the standardised mean difference to be due to heterogeneity (see figure 1.15).

Figure 1.15 (a) Forest plot of individual and pooled estimates of standardised mean difference between relatives of schizophrenics and controls in WAIS-R IQ

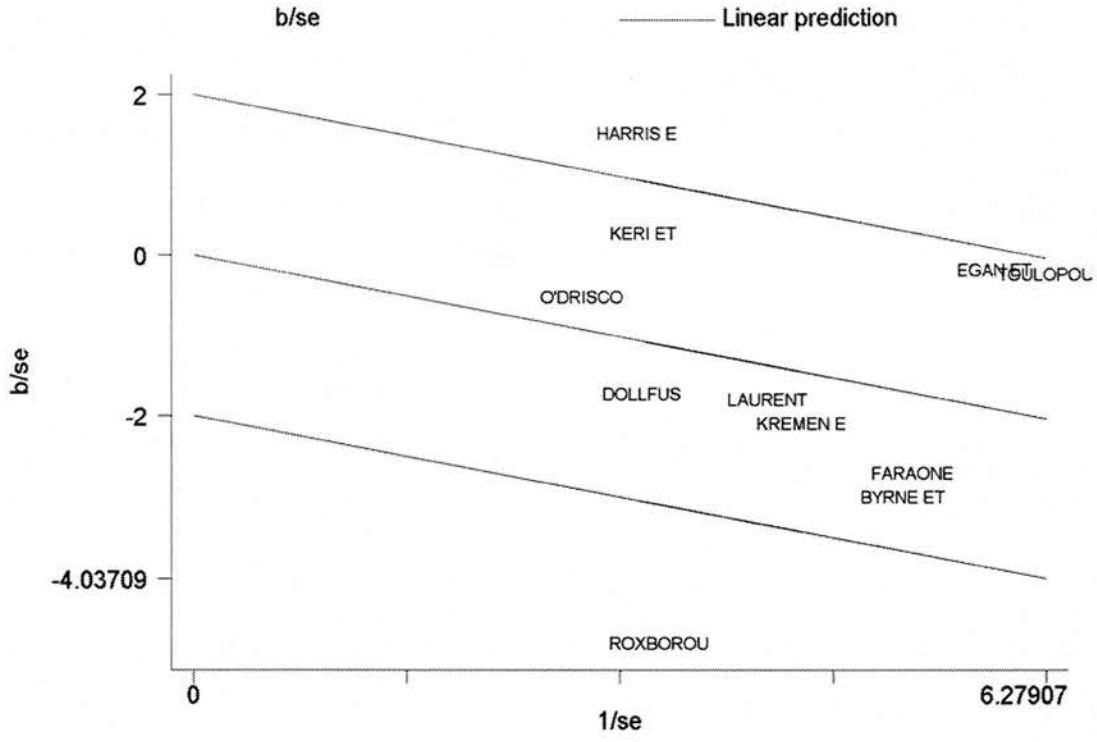


As with verbal IQ, this seems particularly influenced by Roxborough et al (1993) and suggests that the large discrepancy between relatives and controls in this study is not due to the nature of the test, but to the groups themselves (Roxborough et al 1993). Once again, the recruitment of a control group from staff and students at the hospital has likely resulted in slightly larger than average IQ scores in this group. In the other direction, Harris et al (1996) showed a slightly better short form WAIS IQ performance (block design and vocabulary) in parents of patients relative to controls, while schizophrenic probands showed equivalent performance to controls on the same estimate. This is not a feature of the short form, because several other studies also used this estimate and demonstrated significant differences. It may however be due to the mixture of positive and negative history parents

of schizophrenics, such that negative history parents are unlikely to be genetically predisposed to the development of schizophrenia. Alternatively, the recruited control group were students from a technical college, with a mean age of 29 years, while parents were at least double this in age. Parents may therefore have had greater levels of education and life experience relative to the control group, leading to differences in general IQ score (Harris et al 1996).

Heinrichs and Zakzanis (1998) reported separate effect sizes for WAIS-R IQ, non-WAIS IQ, performance IQ, verbal IQ and vocabulary in their meta-analysis of cognition in schizophrenia and controls (Heinrichs and Zakzanis 1998). Performance IQ based on 17 studies showed the greatest effect size (d=1.46) but with the largest heterogeneity, next to WAIS-R IQ based on 35 studies (d=1.24), verbal IQ (d=0.98), vocabulary (d=0.69) and non-WAIS-R IQ (d=0.63).

Figure 1.15 (b) Galbraith plot of studies of WAIS-IQ



1.6.4 Discussion

This quantitative meta-analysis reviewed the literature between 1965 and 2004 and compared effect sizes in a number of aspects of memory function, bringing together scores on the same or similar tests across studies. This has permitted a quantification of the nature of the memory impairment in healthy relatives of schizophrenics when compared with controls, and a qualitative examination of similarities with the deficits reported in previous meta-analyses in schizophrenia. Despite the extent of our search of the literature, the earliest relevant study was published in 1993. This perhaps reflects the more recent interest in declarative memory function in families of schizophrenics. Indeed, a selection of early papers placed an emphasis on either language or general information processing deficits such as attention and sensory processing (Condray et al 1992; Maier et al 1992; Pollin and Stabenau 1968), or did not examine aspects of memory as separate processes (Chazan et al 1986).

1.6.4.1 Summary of results

Although the results of the meta-analysis show effect sizes to be in the small to moderate range (Cohen 1988), it is clear that unaffected relatives of schizophrenics perform less well than controls on tests of verbal and non verbal declarative memory. Furthermore, confidence intervals for all tests overlap, suggesting a global trait deficit. These differences are compelling, particularly when it is appreciated that the relative samples are comprised of healthy, non-psychotic and in some cases high functioning relatives of schizophrenics. With respect to previous meta-analytic studies in schizophrenia, the pattern of impairment here is such that unaffected relatives perform better than schizophrenic patients, when compared to controls. This suggests that impairments on measures of both verbal and non-verbal memory are at least partly reflective of a genetic vulnerability to schizophrenia, but that the more severe deficits apparent in schizophrenic patients may be additionally attributable to a disease related process. This implies a disease-related component to memory dysfunction in schizophrenia and may be considered further evidence that declarative memory impairment is a possible 'intermediate phenotype' for the disorder, albeit a family-specific one.

Our results showed the largest effect size to be in the immediate verbal recall of trial 1of the AVLT. However, given the small number of included studies in this instance, this effect should be considered

tentatively. Conversely, the smallest effect sizes are also apparent on measures of verbal immediate memory, for both digit span tasks, and visual delayed recall. There was a slightly larger effect size for the backward over the forward aspect. We can perhaps reconcile these findings by examining the differences in difficulty between both types of task. The phonological representation of a maximum of 8 meaningless digits may be less attentionally and functionally demanding than the maintenance of a list of 15 seemingly unrelated words (both in meaning and articulation). Furthermore, the smaller effect sizes for digit span imply that both the phonological loop and to a lesser extent the store components of verbal working memory are relatively intact. It is plausible that the processes exerted during the acquisition of words involve both spontaneous semantic and phonological encoding, and that the brain networks supporting the former may be recruited more effectively in controls than in unaffected relatives of schizophrenics.

Effect sizes for verbal fluency were non-significantly smaller than those for story recall and verbal list learning. Verbal fluency has previously been included in studies as a measure of executive function. These results are therefore less surprising, given the weaker evidence for executive deficits in unaffected relatives (i.e. WCST-(Sitskoorn et al 2004a)). It is possible that these tests place less demand on unaffected relatives than on schizophrenic patients, and that the latter group may reveal compromised performance partly because of slowed information processing speed. Moreover, the brain networks supporting verbal fluency may be particularly deficient in those affected by the disorder, so that executive function is predominantly a feature of the disease process rather than a trait deficit. Interestingly, the effect size for phonological fluency was non significantly greater than that for semantic fluency, the opposite pattern to that seen in patients. Given the non-overlap with Heinrich and Zakzanis's confidence intervals for word fluency in patients relative to controls (0.91-1.80), this may again suggest a separate non-genetic disease related deficit (Heinrichs and Zakzanis 1998).

Effect sizes were in the moderate range for immediate and delayed verbal story recall and both measures of verbal learning (total list recall and paired associate learning). Despite an overlap in confidence intervals, the effect sizes for both immediate and delayed story recall were greater in

magnitude than those for verbal learning. Previous attempts to quantify verbal memory impairment have often amalgamated both verbal story recall scores with immediate and delayed list recall scores on the CVLT or RAVLT. However, story recall would appear to be distinct from list recall, in that there is no inherent facilitation of learning or enhanced encoding by either repetition, implicit semantic categorisation, cued recall or recognition. The latter result therefore supports the notion that repeated exposure, forced association and cued recall, all aid memory for information. Following an encoding task requiring a size judgement decision about words, Sponheim et al (2004) showed poorer verbal recognition memory in schizophrenic patients relative to controls and unaffected relatives, while relatives and control did not differ. Conversely, relatives showed significantly poorer verbal recall for the same material compared to controls. Correlation analyses revealed that depth of encoding in the control and patient group predicted free recall performance, but not in the biological relatives. Similarly, while priming effects were associated with encoding in the relatives, this was not apparent in the control group. This implies that explicit recall in the relatives may have relied on familiarity rather than explicit recollection, or alternatively on implicit processes facilitated by the size judgement task. Controls did not show the same improvement from recall to recognition apparent in the relatives group because they relied on explicit recollection for both aspects of the task (Sponheim et al 2004).

The difference in effect size magnitude between story recall and verbal learning might reflect the fact that story recall demands a higher level of organisation of encoded information, based on only one exposure to the material. Indeed, serial clustering strategies, often used in list recall tasks, will be relatively inadequate in aiding later recall. Effective executive control and context processing at encoding is therefore necessary to facilitate a more accurate recall of the story's ideas. If immediate encoding associations are ineffective, this will impact upon the eventual recall of the words and ideas from the story. This suggests that encoding processing may be fundamental to the memory impairment apparent in both schizophrenic patients and their unaffected relatives, and is supported by the results of the meta-analysis of immediate verbal recall. If the brain networks recruited during information acquisition and spontaneous organisation are less effective in relatives than in controls, eventual recall will be compromised. More severe information acquisition and a failure to benefit

from the provision of explicit external cues to aid information organisation have previously been reported in schizophrenic patients (Calev et al 1983; Chan et al 2000; Gold et al 1992b; Manschrek et al 1997). Indeed, Cannon et al (2000) showed less semantic clustering of the CVLT list in monozygotic and dizygotic twins discordant for schizophrenia relative to controls, and assert that genetic liability for schizophrenia may impact upon prefrontal cortical brain systems, crucial for the effective organisation of material during acquisition (Cannon et al 2000b). Tuulio-Henrikson et al (2003) showed traits reflecting encoding (i.e. semantic clustering, recognition memory and intrusions) to show significant additive heritability estimates, implying dysfunctional encoding may be a heritable component in the families of schizophrenics. These findings support the view that encoding dysfunctions represent both a trait and disease related deficit in schizophrenia (Tuulio-Henriksson 2003).

Both Braver et al (1999) and Frith (1992) argue that despite the diversity of cognitive impairments apparent in schizophrenia, the common underlying feature is a defective internal monitoring system, specifically in the 'internal representation and use of context information' when exerting control over and guiding behaviour (Braver et al 1999; Frith 1992). Macdonald et al (2003) tested this hypothesis in unaffected relatives of schizophrenics using a context-processing task (the modified expectancy AX task), where the letter X becomes a target only when preceded by the letter A. Distractor trials included BX, BY and AY. Both schizophrenic patients and unaffected siblings performed worse than controls in the context processing condition (BX). Conversely, controls performed worse than all other groups in the expectancy condition (AY). This was interpreted as an example of both patients and their unaffected siblings failure to effectively use context (A) to inform their response to the target X, and is evidence for a genetic contribution to a context processing deficit in schizophrenia (MacDonald et al 2003b).

The processing of words linked meaningfully in a sentence or story is dependent not only on the lexical properties of those individual words, and an understanding of syntactical and grammatical relationships between those words, but also on the integration of these words and their meanings into a coherent whole. Condray et al (1992) compared schizophrenic patients, their schizophrenia

spectrum disorder brothers, non-spectrum disorder brothers, unaffected brothers and matched controls, in language comprehension, using the relational concepts factor scale of the Luria-Nebraska Neuropsychological Battery. Schizophrenic probands and brothers with schizophrenia-spectrum disorder showed poorer language comprehension than normal controls. However, language performance did not significantly differ between schizophrenics and their unaffected brothers, despite intact performance in measures of executive function and general intellectual ability. This implies a continuum of language dysfunction associated with familial liability to schizophrenia, but worse in those with a related spectrum disorder or with schizophrenia (Condray et al 1992). The semantic integration hypothesis asserts that lexical encoding is preserved in schizophrenia, and like controls, patients are sensitive to grammatical and syntactical sentence structure during sentence processing. However, patients may be impaired in tasks requiring semantic integration (Nathaniel-James and Frith 1996) Knight and Sims 1979 as cited in (Condray et al 1992)). It is possible therefore, that this hypothesis may be valuable when extended to include biological relatives of schizophrenics.

Our meta-analysis has also shown that effect sizes for immediate and delayed non-verbal memory appear to be slightly less than those for immediate and delayed story recall, with immediate visual recall comparable to those for verbal learning, but delayed recall the smallest of all effect sizes reported. This effect has previously been described in a meta-analysis of cognition in schizophrenia, and suggests that memory deficits in relatives and in patients are not restricted to the verbal modality (Heinrichs and Zakzanis 1998). However, despite an overlap in confidence intervals, the slightly greater deficit in story recall implies that memory for visual figures is marginally better than memory for words and ideas. The tasks used for these domains were not matched for difficulty, so that it is plausible that the measure of story recall is more demanding for relatives than that for visual recall. This finding might also reflect the contextual component to the story recall test previously discussed, which may be less prominent during tests of visual memory. Alternatively (or in the same way), it could imply that left lateralised brain networks supporting verbal processing may be more impaired than right lateralised networks recruited to support visuo-spatial processing. Related to this point is the observation that the material used in WMS Visual reproductions test is verbalisable, such that the task may be testing both visual and verbal processing (Saykin et al 1991; Saykin et al 1994).

Finally, an additional investigation of effect sizes for measures of intellectual function in the studies considered provides us with an overview (albeit narrower) of neuropsychological deficits alongside general intellectual ability. Our meta-analysis showed the effect size for measures of crystallised intelligence (i.e. NART and WRAT-Reading) to be non-significantly greater than that for measures of fluid intelligence (i.e. WAIS-R). Heinrichs and Zakzanis (1998) reported verbal IQ and vocabulary effect sizes in schizophrenia to be greater than for non-WAIS tests of intelligence, but less than those for performance and WAIS-R IQ, the opposite to the pattern described here (Heinrichs and Zakzanis 1998). This could be due to the reliance of verbal IQ tests on previous educational attainment and age. Our current findings should be considered tentatively in light of the heterogeneity across studies. As discussed previously, this may be influenced considerably by the selection of control groups in some studies. In addition, the significant publication bias for verbal IQ suggests that the nature and result of studies reporting verbal IQ comparisons may have influenced publication. The restriction of the IQ meta-analysis to those studies including specific tests of memory has doubtlessly limited the inclusion of studies reporting more varied results. It is therefore possible that an unrestricted and more comprehensive meta-analysis of intelligence in unaffected relatives and controls would allow for a more unambiguous interpretation of the results. Importantly, despite an overlap in confidence intervals, effect sizes for measures of intellectual function are non-significantly less than those for both verbal learning and memory, suggesting that neuropsychological memory deficits are not secondary to a global intellectual dysfunction. This is especially true given that a number of studies introduced measures of intelligence as covariates in their neuropsychological analyses, and the adjusted mean neuropsychological scores were included in the meta-analysis (Byrne et al 1999; Dollfus et al 2002; Kremen et al 1998b; Roxborough et al 1993). Therefore, in some cases, effect sizes for memory may be underestimated relative to measures of intellectual function.

1.6.4.2 Limitations

We have presented evidence for functional deficits in memory in unaffected relatives of schizophrenics, but have chosen not to consider these in comparison to other areas of function such as executive function and attention. This may be considered a limitation to our analysis, given that our

effect sizes for story recall and verbal fluency may reflect the influence of executive processes (i.e. context processing). However, Sitskoorn et al (2004) in a recent meta-analysis of cognition in relatives of schizophrenics and controls investigated measures of attention and executive function in addition to verbal memory, and showed their largest effect size, based on 15 studies, to be in verbal memory (d=0.54, 95% confidence intervals 0.43-0.66) and incorporated the WMS, CVLT and RBMT (Sitskoorn et al 2004a).

Our findings are additionally limited by the number of tests applied across studies, which were available to us for analysis. A number of measures of memory such as associative and item recognition or cued recall, were not available for inclusion, possibly due to their being less affected in schizophrenia than other unaided forms of memory retrieval. These features of memory have therefore not been quantified in this meta-analysis. Several other studies have used varying and often idiosyncratic forms of measurement, which could not be included in our meta-analysis, but may impart an additional insight into the nature of memory processes in this group. Similarly, several important studies were excluded because of aggregated scoring. We have tried to address these limitations by including descriptions of some of these studies in our qualitative analysis, and these excluded studies appear to pursue similar results to those included.

Significant heterogeneity (i.e. Verbal IQ, WAIS IQ) and trends for significant heterogeneity (i.e. immediate visual memory recall, semantic fluency) were demonstrated on some tests. Possible sources of variance across studies have been considered and discussed. However, this meta-analysis may be limited by the decision not to remove those publications, which after analysis appeared to be responsible for the variance in some tests. In the same way, for measures of IQ, the decision not to extend the meta-analysis beyond those studies included for their measures of memory, may have lead to a skewed interpretation of the standardised mean difference between groups and its relationship to declarative memory.

While this meta-analysis concerns the comparison of individuals at genetically enhanced risk for the development of schizophrenia, differences in genetic loading within this sample may have obfuscated

true differences between groups. Only a small number of studies have addressed the effects of genetic loading on cognitive performance (Byrne et al 2003; Faraone et al 2000; Glahn et al 2003; Shedlack et al 1997; Tuulio-Henriksson 2003). Glahn and others (2003) showed a negative relationship between genetic loading for schizophrenia (i.e. healthy controls > dizygotic twins > monozygotic twins > patients) and performance on a spatial delayed response task, while Tuulio-Henriskson and others showed an effect of familial loading (i.e. multiplex families versus simplex families) on a test of backward visual span. Faraone and others also showed greater impairment in individuals with multiple rather than one relative affected by schizophrenia, on immediate and delayed story recall and immediate visual recall, while Byrne and others (2003) showed a negative correlation between genetic liability (i.e. more than one affected first degree relative > one affected first and second degree relative > affected second degree relatives) and delayed story recall, semantic verbal fluency and inhibition response errors on a word completion test. These results suggest that some cognitive deficits may increase with genetic loading for the disorder. For this reason, only the means from the simplex group of Faraone et al (2000) were included in the meta-analysis. This was due to the preponderance of other studies using parents or siblings from singly affected families. In retrospect this may limit our analysis because unaffected relatives from multiply affected families may be under represented, and in a rerun of this analysis, it might be pragmatic to combine the means of both the simplex and multiplex groups. However, given the results of Faraone et al (2000) it is also possible that unaffected relatives of multiplex families represent a distinct sub-group of genetically vulnerable individuals. Future meta-analyses may therefore benefit from conducting separate analyses of individuals with different degrees of genetic loading for the disorder.

Secondly, although samples of genetically at risk individuals under the age of sixteen were excluded, a number of included studies still contained individuals not yet beyond the age of maximum risk for development of the disorder (i.e. < 35 years). In such a way, mean performance in relative groups may be influenced by participants who have yet to develop the disorder (Byrne et al 2003; Byrne et al 1998; Byrne et al 1999; Faraone et al 2000; Franke et al 1999; Gochman et al 2004; O'Driscoll et al 2001). There is evidence for general intellectual deficits in high-risk children and premorbidly in children who go on to develop schizophrenia in adulthood. While we cannot yet predict who will

develop schizophrenia, future meta-analyses may benefit from cross sectional analyses based on age of risk (e.g. 16-35 years, 35-45 years and 45+ years).

1.6.4.3 Final conclusions

In summary, we have shown small to moderate effect sizes for varying measurements of memory in unaffected relatives of schizophrenics compared to controls. Declarative memory therefore holds promise as a neuropsychological indicator of genetic vulnerability to schizophrenia. Effect size differences across tests may reflect differences in task difficulty, but could also indicate a specific deficit in verbal encoding in unaffected relatives, a deficit previously highlighted in schizophrenia (Cirillo and Seidman 2003). While 95% confidence intervals for all tests overlapped, effect size differences also give credence to studies choosing to separate measures of memory for investigation of component processes such as encoding and retrieval. Future research should therefore concentrate on the functional imaging of encoding and retrieval in unaffected relatives of both high and low genetic loading, and both beyond and within the age of maximum risk for the disorder, in the hope of providing an insight into the function of brain networks implicated in these tasks.

1.7 Cognitive performance over time in unaffected relatives of schizophrenics

Longitudinal studies of neuropsychology in schizophrenia suggest that cognitive deficits are present and relatively stable with the course of the schizophrenic illness. It is now also clear from the literature that memory, attention, executive and intellectual function are also impaired in relatives of schizophrenics, albeit to a lesser degree than in schizophrenia patients. However, the stability of these deficits in relatives is less reliably demonstrated.

Johnson et al (2003) investigated the relationship between schizotypy symptoms and genetic risk for schizophrenia, and showed symptoms to interact with genetic risk on several aspects of cognitive function. However, in participants with schizotypy symptoms but without family history for schizophrenia, cognitive deficits were not apparent. Only a measure of spatial working memory showed independence from symptoms but was related to genetic risk for schizophrenia. This suggests

that cognitive deficits are not secondary to schizotypy symptoms, but that both may be a manifestation of the same susceptibility loci (Johnson et al 2003).

To date, only two family studies have provided evidence of longitudinal performance in unaffected relatives considered beyond the age of risk for development of the disorder. Faraone et al (1999) showed unaffected relatives with a mean age of 42 years to have stable poorer performance on memory (visual and verbal), attention and executive function (although a slight improvement over time) relative to controls over four years (Faraone et al 1999), while Wittorf et al (2004) showed no change in neuropsychological performance of unaffected relatives with a mean age of 43 years over one year, although improvements in performance were apparent on tests of attention and visual recall (Rey Complex Figure Test)(Wittorf et al 2004). This implies that deficits in unaffected relatives, who are unlikely to develop schizophrenia, remain stable and less severe than those in schizophrenic patients over time.

However, without measures of performance over time in unaffected relatives who have yet to pass through their period of maximum risk for development of the disorder (15-25 years), it is difficult to establish how far deficits reflect genetic liability, to what extent they are features of a disease process and at what point deficits worsen in those who later develop the disorder. Evidence from prospective high-risk studies shows that following participants up to adulthood may provide an insight into cognitive predictors for schizophrenia and related psychoses. Erlenmeyer-Kimling et al (2000) identified verbal short term memory in high-risk children as a sensitive predictor (83%) for schizophrenia-related psychosis development and showed attentional deficits (as measured by CPT, WAIS Digit Span, and the Attention Span Task) in offspring of schizophrenic patients to identify 58% of participants with schizophrenia related psychoses in the New York High-Risk Project (Erlenmeyer-Kimling et al 2000). While the Edinburgh High Risk Study (EHRS) reported a lack of significant differences between the high-risk and control groups in sustained attention (CPT), it did report a decrement in verbal memory performance between the first and second neuropsychological assessments, in high-risk individuals (between the ages of 16 and 25 years) who had developed attenuated psychotic symptoms at either the first or second assessments (Cosway et al 2002). The

latter finding could reflect state related interference at the time of assessments because of symptom development, but could alternatively be indicative of the development of the disease process before the onset of schizophrenia per se. Thus, changes may be occurring in genetically at risk participants who will develop psychotic symptoms or schizophrenia at two different developmental periods (i.e. prenatal/infancy and adolescence).

1.8 Edinburgh High-Risk Study

Established in 1994 by Professor Eve C Johnstone and others, in the Department of Psychiatry at the University of Edinburgh, the Edinburgh High Risk Study (EHRS) is a prospective longitudinal study of individuals between the ages of sixteen and twenty-five with at least one affected first or second degree relative. In order to reduce the high rates of attrition common in other high-risk projects, this study was designed to follow young adolescents through their period of maximum risk for the development of schizophrenia, with the expectation of schizophrenia onset in 10-15% of the sample within a ten-year period.

During the first five-year phase of the study, neuropsychological and clinical assessments were conducted in the high-risk participants and controls at regular intervals of eighteen to twenty-four months, consisting of three assessment rounds (July 1994-July 1999). During the last five year phase of the study, neuropsychological and clinical assessments continued to be conducted in high-risk and controls participants, along with structural and functional magnetic resonance imaging scans, at regular intervals of eighteen to twenty four months, also consisting of three assessment rounds (July 1999-July 2004) (see Appendix 2: Table 2A). The main aim of the study was to determine those features, which distinguished healthy high-risk participants from controls, and high-risk participants who became ill from those who did not, through neuropsychological, structural and functional brain assessments over time.

1.9 Aims and hypotheses of investigations 1-4

Our discussion of the literature concerning the development and course of neuropsychological deficits in schizophrenia patients and their unaffected relatives has raised several issues and has informed our

experimental aims and hypotheses. Firstly, that in spite of a global intellectual dysfunction, and even after controlling for the effects of impaired intellectual ability, both groups show persistent deficits on tests of memory and to a lesser extent attention and executive function. In unaffected biological relatives, these deficits may be reflective of the same underlying brain abnormalities found in schizophrenia, and implicate a wide range of brain networks including the frontal, temporal, and parietal lobes. However, the specific nature of memory impairment in schizophrenia is still unclear, and even less so in unaffected relatives or those relatives who go on to develop the disorder. Moreover, the relationship between genetic risk, psychotic symptoms, and cognitive deficits is complex. Evidence of psychotic symptom improvement in the presence of impaired cognitive performance in patients, points to at least a degree of independence of one from the other. However, recent evidence suggests the three may interact, such that symptoms and deficits are manifestations of the same susceptibility loci in individuals at genetically enhanced risk for the disorder (Johnson et al 2003).

Subtle neuropsychological deficits in unaffected relatives of schizophrenics who don't develop schizophrenia may be reflective of a genetic liability to the disorder, although the relationship between deficits and genetic loading is also unclear. Furthermore, poorer intellectual performance in young individuals who develop schizophrenia in adulthood and the presence of specific neuropsychological impairments in unaffected relatives and first episode patients, indicates that structural and functional brain changes may have occurred prior to the manifestation of the characteristic signs and symptoms of schizophrenia, while a predisposition for later psychosis development may already be present as early as infancy. This begs the question therefore, at what stage do cognitive deficits arise in schizophrenia and can they be predictive of the disorder in individuals at genetically enhanced risk for schizophrenia? The fact that these impairments may be less severe than those reported in chronic schizophrenia patients, further implies that cognitive deterioration might occur after disease onset. However, evidence is equally weighted against cognitive deterioration in schizophrenia and generally supports the existence of stable neuropsychological dysfunction in schizophrenia. This again suggests that deterioration may be occurring some time before disease onset and does not worsen beyond this point.

1.9.1 Investigation 1: Putative neuropsychological predictors of schizophrenia in a high-risk group

Baseline performance differences between the high-risk group and healthy controls on tests of intellectual and executive function, learning and memory have previously been demonstrated in the Edinburgh High Risk Study (EHRS) (Byrne et al 2003; Byrne et al 1999; Cosway et al 2000). These findings are supported by evidence from family and high-risk studies of neuropsychological impairment in unaffected relatives of schizophrenic patients. However, it is unclear how far these deficits distinguish relatives of schizophrenics who will not develop schizophrenia, from those who will. A recent finding from the New York high Risk Study suggests that levels of impairment on tests of memory and attention in high-risk children are reasonably predictive of those who will develop schizophrenia related psychoses in adulthood (Erlenmeyer-Kimling et al 2000).

Given these initial findings, our first investigation aimed to further demonstrate performance differences at the baseline assessment within the high-risk group itself, with high-risk participants classified according to susceptibility to psychotic symptom experience over the course of the study, and subsequent development of schizophrenia at the time of analysis. Bearing in mind that all participants at baseline assessment were essentially well, we hoped to show differences in performance between those high-risk participants who have remained well and those who have gone on to develop schizophrenia, which could be 'predictive' of future schizophrenia development (i.e. (Erlenmeyer-Kimling et al 2000). Our first hypothesis was therefore:

Within the high-risk participant group, those participants who go on to develop schizophrenia will perform less well relative to those participants who do not on baseline neuropsychological assessments.

1.9.2 Investigation 2: Neuropsychological performance over time in a high-risk group:

Due to the extended period of time over which this group has been studied, our second investigation aimed to characterise the course of deficits in high risk participants who develop psychotic symptoms, and or schizophrenia over time, relative to those who do not (i.e. those in the high-risk group who, to

the best of our knowledge, have never in the course of the study experienced any psychotic symptom (i.e. HR-), those who have at some point in the course of the study experienced any psychotic symptom (i.e. HR+), those who are now diagnosed as schizophrenic (i.e. SCZ) and healthy controls (i.e. C)). Given that participants in our HR- and HR+ group have not developed schizophrenia in the 10 years of the study, it could be argued that few will now go on to develop the disorder. With this in mind, and based on previous evidence of stable deficits in those who are beyond the age of maximum risk for the disorder and therefore unlikely to become ill (Faraone et al 1999; Wittorf et al 2004), we hypothesised that:

High-risk participants who have not developed schizophrenia will demonstrate stable performance deficits compared to controls over time (between their first and latest assessment)

Experience of psychotic symptoms in high-risk participants does not imply that individuals will develop schizophrenia. Similarly, an absence of psychotic symptoms at clinical assessment does not guarantee that individuals will not develop schizophrenia. However, there is a qualitative difference between those high-risk participants who have and those who have not experienced any psychotic symptom, such that a liability to the experience of psychotic symptoms in a high-risk group could be considered an intermediate phenotype for the disorder. For those participants in the high-risk group who have not experienced any psychotic symptom during the course of this study, it could be argued that unlike the HR+ group, they do not exhibit the intermediate phenotype and may be less likely to show fluctuations in performance over time, or eventually develop schizophrenia. We therefore further hypothesised that:

Within the high-risk participant group, those participants who have ever experienced psychotic symptoms and those who are now diagnosed as schizophrenic will perform less well on neuropsychological tests compared to those who have never experienced any psychotic symptom and controls at both first and latest assessments.

A previous comparison of performance in the EHRS high risk participants who had or had not developed symptoms over the first and second assessments (over a period of approximately 18-24 months), suggested that delayed verbal recall had deteriorated to a greater extent in those who had developed any psychotic symptom between or at either the first or second assessments. This implied that psychotic symptom development or presence might be associated with a decline in verbal memory ability, due to either state related interference (the experience of psychotic symptoms during testing) or as a precursor to psychosis (due to underlying structural or functional brain changes). Due to the intermittent experience of psychotic symptoms in our HR+ group, we were unable to make predictions as to the direction of performance over time (between the first and most recent assessment) in this particular group. However, given that schizophrenia patients have been shown to exhibit poorer general neuropsychological performance than their close relatives, we predicted that cognitive decline might be apparent in those who have subsequently developed schizophrenia between two assessments prior to illness onset. Our fourth hypothesis therefore stated:

Within the high-risk participant group, participants who are now diagnosed with schizophrenia will show a decline in neuropsychological performance over time, relative to the other high-risk participants and controls.

1.9.3 Investigation 3: Neuropsychological performance over time and genetic liability:

Where neuropsychological performance over time revealed significant main effects of group or group by time interactions, our third investigation aimed to explore the specific influence of genetic liability on performance over time within the high-risk participant group only. Initial recruitment involved the scrutiny of detailed family trees for all high-risk participant families, thus affording us the opportunity to classify those in the high-risk group by closeness and number of affected relatives. Although the development of schizophrenia in this group cannot be solely attributed to genetic vulnerability, a family history of schizophrenia conveys some form of predisposition to the development of the illness and the presence of a similar neuropsychological profile to schizophrenic patients. A previous investigation of the relationship between genetic liability and neuropsychological performance at

baseline revealed an inverse relationship between genetic loading and executive function, learning, and memory measures (Byrne 2003). Our fifth hypothesis therefore stated that:

Within the high-risk participant group, a greater familial loading would be negatively associated with neuropsychological function over time.

1.9.4 Investigation 4: Verbal and Visual Learning in the 1st 100 participants of the EHRS to undergo a functional MRI scan

Given the previous baseline results suggesting a memory deficit in high-risk participants relative to controls, our fourth investigation, presented in chapter 3, aimed to quantify the nature and extent of the memory deficit in the EHRS, using performance data on tests of verbal and visual memory not previously analysed in the EHRS group. These tests were introduced at the beginning of the second study phase and were accompanied by functional MRI in the same participants during a verbal memory paradigm, which will be discussed in detail in chapter 5.

A review of the literature suggests declarative memory is a core deficit in schizophrenia, characterised above all by poor verbal encoding and retrieval. Our systematic review also suggests that this deficit is paralleled in healthy biological relatives, most prominently in immediate verbal recall and memory for prose while assisted memory recall, such as recognition, has generally been shown to be intact in patients and their relatives (Sponheim et al 2004). This indicates that fundamental to a verbal declarative memory deficit is impaired information acquisition and a failure to organise material effectively for future recall. We therefore hypothesised that on measures of the California Verbal Learning Test (CVLT):

High-risk participants will show intact recognition performance, but perform less well on measures of verbal information acquisition and recall, and demonstrate different learning strategies during trials one to five, when compared to controls.

Visual memory performance in schizophrenia is less consistently investigated relative to verbal memory performance. Some evidence suggests equivalent performance impairment in both modalities in schizophrenia (Tracy et al 2001) while other evidence suggests a less pervasive, and more heterogeneous visual memory deficit when compared to verbal memory measures (Heinrichs and Zakzanis 1998). This was reflected in our meta-analysis of memory impairment in relatives of schizophrenics, which suggests that memory impairment does extend to the non-verbal domain, but may be more heterogeneous and less severe. We aimed to demonstrate the extension of declarative memory impairment to both modalities in relatives compared to controls. Given the evidence, we hypothesised that:

High-risk participants would perform less well relative to controls on aspects of visual recall, as measured by the Rey Complex Figure Test (RCFT).

Chapter 2: Methods and results of investigations 1, 2 and 3

The methods and results for neuropsychological investigations 1-3 in the Edinburgh High-Risk group will be presented serially in this chapter. This is due to the slight differences in the sample numbers used for each investigation, and allows for a more informative description of participants in each instance. It is hoped that this will additionally enhance the coherence of each individual investigation. The aims and hypotheses for these investigations were previously introduced at the end of Chapter 1, but will be reiterated where necessary in the methods sections. Finally, a discussion of the results of experiments 1 to 3 is also presented in this chapter.

2.1 Methodology: Investigation 1

2.1.1 Design

As described in Chapter 1, analyses conducted by the EHRS have previously demonstrated differences in performance between the high risk group and controls at baseline on some of the neuropsychological tests employed (Byrne et al 2003). Therefore, in an investigation of baseline predictors of psychosis, differences on these neuropsychological tests at the first assessment were compared within the high-risk participants only. Group comparisons were made between three sub-groups of high-risk participants. The first group included those high-risk participants who subsequently developed schizophrenia (SCZ). The remaining participants were allocated to one of two high-risk groups according to the presence (HR+) or absence (HR-) of psychotic symptoms at the first assessment, as measured using the Present State Examination (PSE).

In a Multivariate Analysis of Variance (MANOVA), followed by one-way Analyses of Variance (ANOVAs), participant group was introduced as the between-group factor and individual neuropsychological test performance at baseline as the within-group factor. Planned contrasts were conducted in order to address the two a-priori hypotheses (as outlined in Chapter 1). To reiterate, it was first of all hypothesised that those who subsequently developed schizophrenia would perform less well relative to the rest of the high risk group on neuropsychological tests, which could be predictive of future psychosis (i.e. predictive effect). Secondly, it was hypothesised that those in the high-risk group who experienced any psychotic symptom at this baseline assessment would perform less well

relative to high-risk participants who had not experienced any psychotic symptom at this assessment, due to the interfering effect of symptoms on general performance (i.e. state effect).

2.1.2 Participants

2.1.2.1 Recruitment: high-risk participants

Ethical approval was granted for recruitment in ten Scottish Health Boards (i.e. Lothian, Dumfries and Galloway, Lanarkshire, Tayside, Borders, Argyll and Clyde, Highland, Western Isles, Fife and Forth Valley; Byrne 2001). Potential high-risk participants were then initially identified through an analysis of medical records of individuals admitted to psychiatric hospitals in Scotland with a clinical diagnosis of schizophrenia and potentially unaffected 1st and 2nd degree family members in the specified age group of sixteen to twenty five years.

Research diagnosis of DSM-III-R classification of schizophrenia was confirmed for each individual by applying the Operational Criteria Checklist (OPCRIT) to the medical case notes. The consultant, GP, social worker, key worker and community psychiatric nurse involved with the proband were contacted and after consultation, permission was sought to approach the identified proband. Following an interview and informed consent from these patients to approach family members, potential high-risk individuals were contacted, with the help of a well adult relative. Individuals who met the criteria for inclusion (i.e. those individuals aged between 16 and 25 years and with no previously diagnosed psychotic disorder) and were willing to participate in the study on a voluntary basis were asked to read an information sheet (see Appendix 2: Figure 2A) and sign a consent form (see Appendix 2: Figure 2B), which detailed the nature and conditions of participation. Once individuals had signed the consent form they were required to undergo a structured psychiatric interview (PSE), which establishes the presence of current psychotic, neurotic or depressive symptomatology (Byrne 2001; Hodges et al 1999; Johnstone et al 2000). The age of the sample at the outset of the study was important to ensure that the high-risk participants would pass through their period of maximum risk during the study. It was expected that 10-15% of the original high-risk sample would develop schizophrenia in the course of this study (Johnstone et al 2000).

2.1.2.2 Recruitment: controls

Controls were not included in this analysis of baseline performance, because comparisons between controls and high-risk participants have already been conducted. However, for the purposes of later investigations including control participant performance, potential control participants were originally identified from local Edinburgh youth groups and from a sample of friends of the high-risk participants. Forty-three individuals with no personal or family history of a psychotic disorder, and similar in age, sex, and socio-economic background to the high-risk participants, were identified within this group. Willing participants were asked to sign the same consent form presented to high-risk participants, detailing the nature and conditions of participation (see Appendix 2: Figure 2A & 2B). Of this original sample, 36 individuals attended for baseline neuropsychological and clinical assessments between 1994 and 1999. (Note: A more detailed description of participant recruitment can be viewed in previous publications based on this study i.e.; (Byrne 2001; Hodges et al 1998; Hodges et al 1999)

2.1.2.3 EHRS Sample

In the first five years of the EHRS 229 high-risk participants and 43 controls were initially identified and recruited. Of this number, 162 well high-risk individuals between the ages of 16 and 25, with at least one first or second degree relative with schizophrenia, and 36 matched controls provided basic demographic data (Johnstone et al 2000). Within this sample, baseline neuropsychological data are available for 157 high-risk participants and 36 controls, whereas complete clinical data are available for 154 high-risk participants. At this time, 18 of this latter sample of 154 have now been diagnosed with schizophrenia.

2.1.2.4 Sample for analysis of baseline neuropsychological performance

Full baseline clinical and neuropsychological data are available for 154 high-risk participants (see Appendix 2: Table 2A). Data were unavailable at the time of this analysis for one high-risk participant who was recruited for the first time in August 2003. This individual has therefore not been included in the present analyses, resulting in a total sample size for this analysis of 153 high-risk participants.

2.1.2.5 Psychopathology

Psychopathology was elicited by applying an one hundred and forty item standard psychiatric interview, i.e. Present State Examination (PSE, 9th edition; (Wing et al 1974) at the time of the first neuropsychological assessment (and thereafter at 18-24 month intervals), and was administered by experienced clinicians (i.e. Professor E.C. Johnstone, Dr D.C. Owens and Dr S.L. Lawrie). It was not possible for the clinicians to remain blind to the participant's group, due to the repetitive nature of the PSE over the ten years of the study. However, the former two clinicians have worked together for approximately thirty years. The PSE explores the incidence of psychotic symptoms (hallucinations and delusions), other perceptual disorders, depressed mood, psychosomatic symptoms, and neuroticism. It does not address functional deterioration because this group were not considered 'help-seeking'. The interview was videotaped with permission and lasted approximately 1 hour. Based on this examination, the presence or absence of psychotic symptoms was established and a score was assigned.

Additional clinical assessments conducted included the Schedule for Affective Disorders and Schizophrenia-Life-time Version (Endicott and Spitzer 1978), the Structured Inventory for Schizotypy (Kendler et al 1989) and the Rust Inventory for Schizotypal Cognitions (Rust 1988). The Positive and Negative Symptoms Scale (PANSS) was also introduced in the second phase for the assessment of symptom severity. A life-events questionnaire was used to assess life events at baseline assessment only (Paykel et al 1971), along with assessments of neurological soft signs (Buchanan and Heinrichs 1989) and minor physical anomalies (Waldrop and Pederson 1968), both also collected at the baseline assessment only. These additional assessments are not considered in this thesis.

PSE examinations at baseline form the basis of our high-risk negative and high-risk positive group categorisations. High-risk positive participants (i.e. HR+ (time1); N=28) are those who manifested any psychotic symptoms at the first PSE (i.e. a score of 2 or 3 as described in Table 2.1), such as isolated delusions, hallucinations, or perceptual distortions. High-risk negative participants (i.e. HR- (time1); N= 107), on the other hand, are those who did not experience any psychotic symptoms at their first PSE (i.e. a score of 1 or 0 as described in Table 2.1). Finally, an additional group was

identified which was comprised of those participants in the high-risk group who although considered psychologically well at their first assessment, have now been determined to be schizophrenic (i.e. SCZ; N=18). This diagnosis was based upon both the PSE & the ICD-10 (World-Health-Organisation 1992) definitions of schizophrenia established at interview. In some instances, participants fell ill between assessments and were admitted to local services. Local GPs, consultants, and families were collaborators in the project, and all cooperated in informing the study of any changes or deteriorations in state as and when they occurred. Therefore on two occasions clinicians conducted interviews during the participant's hospital admission. Participants who were diagnosed as schizophrenic became ill on average 3.6 years (s.d. = 1.1) after their first assessment.

Table 2.1: PSE Scores

Score	*Diagnosis*
4	Schizophrenia.
3	Definite psychotic symptoms and specific psychotic features fully rated (isolated delusions or hallucinations present, of which the individual is aware).
2	Possibly psychotic (perceptual distortions) or partially held/attenuated psychotic symptoms (the individual questions the existence of such symptoms and may attribute them to the imagination).
1	No psychotic symptoms, but definite non-psychotic (neurotic or depressive) symptoms.

2.1.3 Demographic details

There were no statistically significant differences between the three high-risk sub-groups with regards to age ($F_{(2, 150)} = 2.0$, $p = 0.13$), gender ($\chi^2 = 4.7$ (2), $p = 0.09$), or handedness ($\chi^2 = 1.2$ (2), $p = 0.5$) (means and frequencies for these characteristics can be found in Table 2.2). Therefore, it can be assumed for all other data analyses that the three sub-groups of high-risk individuals were appropriately matched.

Table 2.2: Demographic characteristics within the high-risk sub-groups

Demographic characteristic	HR- (time1) Mean (SD)	HR+ (time1) Mean (SD)	SCZ Mean (SD)	p
Numbers	(N=107)	(N=28)	(N=18)	
Age	21.3 (3.0)	20.9 (2.7)	19.9 (2.6)	NS [a]
Gender (N)	56M: 51F	9M: 33F	7M: 6F	NS [b]
Handedness* (N)	17R: 0L: 2M	92R: 9L: 5M	26R: 0L: 2M	NS [c]

[a] One-way ANOVA, [b] Pearson's Chi-Square Test of Association [c] Kruskal-Wallis Chi-Square Test
* Measured using the Annett Handedness Inventory, M=mixed handedness

2.1.4 Materials

Neuropsychological Tests

Only those tests which showed statistically significant differences between the high-risk group and controls at baseline (Byrne et al 2003) were selected for inclusion in this particular phase of the investigation.

2.1.4.1 Premorbid Intellectual ability tests

National Adult Reading Test (NART;(Nelson 1982)

The NART was used to estimate pre-morbid intelligence in all participants at the first neuropsychological assessment. The NART requires participants to read aloud a list of fifty phonetically irregular words. Participants are allocated an estimated IQ (i.e. WAIS-R) score based on the number of errors that they make on the assessment. Evidence supports the NART as a stable pre-morbid estimate of IQ, which remains unaffected by acute psychosis or the duration of a schizophrenic illness (Morrison et al 2000).

Speed and Capacity of Language Processing Test (SCOLP; the Spot the Word test; (Baddeley et al 1992)

The Spot the Word test is a measure of both vocabulary and verbal intelligence and correlates highly with the NART (Baddeley 1992). This assessment comprises the visual presentation of sixty pairs of words, with one in each pair being a real word and one a non-word (e.g. bread-glot). Participants were required to identify the real word in each pair, without time constraint.

2.1.4.2 Current intellectual ability tests

SCOLP (Speed of Comprehension test; (Baddeley et al 1992)

The Speed of Comprehension test is a measure of speed of information processing, although it has previously been administered as a measure of semantic memory integrity (McKenna et al 1994). This measure comprises a mixture of one hundred true and false sentences (e.g. 'pythons move around searching for food' or 'Nuns are made in factories'). The decision as to whether a statement is true or false is based on the match or mis-match of subject and pre-dictate in the sentence. Participants were

required to correctly verify as many sentences as possible within a two-minute period. Poor performance may be an indication of general slowing of processing. However, the performance on the Speed of Comprehension test is correlated with that on the Spot the Word test, such that any discrepancy between the two (i.e. poorer performance on Speed of Comprehension relative to Spot the Word) may be an indication of reduced language comprehension ability, or a drop in intellectual function from premorbid levels. Subtracting the scaled speed of comprehension score from the scaled spot the word score will give the discrepancy score. No significant differences between the high-risk group and controls were reported on this score at baseline.

Wechsler Adult Intelligence Scale-Revised (WAIS-R; (Wechsler 1981)

The WAIS-R provides a measure of current IQ based on a participant's performance on a number of measures of verbal and visual ability (i.e. eleven in total). Performance on these measures can be used to ascertain three measures of IQ: (1) verbal IQ; (2) performance IQ, and (3) full scale IQ. In the current study an estimate of the full-scale intelligence quotient was derived from performance on all measures of the WAIS-R. Estimates of WAIS-R verbal IQ (based on the verbal sub-tests *Information, Comprehension, Arithmetic, Similarities, Digit Span and Vocabulary*) and WAIS-R performance IQ (based on the performance sub-tests *Digit Symbol, Picture Completion, Block Design, Picture Arrangement and Object Assembly*) were also derived. Participant's scores on both the Digit Symbol and Block Design tasks were also separately noted.

WAIS-R Digit Symbol

Described as a test of 'complex' attention, the Digit Symbol task is believed to measure sustained attention, visuo-motor control and psycho-motor speed (Lezak 1995). Indeed, it is possible that upwards of 50% of the total score can be attributed to copying speed alone (Lezak 1995). In normal controls psychomotor speed is the primary measurement of this test and is unaffected by general intellect, learning or memory (Lezak 1995). Unfortunately, its relative independence from other cognitive functions makes it insensitive to specific areas of brain dysfunction, and it may be affected by a combination of cognitive factors. During performance of the digit symbol task, participants in

this study were timed using a stopwatch and given ninety seconds in which to copy the symbol corresponding to the number denoted in a key (see Figure 2.1).

Figure 2.1: Example of WAIS-R Digit Symbol Substitution test

Digit Symbol Key

1	2	3	4	5
-	⊥	]	└	[

Portion of table- participants to put in the symbol, which corresponds to same number in key

2	5	3	1	4

WAIS-R Block Design

The block design task is proposed to be a test of construction, visuo-motor control, speed and visuo-spatial conceptualisation and in normal participants is associated with mainly right posterior parietal brain regions (Lezak 1995). Participants were presented with four or nine white and red blocks (each block has two white and red sides and two half white and red sides split along the diagonal) and asked to use them to construct a replica of the nine designs presented in the booklet. This was timed using a stopwatch with limits of sixty seconds on the first two designs and one hundred and twenty seconds on the last (more difficult) seven designs. Participants' were allocated an overall score based on both completion speed and accuracy (i.e. higher score for more difficult puzzle completed in faster time period). High performance on this test may be due to participants forming a gestalt or unified mental concept of the design. A more typical (or average) performance can be seen in participants who use a block by block trial and error approach, segmenting the design and constructing based on its individual parts.

2.1.4.3 Executive function tests

Hayling Sentence Completion Test (Burgess and Shallice 1996)

The HSCT is essentially a test of executive function. The test is comprised of two sections, of fifteen sentences (i.e. 30 in total). Each sentence in both sections has the last word missing. Section 1 tests verbal initiation skills and requires the participant to sensibly complete each sentence with a suitable

word (i.e. He posted a letter without a __. A sensible completion would be 'stamp'). Section 2 tests response suppression, by requiring participants to complete each sentence with a word that is unrelated to the meaning of that sentence (i.e. The dough was put in the hot__. An unconnected word would be, for example, 'banana'). In section 2, two types of error response are possible. The first is a type A error (sensibly completing sentence i.e. The dough was put in the hot 'oven') and the second a type B error (completion word is still connected to sentence in some way i.e. The dough was put in the hot 'sink', because sink and oven are semantically related). Response latency was timed using a stopwatch, which was started as soon as the experimenter finished reading the sentence and stopped as soon as the participant had responded. A total scaled score includes both response time and error commission over both sections. Only scaled times for sections 1 and 2 and scaled scores for type A and B errors were included in the analysis.

Stroop Colour Word test (Golden 1978)

The Stroop test is designed to measure both response suppression and selective attention. Participants were required to name the colour of blocks visually presented in trial 1. In trial 2, they were asked to read out the names of colours printed in black ink. In the interference trial 3, participants were then asked to name the colour of ink that the 'colour name' words were printed in. Response latency for each trial was timed using a stopwatch. Only the times for trial 3 and trial 3 minus trial 1 were included in the analysis.

Verbal Fluency (F-A-S and four legged animals; (Spreen and Strauss 1991)

This particular measure of verbal fluency is an assessment of both phonological/letter and category verbal fluency. The participant is allowed 1 minute to recite as many words as possible beginning with a specific letter (F, A or S, with the exclusion of proper nouns or derivations of the same word i.e. stay and staying), followed by 1 minute in which to name as many words as possible words within a specific class (four-legged animals). Response inhibition and an organised search of the inner lexicon are required in both aspects of this test making this a measure of both semantic memory retrieval and executive function. The same test was used at all assessment rounds, although it is acknowledged that at repeat assessments it may have been more appropriate to test fluency using

different letter and category cues, to prevent practice effects. However, only verbal fluency for categories was included in the baseline analysis. Verbal fluency (FAS) was excluded from baseline analysis due to non-significant differences between the high risk and control groups (Byrne et al 2003).

2.1.4.4 Verbal memory

Rivermead Behavioural Memory Test (RBMT): Story recall (Wilson et al 1991)

The entire RBMT was administered to participants, but this investigation will focus solely on the story recall aspect of the RBMT, due to a lack of significant differences between the high-risk and control groups on the additional test aspects at phase 1 round 1. This particular assessment is included here as an indicator of verbal declarative memory performance. Story recall includes the assessment of both immediate and delayed (i.e. following an interval of 20 minutes) verbal story recall of a dictated excerpt. Mean scores reported are based on the raw scores of participants on each of these two task levels. Four parallel versions of the RBMT were administered across assessment rounds, to control for practice effects (A-D (Wilson et al 1991).

Auditory Verbal Learning Test (AVLT: (Crawford et al 1989) and Jones p44 (Lezak 1995),(RAVLT:(Rey 1964))

The AVLT is a test of verbal learning and takes approximately 30 minutes to administer. It includes measures of immediate free recall and delayed free recall and recognition of a list of 15 words, presented over 5 trials, followed by the immediate recall of an interference list of 15 similar words. Numerous measures can be derived from the AVLT, such as total number of items recalled, number of errors, type of errors etc. However, only the total number of items recalled over five trials and the number recalled after the delay were included in this analysis, because these measures were significantly different between controls and the high-risk group at baseline. Lezak (1995) noted that when administered at three time periods (baseline, 6 months and 12 months later), practice effects were shown at second administration on trials five and six and maintained at third administration on trial five only of the AVLT, in twenty control participants (Lezak 1995, p428). The Rey Auditory Verbal Learning Test was therefore administered at phase 1 round 1 (Rey 1964), and parallel versions

at phase 1 round 2 (using version of Crawford et al, 1989, as in p 439 Lezak 1995) and phase 1 round 3 (using version of Jones-Gotman et al, 1993, as in p 439 Lezak 1995), to control for practice effects over time.

2.1.4.5 Visual memory tests

Wechsler Memory Scale (WMS-R; (Wechsler 1987): Visual Reproductions

The WMS-R Visual Reproductions requires both the immediate and delayed recall of a briefly presented (ten seconds) figure drawing. Within the test there are four separate trials using four different figure drawings (A-D). Cards A-C contain a single figure, whereas card D contains two separate designs, i.e. one comprising three geometric elements and the other two. This test was only administered at the first two assessment rounds, and was replaced with the Rey Osterreith Complex Figure Test (RCFT) at the beginning of the second study phase. This was partly to minimise practice effects but also due to evidence, that suggests visual material and the WMS is easily verbalisable, and therefore less sensitive to the right temporal lobe than the RCFT (Note: This latter test is described in more detail in experiment 4). Only the total immediate and delayed recall scores were included in the analysis, again due to significant differences between controls and the high-risk group on these measures at baseline.

2.1.4 Statistical analysis

All analyses were performed using the Statistical Package for Social Science (SPSS version 11; SPSS Inc., IL). Normality of distributions was tested using the Kolmogorov-Smirnov test, while homogeneity of variance was assessed using Levene's test. While ANOVAs are considered robust enough to deal with any deviations from normality in distributions (Miller 1996), a non-parametric test (Kruskal-Wallis) was also used for data (e.g. HSCT), which violated the parametric assumption of normality (see Appendix 2: Table 2I, J, K and L for results of normality and homogeneity of variance tests).

In order to investigate whether performance was significantly different between the three high-risk participant groups on neuropsychological tests at baseline, in three separate MANOVA analyses

participant group was entered as a between-group variable with three levels (i.e. HR- (PSE 1); HR+ (PSE 1); and SCZ). Independent neuropsychological assessment measures were entered as within-group variables. The first MANOVA brought together all tests measuring memory (i.e. *RBMT - immediate and delayed recall; RAVLT - trials 1 to 5 and long delay recall; WMS-R - immediate and delayed visual recall; and Verbal Fluency for Categories*). The second multivariate analysis was concerned with tests measuring executive function (i.e. *HSCT - time 1 and 2, errors type A & B; Stroop suppression condition; and Stroop suppression condition control condition*). Finally, the third analysis examined general intellectual ability (i.e. *WAIS-R - FSIQ VIQ & PIQ; WAIS-R Digit symbol; WAIS-R Block design; NART – FSIQ; SCOLP - speed of comprehension, and SCOLP- spot the word*). By grouping neuropsychological assessments in this manner for the purposes of data analysis, we were able to effectively reduce the number of individual analyses calculated, thereby reducing the likelihood of a Type I error. In addition, this method also takes into consideration the relationship between the separate dependent variables (neuropsychological test scores) and has the power to detect whether groups differ along an amalgamated variables dimension, as indicated by the overall significance of the MANOVA (Field 2000). It should also be noted that previous factor analytic studies have also grouped these measures under similar domains of function (Byrne et al 2003).

To further explore on which tests and between which groups any differences may have been present, univariate ANOVA's for each individual within-group variable were also calculated. Although the overall MANOVA is proposed to protect against an inflated Type I error, a significant MANOVA often shows individual differences for some, but not all dependent variables. In this instance it is advisable to apply a Bonferroni correction to the subsequent ANOVAs, which was the post-hoc method adopted in this current investigation (Field 2000). Helmert contrasts were also calculated. These contrasts are planned comparisons between each level of the between-group variable with the overall mean of the remaining levels of the between-group variable, discarding a level from further analysis once it has been compared to all others (Field 2000). These are preferable to post-hoc comparisons because they address a-priori hypotheses about the results of the analysis and further reduce the number of comparisons made (thus reducing the chances of a Type I error). These were

therefore deemed useful in addressing our apriori hypotheses (as outlined previously in Chapter 1), and may be summarised as follows:

(1) HR- (PSE 1) & HR+ (time1) > SCZ (i.e. predictive effect)

(2) HR- (PSE 1) > HR+ (time 1) (i.e. state effect)

2.2 Results: Investigation 1

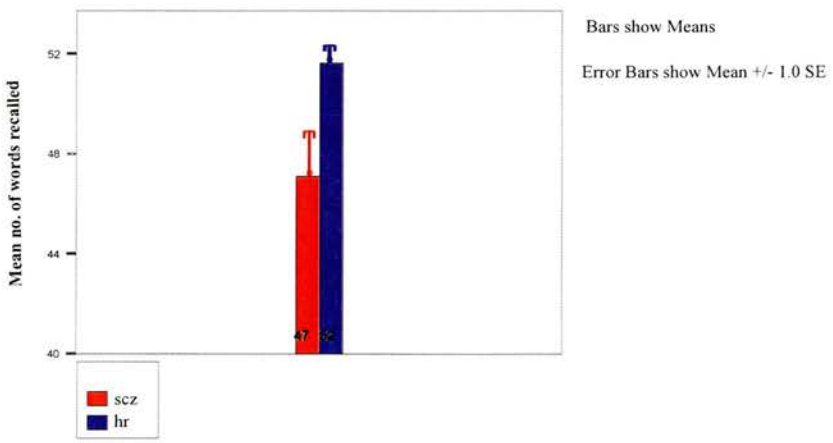
The overall MANOVA for measures of memory at baseline was significant (i.e. Roy's largest root F = (error d.f. = 131) 2.5, p = 0.02), (Note: Roy's largest root is the 'eigenvalue' for the first variate and represents the maximum differences possible between groups and the proportion of explained to unexplained variance). This observation suggests that overall, participant group did have an effect on the baseline neuropsychological tests of memory. The series of one-way ANOVAs showed a significant main effect of group on the RBMT immediate story recall (i.e. $F_{(2, 136)} = 3.5$, $p = 0.01$) and a trend for a main effect of group on the RBMT delayed story recall (i.e. $F_{(2, 136)} = 2.5$, $p = 0.08$). However, after applying the Bonferroni correction these results were no longer statistically significant (i.e. adjusted critical p>0.007).

The overall MANOVA for measures of executive function was not significant (i.e. Roy's largest root F = (error d.f. = 133) 1.4, p = 0.20) and none of the individual ANOVAs produced a significant main effect of group. These observations suggest that participant group had no effect on baseline performance on tests of executive function (N.B: results of the Kruskal-Wallis test are presented alongside the ANOVA results in table 2B).

The overall MANOVA for measures of general intellectual function was also not significant (i.e. Roy's largest root F = (error d.f. = 133) 1.4, p = 0.20) and none of the individual ANOVAs produced a significant main effect of group. These findings suggest that overall participant group had little or no effect on baseline performance on general tests of intellectual ability.

Means, standard deviations, main effects of group and planned contrasts for the individual ANOVAs are presented in Appendix 2: Table 2B. Results of the planned Helmert contrasts for immediate and delayed story recall on the RBMT showed that HR- (time1) recalled more words/ideas than HR+ (time1) (i.e. contrast est. = 1.7, p = 0.01, and contrast est. = 1.4, p = 0.05, respectively). Given that this contrast is based on the possible differences between groups with and without symptoms at the time of the assessment, this may be interpreted as the result of a state effect on immediate and delayed verbal story recall. Results of the contrast for trials 1-5 on the RAVLT at baseline indicated that the HR- (time1) & HR+ (time1) groups (i.e. HR) recall more words over five trials compared to those who go on to develop schizophrenia (i.e. SCZ; i.e. contrast est. = 4.8, p = 0.03). This was the only neuropsychological test to reveal a baseline difference between those who have developed schizophrenia and the rest of the high-risk group. It could therefore be viewed as a predictor for later development of schizophrenia. However, because the F test was not significant (i.e. p = 0.10), it must be considered tentatively (see Figure 2.2).

Figure 2.2: Mean total number of words recalled across five trials of the RAVLT at baseline



2.3 Methodology: Investigation 2

2.3.1 Design

The purpose of this second investigation was to explore performance over time, i.e. between the first and most recent assessment in all participants (see Tables 2.3 and 2.4). It was not possible to investigate performance change across all assessment rounds due to the varying number of participants who attended for neuropsychological and clinical assessments in Phases 1 and 2. This investigation therefore concerns all those in the EHRS who have completed at least two full clinical and neuropsychological assessments of a possible five since the inception of the study ten years ago (see Appendix 2: Table 2A).

The data were analysed using a general linear model repeated measures mixed design analysis of covariance, controlling for the difference in the total number of assessment visits across participants, the time between the first and last assessment and pre-morbid IQ. Participant group was introduced as the between-group factor, with four levels (i.e. C, HR-, HR+ and SCZ) and performance at the first and latest assessment on separate neuropsychological tests as a two level within-group factor. Our hypotheses were outlined in Chapter 1. To reiterate, it was first hypothesised that high-risk participants who did not become ill would show stable performance deficits relative to controls over time. Secondly, it was predicted that those participants who had experienced symptoms at some point in the course of the study and those who are now diagnosed as schizophrenic would perform more poorly than those who have never experienced any psychotic symptom during the course of the study on tests of memory and executive function, across both assessments. It was further hypothesised that those participants who have subsequently become ill would demonstrate a reduction in performance over time relative to the other high-risk groups, which could be related to the onset of schizophrenia.

2.3.2 Participants

2.3.2.1 High-risk participants

118 high-risk participants took part in at least two neuropsychological assessments of a possible five, since the beginning of the EHRS and were therefore included in this analysis. This high-risk sample was comprised of 13 individuals who have now been diagnosed as schizophrenic (i.e. SCZ), 56 high-

risk participants who have experienced psychotic symptoms at some point in the course of the study (i.e. HR+) and 49 high-risk participants who have experienced no psychotic symptoms in the course of the study (i.e. HR-). All participants had their first assessments at phase 1 round 1, with the exception of one (phase 1 round 2). The period of the last assessments of all participants varied (see table 2.5).

2.3.2.2 High-risk participants who have not experienced a psychotic symptom in the course of the study (i.e. HR-)

The HR- group included participants who, to the best of our knowledge, had not experienced any psychotic symptom at any point in the course of the study. For those participants who had attended for a maximum of two clinical and neuropsychological assessments, feedback from GPs involved with those individuals was relied upon to verify that they remain well. Nonetheless, it is difficult to fully control for the possibility that individuals classified as HR- may have experienced any psychotic symptoms at some point between assessments, and that these may have gone unreported and therefore undetected by GPs. Similarly, it is difficult to assure that those participants who were included within this sub-group may not go on to develop schizophrenia, due to the fact that in some cases psychotic symptoms do not necessarily precede the onset of psychosis. In either case however, this misclassification would result in type II rather than type I errors.

2.3.2.3 High-risk participants who have experienced a psychotic symptom in the course of the study (i.e. HR+)

The HR+ group included participants who have experienced intermittent psychotic symptoms over time (i.e. as established by the PSE at each assessment visit; see Table 2.1), but have not developed schizophrenia during and up to the 10 years of the study. In instances where contact was lost with individuals after attending for at least two assessments, updates were requested from their GPs as to their current mental health status in 1999 and 2004. Importantly, in no case were psychotic symptoms in the HR+ group severe enough to meet any operational definitions for schizophrenia or related psychotic illnesses, nor did they require treatment. Although negative symptoms are reported as

prevalent in the prodromal stages of schizophrenia, depressive symptoms as measured by the PSE were apparent in only a small number of cases, and not enough to allow for further analysis.

Psychotic symptom experience is also reported in the general population. The National Comorbidity study reported 28.4% of individuals surveyed to acknowledge experience of psychotic symptoms, while the lifetime prevalence of non-organically based hallucinations in the general population was shown to be 10% for men and 15% for women (Verdoux and Van Os 2002). Similarly, the results from a birth cohort study revealed 20.1% of participants to have reported a delusional experience, and 13.2% to have reported a hallucinatory experience by the age of 26 (Verdoux and Van Os 2002). This evidence suggests that there may be a continuum of psychotic symptom experience, which does not in all cases result in a psychiatric disorder.

If psychotic symptom manifestation is an attenuated form of the underlying pathophysiological process in schizophrenia, then the experience of psychotic symptoms in individuals with a genetic liability to schizophrenia may be further along the continuum to psychosis. This group's apparent liability to psychotic symptoms could therefore be considered an intermediate phenotype.

2.3.2.4 Participants currently diagnosed with schizophrenia (i.e. SCZ)

Participants diagnosed with schizophrenia became ill on average 3.6 years (s.d. = 1.1) after their first and 5.3 (s.d.= 8.7) months after their last clinical and neuropsychological assessment. Clinical and neuropsychological assessments were discontinued in those participants who developed schizophrenia, such that the most recent assessment of all individuals who are now ill was conducted before a diagnosis of schizophrenia. A diagnosis of schizophrenia was made based on both PSE and ICD-10 definitions of schizophrenia. Where participants had not returned for a clinical assessment updates were requested from their GPs as to their current mental health status, and in the event that a change in status had occurred a clinical interview was carried out by a clinician (Professor Johnstone) at their home or in the hospital, to confirm diagnosis (see p114 - 115).

Following the last neuropsychological assessment of two high-risk participants (i.e. A & B) who are both now diagnosed as schizophrenic, it was subsequently discovered that both had experienced severe psychotic symptoms several months prior to the final assessment, prompting admission to a psychiatric ward. These participants did not disclose this at the time of their last PSE. Due to the fact that one of these participants (i.e. A) may have developed the illness by the time of their second and last neuropsychological assessment, they were excluded from the analysis of neuropsychological performance over time. At the time of their final PSE, the other participant (i.e. B) did not meet criteria for a psychiatric disorder, was receiving no medication, and showed unimpaired social functioning, indeed this patient has recently returned to work. Furthermore, the case notes for B suggested that the brief psychotic episode may have been attributable to drug induced psychosis while abroad. It was therefore deemed appropriate to include participant B in the analysis of neuropsychological performance over time.

2.3.2.5 Control participants

A total of 30 control participants have taken part in at least two neuropsychological assessments of a possible five since the beginning of the EHRS and have, therefore, been included in this analysis. All controls were required to complete the PSE in order to identify any incidence of psychotic symptoms in this group. Of the controls, three experienced isolated psychotic symptoms at some point in the course of this study, but were not excluded.

Table 2.3: Experience of Psychotic Symptoms over time in high-risk participants with at least two assessments

HR Group	**Sub-groups**			
Psychotic symptoms change over time	Numbers without any psychotic symptoms (**HR-**)/PSE score 0 or 1	Numbers with psychotic symptoms ever (**HR+**)/PSE score 2 or 3	Numbers with illness (**SCZ**)/PSE score 4	Total
HR+		8		8
HR-	49			49
HR-: HR+: HR-		5		5
HR+: HR-		14		14
HR-: HR+		29		29
HR-: HR- (NOW SCZ)			4	4
HR+:HR+(NOW SCZ)			5	5
HR-: HR+(NOW SZ)			4	4
Total		56	13	118

Table 2.4: Number of neuropsychological assessments in those who have attended at least twice

Group	**C (N)**	**HR- (N)**	**HR+ (N)**	**SCZ (N)**	**Total (N)**
No. Times Assessed					
X 2	8	14	20	8	50
X 3	6	11	11	5	33
X 4	13	17	15		45
X 5	3	7	10		20
N =	30	49	56	13	148

Table 2.5: Period of first and latest assessment for each group

First Assessment (Dates)	**C (N)**	**HR- (N)**	**HR+ (N)**	**SCZ (N)**	**Total (N)**
Phase 1 Rd 1 ('94-'96)	29	49*	55	13	146
Phase 1 Rd 2 ('96-98)			1		1
Phase 2 Rd 1 ('00-'02)	1				1
N =	30	49	56	13	148
Latest Assessment (Dates)					
Phase 1 Rd 2 ('96-'98)	4	10	2	4	
Phase 1 Rd 3 ('98-'00)				3	
Phase 2 Rd 1 ('00-'02)	6	10	25	3	
Phase 2 Rd 2 ('02-'04)	20	29	29	3	
N =	30	49	56	13	

* x2 participants' incomplete data

2.3.3 Demographic details

There were no significant main effects of group for age (i.e. $F_{(3, 144)} = 2.6, p = 0.06$), gender (i.e. $\chi^2 = 2.5$ (3), $p = 0.5$), or handedness (i.e. $\chi^2 = 0.7$ (3), $p = 0.8$). However, there were significant main effects of group on the baseline WAIS-R full scale IQ (i.e. $F_{(3, 144)} = 3.1, p = 0.03$) and on the NART estimated full scale IQ (i.e. $F_{(3, 143)} = 3.3, p = 0.02$). Lower baseline IQ scores in the high-risk sample relative to controls were reported in earlier analyses of this data set (Byrne et al 1999; Cosway et al 2000). There were also significant main effects of group on the mean number of days between the first and latest assessment (i.e. $F_{(3, 144)} = 7.8, p < 0.01$), and on the mean number of visits over time (i.e. $F_{(3, 144)} = 3.2, p = 0.02$) (see table 2.6). Bonferroni post hoc comparisons revealed a significantly larger number of days between the first and latest assessment and a greater number of assessments in all other groups relative to those who have developed schizophrenia. This is primarily due to the development of the illness in these participants early on in the study, such that first and latest pre-morbid assessments in this group were closer together in time. In the same way, assessments were discontinued in those who developed schizophrenia, so that they had fewer visits over time than all other groups.

Table 2.6: Demographic characteristics of the HR+, HR- & Control participants

	C (N=30)	HR- (N=49)	HR+ (N=56)	SCZ (N=13)	Test Statistic	P
Mean full scale baseline WAIS-R IQ (SD)	106.3 (8.6)	99.9 (9.3)	98.6 (9.3)	99.3 (9.8)	3.1[1]	0.03*
Mean estimated full scale NART-IQ (SD)	105.3(8.6)	99.9 (9.4)	98.6 (9.3)	99.3(13.6)	3.3[1]	0.02
Mean age (Baseline) (SD)	21.7 (2.4)	21.5 (2.7)	21.2 (3.0)	19.3 (2.4)	2.6[1]	0.06
Mean age (Latest assessment) (SD)	27.5 (2.3)	26.7 (3.9)	26.5 (3.5)	22.8 (3.1)		
Male N (%)	16 (53.3)	27 (55.1)	23 (41.1)	7 (53.8)	2.5[2]	0.5
Female N (%)	14 (46.7)	22 (44.9)	33 (58.9)	6 (46.2)		
Left hand N (%)	2 (6.7)	4 (8.2)	5 (8.9)	0	1.8[3]	0.9
Right hand N (%)	26 (86.7)	43 (87.8)	47 (83.9)	12 (92.3)		
Mixed hand (Annett Handedness Scale) N (%)	2 (6.9)	2 (4.1)	4 (7.1)	1 (7.7)		
Mean days between assessments (SD)	2150.7 (747.0)	1931.0 (788.5)	1956.5 (603.3)	1063.3 (480.8)	7.8[1]	0.001**
Mean number of times assessed (SD)	3.4 (0.9)	3.3 (1.0)	3.3 (1.1)	2.4 (0.5)	3.2[1]	0.02**

1 One-way ANOVA; 2 Pearson's Chi-squared; 3 Kruskal Wallis test; * C > HR+; ** All groups > SCZ (Bonferroni post-hoc, $p<0.05$)

2.3.4 Materials

As described in detail in section 2.1.1, only those tests which showed a statistically significant difference between the high-risk group and controls at baseline (Byrne et al 2003; Byrne et al 1999), were included in this second investigation. These include RBMT story recall, AVLT trials 1-5 and long delay recall, Verbal fluency for letters and category, Stroop, HSCT time section 1 and 2, and type A and B errors, SCOLP, WAIS-R Block design and WAIS-R digit symbol. Moreover, not all tests administered at baseline were repeated throughout the study phases, therefore analysis of performance over time was not possible (see Appendix 2: Table 2H).

The WMS-R Visual Reproductions test was not included in the analysis of performance over time due to its exclusion from the third round of assessments (i.e. it resulted in too few participants being assessed on two occasions using this particular test), and its replacement in the second phase with the Rey-Osterrieth Complex Figure test. Three different versions of the AVLT were used across three assessments, before its replacement with the California Verbal Learning Test. The AVLT over time was therefore based on the first and last assessment out of a possible three.

Due to the length of time required to administer the WAIS-R IQ test battery in full, it was administered in totality at baseline only. Thereafter, only a selection of the WAIS-R sub-tests was included in the neuropsychological assessment phases (i.e. *Digit Span; Arithmetic; Digit Symbol; and Block Design*). Due to a large amount of missing data on the WAIS-R Arithmetic sub test (i.e. no participants currently classed as SCZ have scores on this test after baseline), and the lack of significant differences between high risk and control groups at baseline on this sub test, it was decided not to include this measure in the current analyses. The WAIS-R Digit Span task also showed no significant differences between the high-risk and control groups at baseline and has therefore been excluded from these analyses. Finally, WAIS-R Block design and WAIS-R Digit symbol, which were administered to participants on more than one occasion and have shown significant differences between the high-risk and control groups at baseline, were included in the analysis of performance over time.

2.3.5 Statistical Analysis

All analyses were performed using the Statistical Package for Social Science (SPSS version 11; SPSS Inc., IL). Normality of distributions was checked using the Kolmogorov-Smirnov test, and homogeneity of variance using Levene's test. Where distributions were non-normal, data were transformed (see Appendix 2: Table 2I, J, K and L for results of normality and homogeneity of variance tests).

General Linear Model Repeated Measures Mixed Analysis of Covariance (ANCOVA):

In order to determine any change in performance between the first and latest assessment of each participant (longitudinal within and between subject differences), neuropsychological test performance scores were individually introduced to a General Linear Model Repeated Measures Mixed ANCOVA. This included a within-subjects factor of time, with 2 levels (i.e. performance score at the first and latest assessment), and a between-subjects factor of group, with 4 levels (i.e. SCZ, HR+, HR- & C).

Significant group by time interactions would therefore be considered an indication of a differential change in performance in one group relative to all others over time.

Planned Helmert contrasts were also calculated to further investigate variations in performance between groups where between-group effects were significant. As described previously, Helmert contrasts are planned comparisons between each level of the between-group variable with the overall mean of the remaining levels of the between-group variable, discarding a level from further analysis once it has been compared to all others. These are preferable to post-hoc comparisons because they address previously formed hypotheses about the outcome of the analysis and further reduce the number of comparisons made. These were therefore used to address our apriori hypotheses (as outlined previously in section 2.1), and included the following comparisons:

(1) C >HR & SCZ (i.e. trait effect)

(2) HR- >HR+ & SCZ (i.e. intermediate phenotype effect)

(3) HR+ > SCZ (i.e. full phenotype effect)

Covariates:

Two covariates were also introduced into our models in order to control for any additional variance: the total number of visits for each participant (i.e. range: 2- 5), which could have contributed to a practice effect, and the amount of time between each participant's first and latest assessment. Due to an absence of significant group by gender interactions reported previously for this data set (Byrne et al

2003), it was decided not to include gender as a variable in our analyses. Only the adjusted means following ANCOVAs are presented in tables in the following results section.

The significant baseline differences between groups on both WAIS-R IQ and pre morbid NART-IQ highlighted the need to control for the general intellectual differences between groups when analysing neuropsychological performance over time (Byrne et al 2003). For this reason NART-IQ (considered a stable measure of general intellectual ability over time) was entered as a third covariate into the analysis of covariance. Results both before and after controlling for NART-IQ are presented in the results section. This is due to an appreciation of the fact that by controlling for NART IQ, a proportion of the variance central to neuropsychological deficits apparent in this group when compared to controls may be removed. However, in the same way, without attempting to control for initial differences in intellectual performance, any ensuing neuropsychological test performance differences between groups could be construed as attributable to the effects of these differences in intellectual ability.

One- Way Analysis of Variance and Covariance (ANOVA & ANCOVA)

Although a previously published comparison of baseline performance in the high-risk and control groups showed differences on the tests selected here for further analysis, it was considered pertinent to re-compute the baseline analysis for the current sample, along with a separate analysis of performance at the latest assessment. This would allow for comparison of discrete performance differences between groups at the first and at the latest assessment (cross-sectional between subject differences). Neuropsychological performance scores at the first assessment were introduced to one-way ANOVAs as single level within subject factors, along with a 4 level between subject factor of group (i.e. SCZ, HR+, HR- & C). Neuropsychological performance scores at the most recent assessment were introduced to one-way ANCOVAs in the same way, with the addition of the covariates of time between and number of assessments. It was decided not to use multivariate analysis of variance (MANOVA), due to the smaller number of participants assessed for a second time on the AVLT, which would have resulted in reduced numbers for all memory tests in the MANCOVA and thus a

reduction in power to detect significant effects. The same planned Helmert contrasts as used in the repeated measures ANCOVA were also computed to further explore between group effects.

Bonferroni corrections

Due to the large number of individual tests conducted, Bonferroni corrections were applied in order to reduce the possibility of a type I error. This is a multiple comparison correction used when several independent tests are calculated simultaneously because although the alpha level may be appropriate for individual comparisons, it must be adjusted for multiple comparisons in order to control for spurious false positives. These were calculated for tests within each functional domain. Degrees of freedom vary due to incomplete or missing data on some tests (Note: see tables for neuropsychological test performance means, standard deviations and results of the Analyses of Covariance). For tests of memory, the adjusted critical value was $p<0.01$, for executive function $p<0.007$ and for general intellectual function $p<0.01$.

2.4 Results: Investigation 2

2.4.1 Cross sectional between subject differences

Memory tests

Means, standard deviations and results of univariate ANOVAs and repeated measures ANCOVAs are presented in Appendix 2: Tables 2C (Memory tests), 2D (executive function tests) and 2E (general IQ tests). For baseline assessments, the results of the ANOVAs showed a significant main effect of group for both RBMT immediate and delayed story recall (i.e. $F_{(3, 135)} = 5.7$, $p<0.001$; $F_{(3, 135)} = 5.6$, $p<0.001$), and a trend for significance on RAVLT trials 1-5 (i.e. $F_{(3, 137)} = 3.1$, $p<0.05$) and RAVLT long delay recall (i.e. $F_{(3, 137)} = 2.2$, $p = 0.09$). Planned contrasts showed controls to recall more words at the first assessment for both immediate and delayed story recall (i.e. est. diff = 2.9, $p<0.001$;est.diff = 2.9, $p<0.001$), RAVLT trials 1-5 (i.e. est.diff = 5.0, $p<0.05$), and RAVLT long delay recall (i.e. est.diff = 1.4, $p<0.05$). HR+ also showed greater recall relative to SCZ on RAVLT trials 1-5 (i.e. est.diff = 5.2, $p<0.05$).

For the latest assessments, the results of the ANCOVAs for each test showed that there was trend for a significant main effect of group for immediate story recall (i.e. $F_{(3, 133)} = 3.1$, $p = 0.03$). There was no significant main effect of group for delayed story recall (i.e. $F_{(3, 133)} = 2.5$, $p = 0.06$) or AVLT long delay recall (i.e. $F_{(3, 94)} = 2.1$, $p = 0.1$). Planned contrasts showed C to recall more words than HR at the latest assessment on immediate and delayed story recall (i.e. est. diff = 1.8, $p<0.05$; est. diff = 1.9, $p<0.01$). HR- also recalled more words than the rest of the HR group, with a trend for significance on immediate story recall (i.e. est. diff = 1.8, $p<0.05$) and AVLT long delay recall (i.e. est. diff = 1.8, $p<0.05$).

Executive function tests

The HSCT data were not normally distributed. Two measures were successfully transformed to normal using a natural log transformation (time on section 1 and 2). For baseline assessments, the results of the ANOVAs showed a trend for a significant main effect of group for verbal category fluency (i.e. $F_{(3, 139)} = 3.2$, $p<0.05$). Planned contrasts showed C to perform better at the first assessment than HR on verbal category fluency (i.e. est. diff = 2.5, $p<0.05$). No other executive function tests showed significant differences between groups at baseline in this sample. At the latest assessment, ANCOVAs showed no significant main effects of group for any of the tests of executive function.

General intellectual function

For baseline assessments, the results of the ANOVAs showed significant main effects of group on both WAIS-R Block Design (i.e. $F_{(3, 144)} = 4.2$, $p<0.01$), and trends for significance on WAIS-R Digit Symbol (i.e. $F_{(3, 144)} = 3.5$, $p<0.05$), and SCOLP Spot the Word (i.e. $F_{(3, 137)} = 3.2$, $p<0.05$). Planned contrasts showed C to perform better than HR on Block design (i.e. est. diff = 2.1, $p<0.001$), Digit symbol (i.e. est. diff = 1.5, $p<0.01$) and Spot the Word (i.e. est. diff = 3.1, $p<0.01$).

At the latest assessment, ANCOVAs showed significant main effects of group for Block design (i.e. $F_{(3, 137)} = 4.3$, $p<0.01$), and a trend for a significant effect on Digit symbol (i.e. $F_{(3, 140)} = 2.9$, $p<0.05$), but there was no significant main effect of group for any other general intellectual function tests. Planned

contrasts revealed C to perform better than HR on Block design (i.e. est. diff = 1.4, $p<0.05$). Interestingly, HR+ performed significantly worse than those who are now SCZ at the latest Block design assessment (est. diff = 2.1, $p<0.05$). C also performed significantly better than HR on Digit symbol (i.e. est. diff = 1.7, $p<0.01$).

2.4.2 Longitudinal within and between subject differences

RBMT story recall

There were no significant time by group interactions or main effects of time for immediate story recall (i.e. $F_{(3, 133)} = 0.9$, $p = 0.4$) or delayed story recall ($F_{(3, 133)} = 0.7$, $p = 0.4$), but there were significant main effects of group on the immediate (i.e. $F_{(3, 133)} = 5.11$, $p = 0.002$), and delayed (i.e. $F_{(3, 133)} = 5.02$ $p = 0.003$) recall conditions. Planned contrasts showed that control participants performed significantly better than the HR group on immediate (i.e. est. diff = 2.2, $P<0.001$) and delayed (i.e. est. diff = 2.4, $p<0.001$) recall across both assessments (see Appendix 2: Table 2C and Figures 2.3 and 2.4). These main effects of group became trends after controlling for NART IQ (i.e. $F_{(3, 133)} = 3.4$, $p = 0.02$; and $F_{(3, 133)} = 3.3$, $p = 0.02$, respectively).

Figure 2.3: Mean RBMT immediate story recall over time

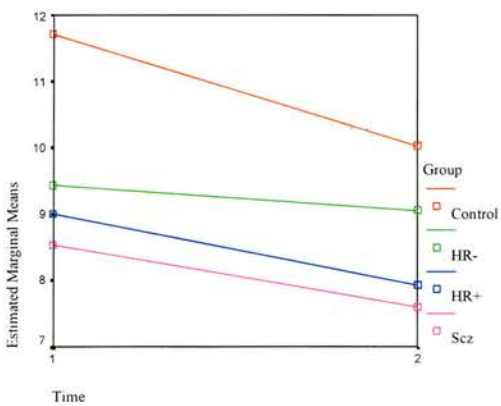
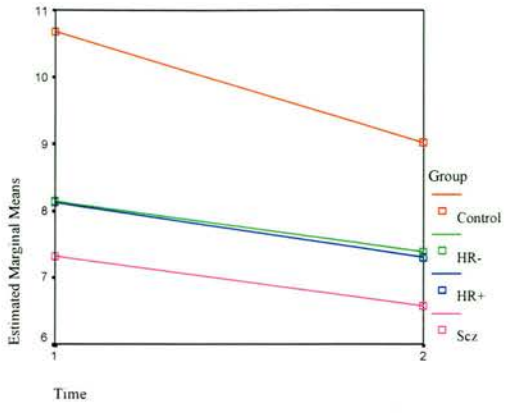


Figure 2.4: Mean RBMT delayed story recall over time



AVLT

There were no significant interactions of time by group. However, there was a significant main effect of time (i.e. $F_{(1, 88)} = 9.8$, $p = 0.002$) for the long delay recall condition, suggesting that performance on this test was not stable across all participants (see Appendix 2: Table 2C and figure 2.5). There was also a trend for a significant main effect of group in the long delay recall condition (i.e. $F_{(3, 88)} = 3.3$, $p = 0.02$). Planned contrasts indicated that C performed better than HR (i.e. est. diff = 1.3, $p<0.02$) and HR+ better than SCZ (i.e. est. diff = 1.8, $p<0.02$). However, this was somewhat reduced after controlling for NART-IQ (i.e. $F_{(3, 88)} = 2.6$, $p = 0.04$) (see figure 2.6). Although there were no significant main effects of group (i.e. $F_{(3, 88)} = 2.4$, $p = 0.07$) or interactions (i.e. $F_{(1, 88)} = 0.6$, $p = 0.4$) on total learning over trials 1-5, contrasts showed C to recall more words across both assessments than HR (i.e. est. diff = 4.1, $p = 0.03$) and HR+ to recall more words across both assessments than SCZ (i.e. est. diff = 6.0, $p = 0.02$).

Figure 2.5: Mean AVLT long delay recall over time

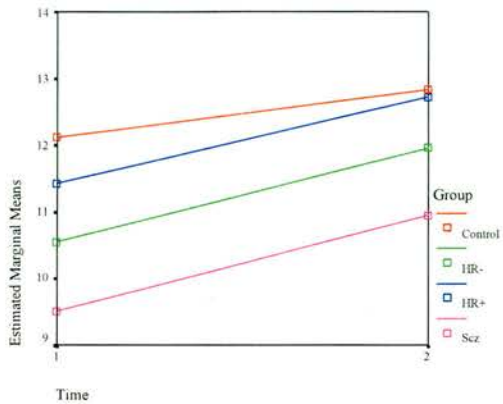
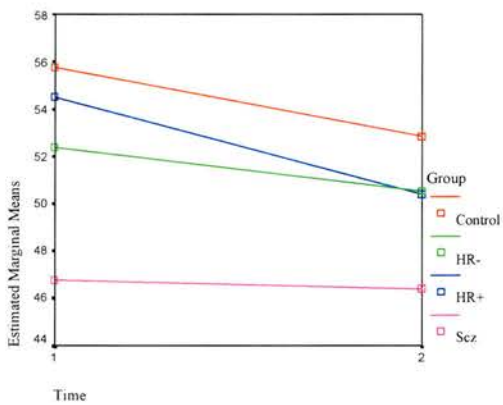


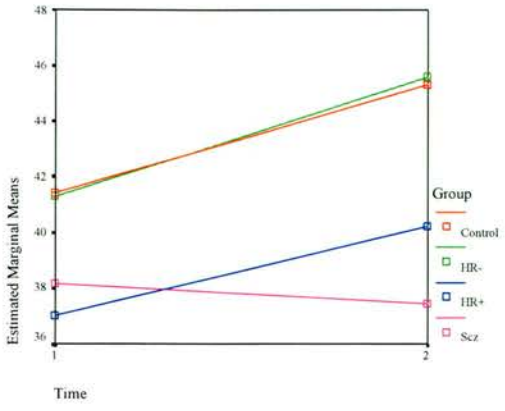
Figure 2.6: Mean AVLT total recall over five trials over time



Verbal Fluency for Letters

There were no significant main effects of group (i.e. $F_{(3,134)} = 2.0$, $p = 0.1$) or time by group interactions (i.e. $F_{(3,134)} = 0.9$, $p = 0.4$) for the verbal fluency for letters task. Nonetheless, from the adjusted mean scores over time for each group, it can be seen that those who go on to develop schizophrenia deteriorate non-significantly over time relative to an improvement in all other groups (see Appendix 2: Table 2D and Figure 2.7).

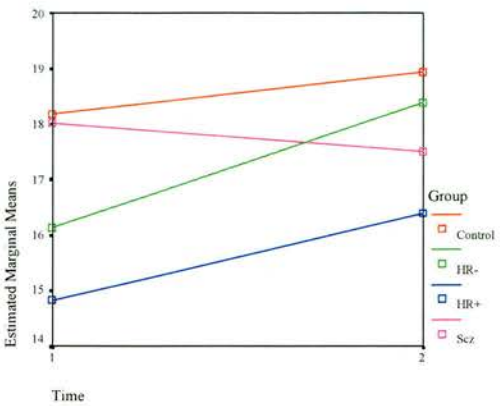
Figure 2.7: Mean verbal fluency for letters over time



Verbal Fluency for Categories

There was no group by time interaction and a non-significant main effect of group on the mean number of words generated on the four legged animal exemplar test (i.e. $F_{(3, 134)} = 3.0$, $p = 0.03$), which was weakened further after controlling for IQ (i.e. $F_{(3, 134)} = 1.9$, $p = 0.1$). The planned contrasts showed no significant differences between groups (see Appendix 2: Table 2D and Figure 2.8). Again, from the mean adjusted scores, those who subsequently became ill show a non-significant decrement in performance relative to the other groups over both assessments.

Figure 2.8: Mean verbal fluency for animal categories over time



HSCT

There was no group by time interaction, but a trend for a main effect of group for response time in section 2 of the HSCT, involving response suppression (i.e. $F_{(3, 133)} = 2.50$, $p = 0.06$). Planned contrasts showed that participants in group C were faster during response suppression than the HR group (i.e. est. diff = 0.6, p = 0.009; i.e. Table 2D). This effect was not significant after controlling for NART IQ (i.e. $F_{(3, 132)} = 2.1$, $p = 0.11$).

WAIS-R - Block Design

There was no group by time interaction, but a significant main effect of group for WAIS-R block design (i.e. $F_{(3, 137)} = 4.2$, $p = 0.007$). Planned contrasts indicated that the C group performed better than the HR group (i.e. est. diff = 1.4, p = 0.03; see Table 2E). This effect was lost after controlling for NART-IQ (i.e. $F_{(3, 137)} = 2.3$, $p = 0.07$).

WAIS-R - Digit Symbol

Again, there was no group by time interaction, but a significant main effect of group (i.e. $F_{(3, 140)} = 3.3$, $p = 0.02$). Contrasts showed C to perform better than the HR group over time (i.e. est. diff = 1.5, p = 0.01; see Table 2E). This effect was lost after controlling for NART-IQ (i.e. $F_{(3, 138)} = 1.7$, $p = 0.2$).

Other measures

There were no significant main effects of group or group by time interactions on the Stroop or SCOLP tests (see Appendix 2: Tables 2D and 2E).

2.5 Methodology: Investigation 3

2.5.1 Design

The third investigation was designed to address the issue of the relationship, if any, between genetic liability and neuropsychological performance over time. Both continuous and categorical measures of genetic liability were computed. In brief, a previous analysis of the relationship between categorical and continuous genetic liability and neuropsychological performance between the first and second assessment rounds of the first phase revealed significant negative correlations between categorical genetic liability and the total RBMT screening score over time, and a trend on HSCT time on section 2 over time. This analysis also showed significant negative correlations between continuous genetic liability and baseline RBMT immediate and delayed story recall and baseline HSCT time on section 2 in the high-risk group as a whole (Byrne et al 2003). In recap, it was hypothesised that performance on tests of executive function and memory over time in our current groups, would be negatively associated with greater familial risk/genetic loading.

2.5.2 Participants

The 118 high-risk participants described in section 2.1 were further classified according to two measures of genetic liability, i.e. one quantitative and one categorical.

2.5.3 Genetic liability measures

Continuous genetic liability measure

A quantitative/continuous measure of genetic liability was calculated in the high-risk group, based on a method developed by Professor Pak Sham. This method involved the generation of a continuous and bimodal distribution of genetic liabilities. This method is described in more detail elsewhere (Byrne et al 2003; Lawrie et al 2001). However, in brief, a multifactorial polygenic liability threshold model of schizophrenia was assumed, with a heritability (h-squared) of 0.7 for liability to schizophrenia. Based on the mean values of the liability above and below a threshold assuming a prevalence of 0.5% of schizophrenia, expected liabilities were 2.86 for schizophrenia patients and –0.14 for the family members. Using multivariate regression, an index of genetic loadings for each individual was calculated based on the expected liabilities, and a continuous and bimodal distribution

of genetic liabilities was generated (Lawrie et al 2001). Figure 2.9 presents the group medians and ranges of quantitative genetic liability estimates. The results of a non-parametric one-way ANOVA showed no significant differences between the high-risk groups in genetic liability estimates, suggesting that contrary to what might have been expected, liability is not significantly greater in those who develop the disorder, or in those who are vulnerable to psychotic symptoms (Table 2.7).

Table 2.7: Results of Kruskal-Wallis one-way ANOVA of group by genetic liability

	HR- (N=49)	HR+ (N=56)	SCZ (N=	χ^2	p
Categorical genetic liability (x 2 2nd: 1st & 2nd: x2 1st degree)	13:27:9	19: 30:7	3: 8: 2	1.4	0.8
Continuous genetic liability (Mean (standard deviation, 25th and 75th percentiles))	0.297 (0.19, 0.099, 0.42)	0.288 (0.20, 0.076, 0.45)	0.255 (0.04, 0.096, 0.40)	0.3	0.8

Figure 2.9(a): Boxplots of median continuous genetic liability estimates in the high-risk group (midline represents median, whiskers represent range, box ends represent interquartile range)

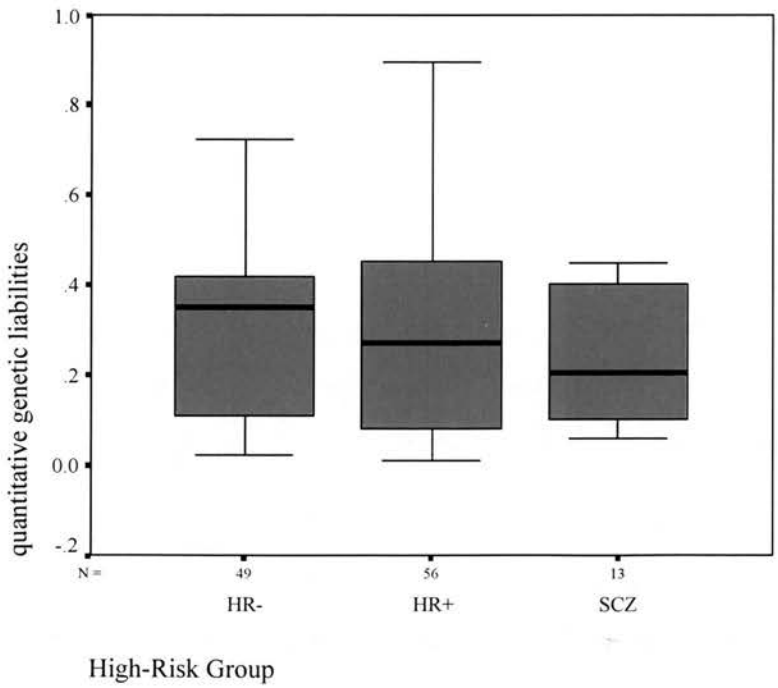
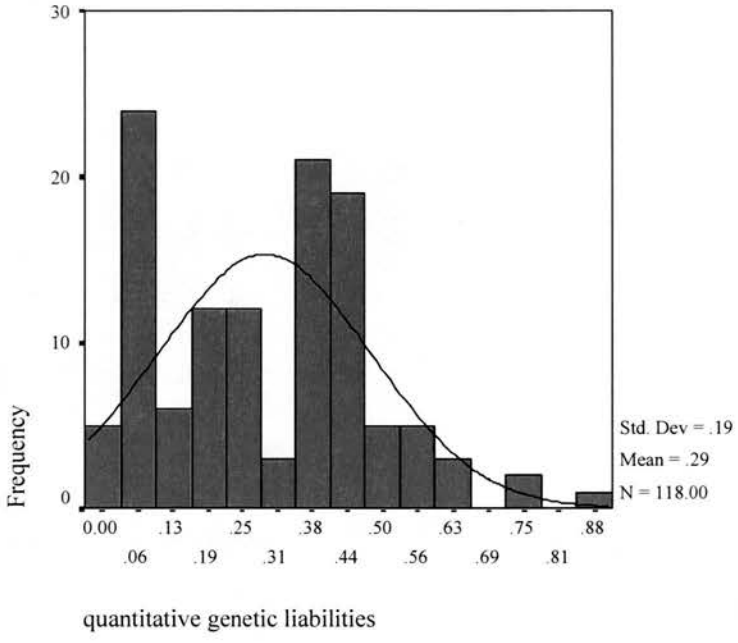


Figure 2.9(b): Histogram of continuous genetic liabilities in the high-risk group



Categorical genetic liability

A categorical measure of genetic liability was also computed for each member of the high-risk group based on data derived from detailed family trees detailing the number and proximity of relatives diagnosed as schizophrenic (see figure 2.10). High-risk participants were grouped into one of three categories. Category 1: at least one 2nd degree relative (i.e. N = 35); Category 2: one affected 1st degree and one affected 2nd degree relative (i.e. N = 65); and Category 3: two or more affected 1st degree relatives (i.e. N = 18). The results of a non-parametric one-way ANOVA showed no significant differences between groups in categorical genetic liability (Table 2.7).

Figure 2.10: Histogram of categorical genetic liability in the high-risk group classified according to experience of psychotic symptoms and subsequent development of schizophrenia

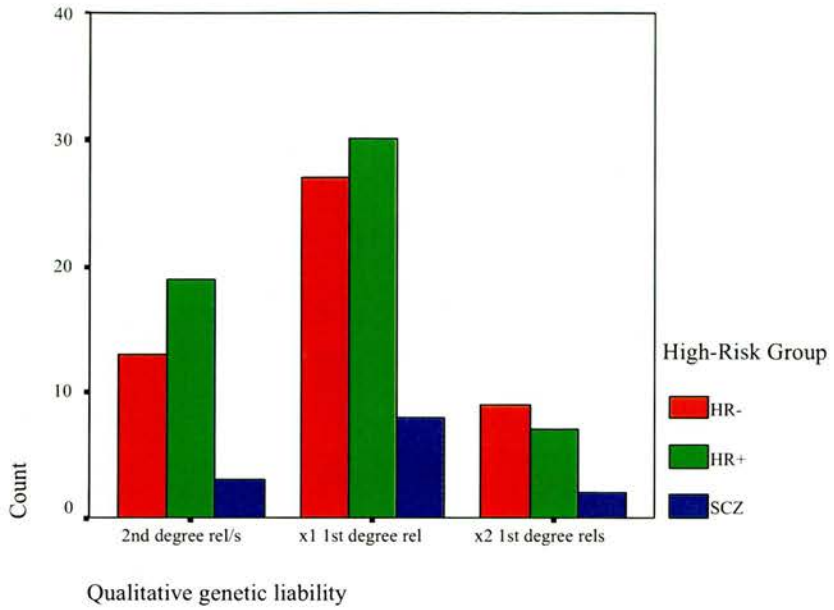
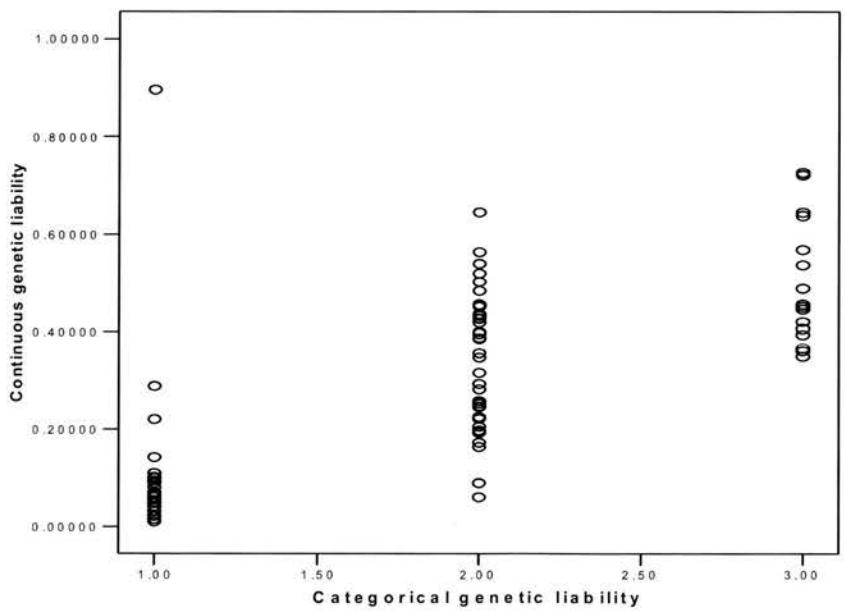


Figure 2.11: Scatter plot of relationship between measures of genetic liability



The Spearman's rho non-parametric correlation showed a significant relationship between categorical and continuous genetic liability measures ($r_s = 0.75$, $p < 0.001$).

2.5.4 Materials

Neuropsychological tests

Those tests used to investigate neuropsychological performance over time in the previous investigation which showed main effects of group or time by group interactions tests are included in this third investigation. These included: the RBMT (immediate and delayed story recall); the AVLT (long delay recall); the Verbal Fluency for Category test; the HSCT (Time on section 2, response suppression condition); the WAIS-R Digit Symbol; and the WAIS-R Block Design.

2.5.5 Statistical analysis

Where initial analyses showed main effects of group over time or time by group interactions, we investigated the effect of genetic liability on performance on these tests over time in the high-risk group only.

All analyses were performed using the Statistical Package for Social Science (SPSS version 11; SPSS Inc., IL). Normality of distributions was checked using the Kolmogorov-Smirnov test, and homogeneity of variance using Levene's test (See Appendix 2: table 2M,N, O and P). Using the same methods described above, in separate repeated measures mixed ANCOVA's; the categorical measure of genetic liability was entered as a three level between subject factor (2^{nd} degree relative, 1^{st} degree relative, x 2 1^{st} degree relatives), and psychopathology as an additional covariate along with time between and number of assessments. Neuropsychological performance over time was entered as a within-subjects factor with 2 levels (i.e. performance score at the first and latest assessment). Planned Helmert contrasts as described above were also computed to investigate further any differences between discrete qualitative genetic liability groups.

For the continuous measure of genetic liability using a multiple linear regression forced entry model, continuous genetic liability was entered as a predictor variable along with group based on psychopathology, as defined in section 2.1. Days between assessments, and the number of assessments across participants were also added as covariates. The difference between the first and latest assessment on relevant neuropsychological tests was entered as the outcome variable. In order to

adjust for multiple comparisons Bonferroni corrections were applied to the critical value of p in this investigation.

2.6 Results: Investigation 3

2.6.1 Categorical genetic liability results

The distributions of the dependent variables were normal for all levels of the independent variable. Given the previous non-normality of the HSCT measures, those variables, which were transformed using a natural log transformation, were used. Means, standard deviations and results of repeated measures ANCOVAs are presented in Appendix 2: Table 2F. Results showed no significant group by time interactions, and only a trend (after bonferroni correction) for a significant overall main effect of qualitative genetic liability on RBMT delayed recall performance over time ($F_{(2, 104)} = 3.1$, $p = 0.05$), and WAIS-R Block Design ($F_{(2, 107)} = 4.7$, $p = 0.01$). Contrasts showed better performance at both assessments overall in those with a minimum of one 2nd degree affected relative, compared to those with one or more 1st degree relatives for delayed story recall (est. diff = 1.5, p = 0.02), and Block Design (est. diff = 1.2, p = 0.06) (see Figures 2.12 and 2.13). Interestingly, Figure 2.13 demonstrates a quadratic trend in the dependent variable across genetic liability categories. There were no other time by group interactions or main effects of group on any of the other neuropsychological tests.

Figure 2.12: Estimated marginal mean scores for RBMT delayed story recall over time in categorical genetic liability groups

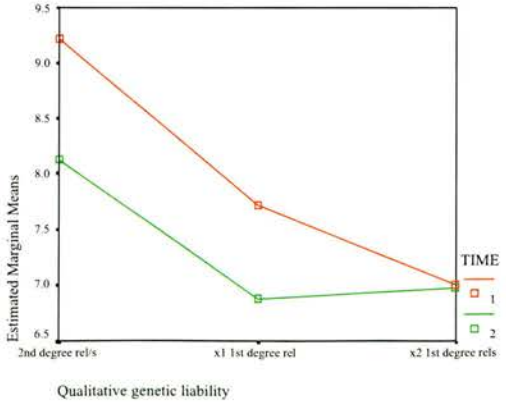
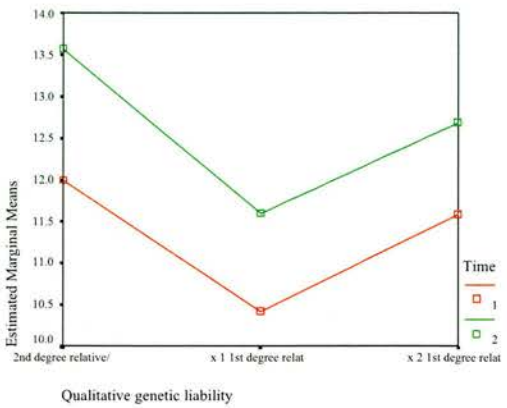


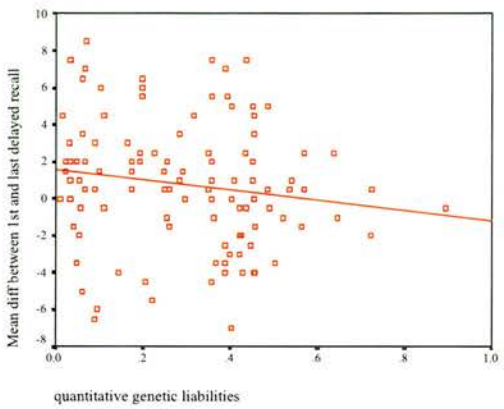
Figure 2.13: Estimated marginal mean scores for WAIS-R Block Design over time in qualitative genetic liability groups



2.6.2 Continuous genetic liability results

Results of the linear regression are presented in Appendix 2: Table 2G. Following Bonferroni correction, results of the regression analyses showed a trend for a significant negative correlation between RBMT delayed story recall difference score and continuous genetic liability (i.e. R= -0.15, p=0.055), and t-tests showed a non-significant influence of quantitative genetic liability on RBMT delayed story recall performance over time, after entering psychopathology, time between assessments and number of times assessed (i.e. $t_{(109)} = 1.69$, p=0.093) (see figure 2.14). Despite this correlation, it is clear from the plot that scores are heterogeneous and widely scattered around the mean. There was also a trend for a significant negative correlation between the difference score on verbal category fluency and continuous genetic liability (i.e. R= -0.16, p=0.043), although no effects reached significance on individual t-tests. There were no significant correlations between continuous genetic liability and the difference score for performance over time on RBMT immediate story recall, aspects of the AVLT, HSCT or WAIS-R subtests over time and none of the models achieved significance (see table 2G).

Figure 2.14: Scatter plot of the negative correlation between RBMT delayed story recall and a continuous quantitative measure of genetic liability in the high-risk group



Chapter 3: Discussion of investigations 1- 3

3.1 Memory

The investigation of memory over time was restricted to those tests used at both intake and follow up, and to those which initially discriminated well between the maximum sample of controls and high-risk participants at baseline. This means that any inferences drawn about verbal memory performance over time in this group, are based on a test of immediate and delayed story recall, and a test of total and delayed list learning.

Analysis of the group means on story recall at baseline shows those who are ill to have scored non-significantly lower than all other groups, suggesting that this is not a strong predictor of schizophrenia. However, at the latest assessment, those who are now ill perform significantly worse than high-risk participants who have experienced psychotic symptoms, suggesting that the development of psychosis may be exerting some influence over story recall performance at this time. Moreover, the smaller group numbers suggest that this could be a type II error.

Our results also demonstrate a consistent poorer performance of the high risk participants as a group on the immediate and delayed story recall of the RBMT, compared to controls, after controlling for IQ, time between and number of assessments. Although all participants show a reduction in performance over the two assessments, the main effect of time was not significant, suggesting that this may be due to regression to the mean (i.e. extreme values in some participants at first testing regress to the group mean at the next testing). Alternatively, a reduction in motivation in all groups due to test familiarity might have led to a drop in scores at follow up. Learning effects would not have been prominent on this aspect of RBMT because different story excerpts were used at each assessment. Moreover, there are no inherent learning strategies (common to list learning tasks) provided during story presentation. Recall is therefore dependent on an understanding of the 'gist' of the story and context processing at the first presentation. This finding supports our first hypothesis of a stable deficit in both affected and unaffected relatives of schizophrenics, which remains unchanged over time.

Although the overall main effect of group on total verbal learning (AVLT trials 1-5) was not significant, there were significant differences between the high-risk and control groups at baseline. It is unclear why there was a non-significant general reduction in performance across all groups. However, this is a similar pattern to that apparent for story recall, so again may be attributable to regression to the mean. The high-risk group also performed less well (i.e. at trend level) compared to controls, overall across both assessments on long delay verbal free recall (AVLT), before and after controlling for NART-IQ, time between and number of assessments. The significant main effect of time for long delay recall also indicates that there was a significant performance improvement across both assessments for all groups. The smaller (although non-significantly so) improvement in the controls and high-risk participants with a liability to psychotic symptoms is possibly due to their already high baseline levels of recall. This change may therefore also be attributable to regression to the mean, but additionally calls into question the stability and reliability of the parallel versions of the AVLT with repeated assessment. Given the lack of group by time interaction, these findings also support our first hypothesis of a stable deficit in both affected and unaffected relatives of schizophrenics, which remains unchanged over time.

Across both assessments, those who are now ill recalled less of a list after a long delay than the high-risk participants who have and have not experienced psychotic symptoms over time. This suggests a possible continuum of verbal memory ability in the high-risk group, with performance slightly worse in those who go on to become schizophrenic. Indeed, performance at baseline on total verbal learning (RAVLT trials 1-5) showed that those who became ill learned and recalled on average fewer words than the rest of the high-risk group, making this a potential neuropsychological predictor of schizophrenia in a high-risk group.

Both measures of genetic liability were negatively associated with delayed story recall performance over time. This suggests a more general association with genetic loading and delayed verbal story recall, given that performance seems to remain stable over time, albeit slightly (non-significantly) worse in those who have symptoms and those who develop schizophrenia. This further indicates that

this is fundamentally a trait deficit, rather than a phenotypic effect (although the development of psychosis may negatively impact on performance).

Our findings lend further support to evidence for verbal memory impairment in healthy relatives of schizophrenics on tests of story recall (Faraone et al 1995; Laurent et al 1999; Toomey et al 1998; Toulopoulou et al 2003a) and list learning (Cannon et al 1994; Egan et al 2000; Harris et al 1996; Lyons et al 1995). This may signify inappropriate encoding and/or retrieval strategy usage, a finding previously reported in first episode patients (Hill et al 2003; Saykin et al 1994). However, results also suggest that relatives are not performing significantly worse than controls on these tests over time, regardless of symptom development. Stable performance over time and across ages in unaffected relatives has been demonstrated previously (Faraone et al 1999; Laurent et al 1999). Indeed, the significantly poorer baseline verbal learning of high-risk participants who went on to develop schizophrenia on average three years later, implies that substantial differential deterioration may already have occurred in this group. This is also supported by the New York High-Risk Study's identification of a short-term verbal memory deficit in high-risk children, which is a sensitive predictor of later schizophrenia-related psychoses (Erlenmeyer-Kimling et al 2000).

This is however not obviously reconcilable with a previous finding from this study of a differential decrement in delayed verbal memory recall (AVLT) between the first and second assessments in those who had symptoms already or had developed them by the second assessment relative to those who had no psychotic symptom experience. It was inferred that this might be due to the interference of symptoms at the time of assessment, and/or a precursor to psychosis in those who would later develop schizophrenia. While the current evidence suggests that a liability to psychotic symptoms does not appear to interfere significantly with performance over time, this may be due to the fact that psychotic symptom experience in the current HR+ group is intermittent and may occur at or between the first and latest assessments in most participants. Furthermore, it is possible that the majority of those within this group will not go on to develop schizophrenia after this time. It is therefore likely that Cosway et al (2000) identified a group by time interaction in an HR+ group composed of a number of participants who would later develop schizophrenia. Given the small numbers who have now

developed schizophrenia and have been included in the current analysis, lack of power may have obfuscated any actual decrements in verbal memory performance over time. This may be true when coupled with the possibility that participants who are now ill will have been assessed at similar times, but while they were individually at varying stages in the disease process. Moreover, this is borne out by the different onset dates across the thirteen people in this group. These issues additionally highlight the difficulties of using group means to draw conclusions about neuropsychological performance. Schizophrenia is notoriously a heterogeneous condition, characterised by a general intellectual deficit. It is likely that differential deficits may underlie this profile, and may equally differ across individuals.

3.2 Executive function

There were no significant overall main effects of group in the verbal category fluency scores, despite initial greater baseline performance in the controls relative to the high-risk participants. However, from the means it can be seen that at baseline those who subsequently became ill produced on average, though non-significantly so, more words than the rest of the high-risk group, and despite a lack of group by time interaction, those with schizophrenia are the only group to worsen in performance on this test over time. This non-significant reduction in performance can be very tentatively interpreted as a possible indication of cognitive deterioration prior to the onset of schizophrenia.

Unaffected relatives of schizophrenics have been shown to be significantly impaired on both phonological and category fluency in some (Keefe et al 1994; Laurent et al 1999), but not all studies (Goldberg et al 1993). Additional evidence suggests a differential impairment in category as compared to letter fluency in schizophrenia (Bokat and Goldberg 2003; Gourovitch et al 1996). As verbal fluency requires strategy and inhibition, if this were purely an executive function deficit, high-risk participants would be equally impaired on both aspects of this task. A search following an exemplar cue may reflect the integrity of the semantic store, suggesting an impairment that exceeds executive function and extends to semantic memory organisation. Alternatively, the timed nature of

this test may disadvantage participants who are affected by a general cognitive slowing. However, without having controlled for speed of processing this cannot be confirmed.

The trend for a significant negative association between performance on verbal category fluency over time and quantitative genetic liability also suggests that an increase in liability is associated with impaired category fluency. However, again, given the absence of any differential changes in performance in any one group, this represents a general association, and not necessarily one associated with change over time.

There was a trend for a significant main effect of group on HSCT response suppression over time before controlling for IQ. This suggests the high-risk group were inhibiting responses with less speed and accuracy than controls, a behaviour previously shown in schizophrenic patients and associated with auditory hallucination severity (Nathaniel-James and Frith 1996). While it is surprising that response inhibition did not more robustly discriminate between high-risk participants and controls, this may be due to test repetition. On first administration, the ability to formulate a strategy to deal with suppression of responses is difficult. However, it is possible that by the second or third assessments, test familiarity will make the task slightly easier. Although this is not supported by a significant main effect of time across groups, all groups appear to show improvement between assessments (although those who are now ill show a stability of performance on section 1).

The lack of significant effects on the other tests of executive function (i.e. Stroop) was also surprising. However, it is entirely possible that executive deficits are associated with the later course of the illness. Alternatively, these tests may not be sensitive enough to detect underlying functional differences between groups.

3.3 Intellectual function

Finally, for Block Design, there was a significant main effect of group at both assessments. Although these became non-significant after controlling for IQ, this is perhaps less valid given the overlap in aspects of function measured. Interestingly, those who are now ill performed better than the rest of

the high-risk group at both assessments. This is similar to the pattern of ability demonstrated by the means on verbal category fluency. Both these findings once again raise the question of heterogeneity of function in schizophrenia, and the possibility that some of those who do develop schizophrenia may not show general intellectual performance deficits. Kremen et al (2004) suggest that without individual case study approaches, it is difficult to extrapolate the true nature of neuropsychological impairments in schizophrenia and by extension relatives of schizophrenics (Kremen et al 2004; Weickert et al 2000). Analogous to this is the question of the underlying neural correlates of block design and verbal category fluency performance, and what preserved function, on the former test at least, might indicate about brain mechanisms. This is especially intriguing given the poorer performance of the participants who are now ill on most other aspects of test performance.

On Block Design, there was also a significant main effect of qualitative genetic liability. However, from the group means this pattern does not appear to be linear, which may explain the failure to find a correlation with a continuous measure of genetic liability. This relationship implies that Block Design performance is superior at higher genetic loadings, relative to those with medium categorical genetic loadings, but equivalent to those with only 2nd degree relatives.

3.4 Limitations

It is possible that our small group numbers, specifically in the control group and in the group of those subsequently developing schizophrenia, will have reduced statistical power, increasing the chances of a type II error and thus precluding detection of significant group by time interactions. Indeed, the pattern of performance on the verbal fluency test suggests that, on this measure at least, there was a non-significant deterioration in verbal fluency in those who develop schizophrenia relative to an improvement in all others. Our conclusions must therefore be considered in light of this study limitation, and we must remain open to the possibility that changes over time might have been demonstrated, given larger group numbers.

Another potential limitation to our current analyses is evident in our controlling for the effect of initial group differences in premorbid NART-IQ. If similar cognitive decline is occurring in other areas of

function, by removing the variance attributable to differences in premorbid intelligence, we may also be removing some of the overlapping variance attributable to differences in other areas of cognitive ability. Our results show significant main effects of NART-IQ throughout all our neuropsychological tests. However, after co-varying for IQ, differences between groups remain on a number of tests, suggesting that although it may account for some of the variability in performance between groups, intelligence is not the sole predisposing factor.

Our co-varying for practice effects and time between assessments is also an additional limitation to our analysis. Unfortunately, in order to include the maximum number of participants, and those who have since developed schizophrenia, inequalities between groups emerged in the average time between and number of assessments. A control of these extraneous factors within the statistical analysis was necessary in order to conclude that any differences were not due to practice or time elapsed between assessments.

3.5 Conclusions

Overall, our results are in keeping with our first hypothesis, that the high-risk participants would continue to perform poorly relative to controls on some neuropsychological tests, but that overall performance would not deteriorate over time, providing evidence of a stable trait deficit and a possible cognitive marker for schizophrenia.

In our genetic liability analyses, both measures appear to account for relatively little variability between groups, although the negative relationship with some tests indicates the expected direction of association, and may be attributed to the fact that most of our high-risk sample has at least two affected relatives, reducing the variability in liability in this group. These weak findings support those previously reported, and suggest that neuropsychological impairments negatively correlate with genetic loading. However, without any significant changes in performance over time, it appears that genetic loading is less related to change and more associated with an overall susceptibility to reduced cognitive performance compared to controls (Byrne et al 2003; Faraone et al 2000).

Our findings do not support our subsequent hypothesis that those in the high-risk group who had experienced symptoms at some point, would demonstrate a poorer performance overall, relative to the other groups. This would imply that performance over time is relatively unaffected by the presence of psychotic symptoms, and that neuropsychological deficits mainly represent an inherent genetic vulnerability to schizophrenia present in all relatives. However, the pattern of our results is generally in the expected direction, with HR+ performance somewhere between HR- and those who are now ill. As discussed earlier, a lack of significant differences overall between those with and without a liability to symptoms may be due to the heterogeneity of our HR+ group and the transient and intermittent psychotic symptom experience either, both or between assessments. High-risk participants have been monitored through the period of their maximum risk and while it is possible that a small number of those who have and have not experienced symptoms will yet progress to schizophrenia, it is likely that the majority will not.

An absence of significant group by time interactions suggests there is no differential decrement over time in those who go on to develop schizophrenia. This finding is compatible with the view that any substantial cognitive decline in schizophrenia is primarily attributable to processes occurring in early development, childhood and/or adolescence rather than nearer the time of psychosis onset (Ang and Tan 2004; Caspi et al 2003; Fuller et al 2002). Fuller et al (2002) investigated school test scores in a sample of adult onset schizophrenic patients and discovered a drop in scores between 13 and 16 years, younger than our high-risk group at baseline. Ang et al (2004) also reported deterioration in mathematics scores in adult first episode schizophrenics between the same ages, 3-8 years prior to schizophrenia development. However, this conclusion must be considered within the context of the methodological limitations of this experiment. It is also possible that small group numbers have precluded detection of significant group by time interactions.

In summary therefore, our results suggest that deficits in neuropsychological performance are at least partly heritable, generally stable over time, and not solely attributable to a difference in intellectual performance. A lack of a differential performance decrement over time in those who became ill could

reflect limited power due to small numbers but supports evidence for structural and functional brain changes a considerable time before the onset of schizophrenia.

Chapter 4: Investigation 4

4.1 Methodology

4.1.1 Design

For those participants who underwent scanning trials as part of the EHRS the California Verbal Learning Test (CVLT(Delis et al 2000)) replaced the previously used RAVLT, and the Rey Complex Figure Test replaced the twice administered WMS-R Visual Reproductions Test. These changes were made at the beginning of the second phase of testing, which also newly incorporated functional magnetic resonance imaging (fMRI) as part of the assessment protocol.

Due to the possible differences in the measurement of memory function between these novel tests and their predecessors – such as the assessment of encoding and learning processes- it was felt pertinent to investigate more fully the performance on the different measures of these tests at first administration in the EHRS. This was achieved by exploring memory performance in the first one hundred participants to attend for a functional MRI scan. This participant sample was also used for our investigation of baseline functional magnetic resonance imaging during a verbal memory paradigm, and is described in more detail in Chapter 5.

Given the encoding deficits described in patients with schizophrenia (see Chapter 1), and the differences in performance on aspects of the CVLT in relatives of schizophrenics (Lyons et al 1995), it was hypothesised that on the CVLT high-risk participants as a group would also show less effective learning and encoding strategies and therefore poorer recall relative to controls across the five list learning trials. Additionally, given the reduced difficulty of recognition relative to recall tasks and the inherent semantic structure to the CVLT word lists, which facilitates recall, it was also predicted that high-risk participants as a group would show equivalent recognition performance to controls.

4.1.2 Participants

The first one hundred participants to attend for a functional MRI scan normally completed neuropsychological and clinical assessments on the same day. The first one hundred participants were selected specifically for this investigation of memory, to complement the fMRI of encoding and

retrieval task analysis. This group was also primarily targeted to coincide with Dr Heather Whalley's recent analysis of the fMRI and Hayling Sentence Completion Test data set in the same participants. Groups were classified in accordance with scores generated on the PSE close to or on the same day as testing (Phase 2 round 1) (Note: see section 2.1 for a more detailed description of the PSE). As in the previous investigations, based on this assessment participants were allocated to one of three experimental groups: controls (C), high-risk participants with any psychotic symptom experience at the time of testing (HR+) and high-risk participants with no psychotic symptom experience at the time of testing (HR -).

Analysis of the demographic data showed no significant main effect of group on age (i.e. $F_{(2, 97)} = 2.1$, $p = 0.12$), but a trend for significance on estimated full scale NART IQ (i.e. $F_{(2, 97)} = 2.8$, $p = 0.065$). The demographic characteristics of the high-risk and control groups are outlined in Table 4.1.

Table 4.1: Demographic characteristics

Demographic characteristic	**C**	**HR-**	**HR+**		**p**
	(N=23)	(N=46)	(N=31)	F	
Age	26.57 (2.6)	26.37 (3.3)	25.06 (3.0)	2.1	0.10
	(N=21)	(N=46)	(N=31)		
NART est. FSIQ	103.30 (9.14)	100.96 (9.3)	97.06 (11.0)	2.8	0.06

4.1.3 Materials

4.1.3.1 The California Verbal Learning Test (CVLT)

The CVLT (2nd edition; (Delis et al 2000) is an assessment of the amount of verbal information which can be learned and recalled, the strategies which are employed during learning and the aspects of the verbal learning process which might be responsible for apparent memory impairments. This type of assessment therefore, provides a more informative analysis of the nature of memory processing in both clinical and non-clinical populations (Delis et al 2000). The CVLT involves the dictation of a list of sixteen words by the experimenter, presented in the form of a shopping list. Encoding of the words is facilitated by the ability to group words into one of four categories (i.e. clothes, fruit, herbs and spices, and tools). Participants must freely recall words across five trials and after a short and long delay period, with one trial of interference (a sixteen word list containing four words from each

of four categories: fish; kitchen equipment; herbs, and fruit). Additional trials include short and long delay cued recall, and recognition.

Numerous measures can be calculated based upon the data collected during performance of the CVLT. A number of these measures are calculated according to the details outlined in the CVLT users manual. We have included measures which allowed for elucidation of the nature of verbal learning in this group (Delis et al 2000):

(1) Immediate Verbal Recall Trials

(a) List A Recall Trial 1

Following the experimenter's reading of the sixteen-item word list A, participants were asked to repeat back immediately as many words as possible recalled from the list. This is a good indicator of initial short-term verbal memory and a low score on this trial relative to all others may reflect auditory attentional difficulties or test-related anxiety.

(b) List A Trials 1-5 total

This is a measure of verbal learning after the presentation and immediate recall of list A five times. List A Trials 1-5 is a measure of the total number of words recalled across all five trials and can provide a 'global measure of immediate free recall performance'.

(c) Learning Slope trials 1-5

This measures the average number of new words learned for each trial (trials 1-5), such that 1 suggests 1 new word per trial, whereas a slope value of 0 indicates no new learning has occurred. This measure was calculated in SPSS using the following formula (x =trial, y = total number correct per trial, n = number of trials in slope and $\sum$ = sum; (Delis et al 2000): $\sum xy - [(\sum x)(\sum y)/n] / \sum x^2 - [(\sum x)^2/n]$

(d) List B Immediate Recall trial

Low scores on this trial as well as trial 1 of list A relative to normal performance on list A total recall trial 1-5, may again reflect attentional difficulties in spite of apparent intact learning ability.

(2) Delayed Verbal Recall Trials

(a) Short-Delay Free Recall trial

This measures verbal recall for list A after a brief delay during which time the interference trial of list B was presented.

(b) Short-Delay Cued Recall trial

This will aid participants' recall after a short delay by demonstrating that the semantic grouping of list items can facilitate later recall. This score will normally be an improvement on the score generated from free recall, due to the semantic strategy, which can be employed.

(c) Long-Delay Free Recall trial

Free recall of all words from list A is required after a 20-minute delay, during which time participants will have been engaged in non-interfering non-verbal memory testing.

(d) Long-Delay Cued Recall trial

This precedes the recognition trial, but follows the long delay free recall trial. This gives participants another opportunity to recall previously learned words, while using a semantic strategy to guide recall.

(3) Retention

For ease of comparison, all raw scores were converted to Z scores for the calculation of retention scores. Z scores were calculated in SPSS using the following formula (x = raw score, M = mean raw score for sample and s.d. = standard deviation): $Z = x - M/s.d.$

A Z score of + 1 means that the score is 1 standard deviation above the mean, whereas a z score of –1 means that the score is 1 standard deviation below the mean.

(a) List B Immediate Recall trial - List A Recall Trial 1 (z scores)

A low standardised (z) score on this trial may reflect high proactive interference, where the previous learning of list A has had a detrimental effect on the ability to learn new list B. All raw scores were converted to z scores before List A trial 1 was subtracted from List B trial 1.

(b) Short-Delay Free Recall Retention score (z scores)

This savings score assesses the extent to which recall on List A trial 5 is equivalent to recall on the short-delay free recall trial. A poor retention score (z score of –1 or below) would suggest retroactive interference due to the List B interference trial, such that attempts to learn the new list B will detrimentally effect subsequent recall of List A. All raw scores were converted to z scores before List A trial 5 was subtracted from short-delay free recall trial

(c) Long-Delay Free Recall Retention score (z scores)

This provides a measure of the forgetting rate between short and long delayed recall, and will reflect the extent to which recall after a short delay is equivalent to that after a longer delay. Where a participant shows improved performance from the short to long task, it could be interpreted as their benefiting from the provision of a semantic structure with which to organise the list. All raw scores were converted to z scores before the short-delay free recall trial was subtracted from the long-delay free recall trial. In order to avoid the confounding effect of retroactive interference from List B, forgetting rate between trial 5 and long delay free recall was also measured (Sitskoorn et al 2004b). Again, all raw scores were converted to z scores before the recall on trial 5 was subtracted from the long-delay free recall trial.

(4) Recognition

(a) Recognition Hits

Following the question 'I'm going to read you a list of shopping items. After each item, say 'yes' if the item was from the Monday list [list A] and say 'no' if it was not', the number of words the participant considers as having been part of List A, equals the number of recognition hits.

(b) Recognition Misses

Correspondingly, this is a measure of the number of 'no' responses given.

(c) False Positives

All 'yes', recognition responses, which are wrong, are classed as false positives. This is often a reflection of impaired source memory, a tendency for confabulation, or a predilection for 'yes' responding.

(e) Discriminability

This provides an overall assessment of general recognition performance and was calculated in SPSS using the following formula: (1- false positives + misses/44) X 100.

(f) Response Bias

A high score for 'yes' response bias indicates a possible tendency for confabulation ($z > +1$), whereas a 'no' response bias could be reflective of lack of effort or confidence in responses ($z < -1$). This was calculated in SPSS using the following formula: false positives-misses/false positives + misses.

(5) Learning Strategies (Trials 1-5)

(a) Chance Adjusted Semantic Clustering (observed – expected semantic clustering):

This reflects the extent of semantic strategy being used to encode and then recall the word list. Chance adjusted scores take into consideration both the observed level of clustering (number of words recalled correctly immediately after a word that is part of the same semantic category e.g. jumper-vest) and the expected level of semantic clustering (the number of words correctly recalled on a trial minus 1 divided by the number of trials). Chance-adjusted scores were calculated by subtracting the expected from the observed cluster scores and dividing by T (the number of trials on which at least 2 or more answers were correct).

(b) Chance Adjusted Serial Clustering (observed – expected serial clustering):

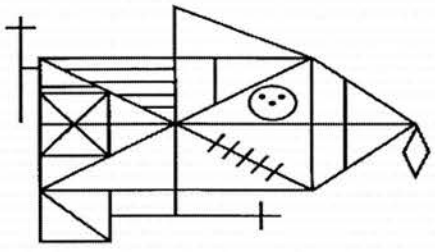
This reflects the number of words correctly recalled immediately after a word, which occurs in the same order on the list read previously, in either a backwards or forwards sequential manner. Chance

adjusted scoring was calculated in the same way as described above for both forwards and backwards serial clustering.

4.1.3.2 Rey-Osterreith Complex Figure Test

This is a standard test of visuo-spatial ability and memory. The measures employed in this assessment are as follows:

Figure 4.1: Rey Complex Figure



(1) Copy trial score & Copy trial time

Participants are given a complex figure drawing and asked to copy exactly what they see with the pencil and paper provided (see Appendix 3: figure 3A). The copy trial time is based on the time taken to complete a copy of the figure, while copy trial score is based on the accuracy of the drawing and placing of the separate elements of the figure.

(2) Immediate recall score (raw scores)

Copying is followed by a short delay time of 3 minutes, after which time the participant is asked to sketch the complex figure once again, this time without the aid of the drawing initially provided. This score is based on the accuracy of the drawing and the placing of the separate elements of the figure.

(3) Delayed recall score (raw scores)

Delayed sketching of the figure is requested thirty minutes after initial administration. The recognition trial is a measure of recognition memory for the elements of the picture and the ability to use cues for the retrieval of figure information.

(4) Recognition (raw scores)

Immediately after the delayed recall trial, participants are presented with 12 of the 18 scoring elements of the figure design, along with 12 designs used as foils. True positive and false positive responses for recognition are totalled. The score for true negatives is equal to twelve minus the false positives and the score for false negatives is equal to twelve minus the true positives. Total correct recognition is based on the number of true positives plus the number of true negatives.

4.1.4 Statistical Analysis

All data was analysed using the Statistical Package for the Social Sciences (SPSS, version 11). Normality of distributions was assessed using the Kolmogorov-Smirnov test, and homogeneity of variance using the Levene's test (see Appendix 3: Tables 3A 3B)

Due to the difference in aspects of memory measured by the CVLT, it was decided not to use a MANOVA to compare group means. Between-group differences were therefore investigated for all measures of the CVLT and RCFT using one-way ANOVAs, entering participant group as the between-subject factor with three levels (C, HR-, HR+) and the individual measures of aspects of memory described above as the within-subject factors. Where measures were not normally distributed, the non-parametric Kruskal-Wallis test was also used. Bonferroni corrections were applied. In applying a Bonferroni correction to each test section of the CVLT, the critical value of p became <0.01 for recall, <0.02 for retention and <0.025 for organisation. For RCFT the critical value of p became <0.01. Given the trend for a significant difference between groups on NART IQ, it was decided to re-run this series of analyses entering NART IQ as a covariate. Planned Helmert contrast (i.e. see previous sections in this chapter for description) also allowed for further comparisons

between groups, where the between-group effect was significant, thus addressing our apriori hypotheses (as outlined in Chapter 1).

4.2 Results Investigation 4

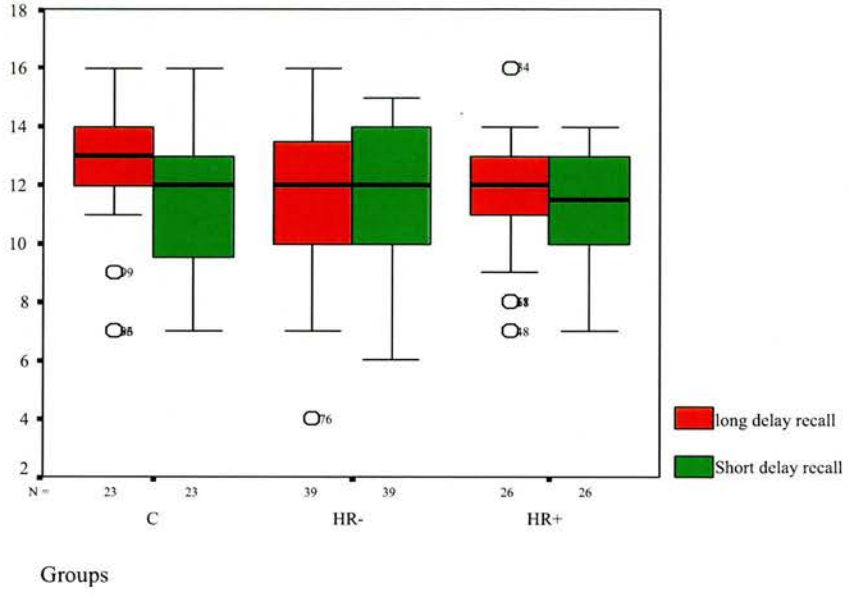
4.2.1 CVLT results

Levene's test of homogeneity of variance showed homogeneity of variance for all groups on all measures. The Kolmogorov-Smirnov test showed a number of measures in some groups to not be normally distributed (see Appendix 3: Table 3C). Means, standard deviations, medians, quartile splits and results of univariate analyses are presented in Appendix 3: Table 3B. Results of the ANOVAs showed a significant main effect of group for one measure of retention- long delay free recall minus short delay free recall (i.e. $F_{(2, 86)} = 4.4$, $p = 0.01$), while List A long delay free recall minus trial 5 recall did not quite achieve significance (i.e. $F_{(2, 86)} = 2.5$, $p = 0.08$). There were also trends for significant main effects of group on three measures of recall- List B immediate recall (i.e. $F_{(2, 86)} = 4.3$, $p = 0.02$), List A long delay cued recall (i.e. $F_{(2, 86)} = 3.2$, $p = 0.05$) and List B trial 1 minus List A trial 1 (i.e. $F_{(2, 86)} = 3.6$, $p = 0.03$). Planned contrasts showed controls to recall more words than the HR group following List B (i.e. est. diff = 1.5 (0.5), $p<0.05$), long delay cued recall (i.e. est. diff = 1.3 (s.e. = 0.5), $p<0.02$) and for list B relative to list A (i.e. est. diff = 0.6 (s.e. =0.2), $p<0.01$). Controls also retained more words than HR between the short and long delay recall tasks (i.e. est. diff = 0.4 (s.e. = 0.1), $p<0.005$). There were no significant main effects of group for measures of organisation on the CVLT. However, total observed and chance adjusted semantic clustering was non-significantly less in the HR group relative to controls (i.e. $F_{(2, 86)} = 2.1$, $p = 0.1$; $F_{(2, 86)} = 1.6$, $p = 0.2$), while combined total chance adjusted serial clustering was non-significantly greater in the HR group relative to controls (i.e. $F_{(2, 86)} = 0.3$, $p = 0.7$) (see figures 4.2- 4.5).

Kruskal-Wallis tests were conducted on those measures, which were not normally distributed at all levels of the independent variable. There was no significant between group difference after bonferroni correction on List A long delay free recall minus trial 5 recall (i.e. $\chi^2_{(2)} = 5.8$, $p = 0.05$).

Given the main effect of group for list B minus list A recall, and long delay minus short delay free recall, we further investigated the difference in recall between these trials within groups using paired t-tests (2 tailed). High-risk participants without and with psychotic symptoms showed no significant difference between the numbers of words recalled on list B relative to list A (i.e. $t = 0.35$ (d.f. = 38), $p = 0.70$; i.e. $t = 1.4$ (26), $p = 0.17$). However, controls showed a significantly greater recall for list B than list A word (i.e. $t = 2.5$ (d.f. = 22), $p = 0.02$). Similarly, high-risk participants with and without symptoms showed no significant difference between recall following the short relative to the long delay (i.e. $t = 0.66$ (d.f. = 25), $p = 0.5$; i.e. $t = 0.9$ (d.f. = 38), $p = 0.35$). Controls however freely recalled significantly more words after a long than a short delay (i.e. $t = -4.11$ (d.f. = 22), $p < 0.001$).

Figure 4.2: Boxplots of group median scores after short and long delay free recall (midline represents median, whiskers represent range, box ends represent interquartile range and circles represent individual case outliers)



After controlling for NART IQ, the main effect for list B immediate recall became non-significant (i.e. $F_{(2, 86)} = 3.1$, $p = 0.05$), as did the recall of list A minus list B (i.e. $F_{(2, 86)} = 2.7$, $p = 0.07$), long delay cued recall (i.e. $F_{(2, 86)} = 1.8$, $p = 0.2$) and long delay minus short delay free recall (i.e. $F_{(2, 86)} = 3.4$, $p = 0.04$).

Figure 4.3: Observed semantic clustering across five trials of the CVLT in HR+, HR- and C

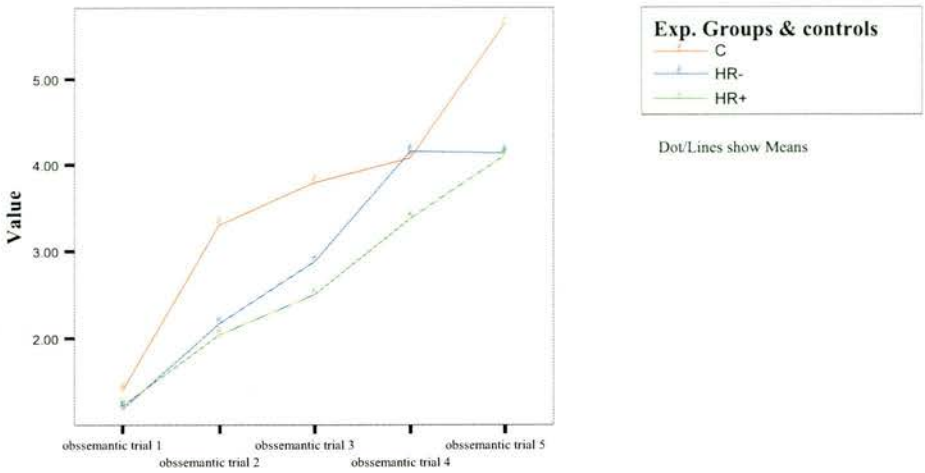


Figure 4.4: Observed serial clustering forwards across five trials of the CVLT in HR+, HR- and C

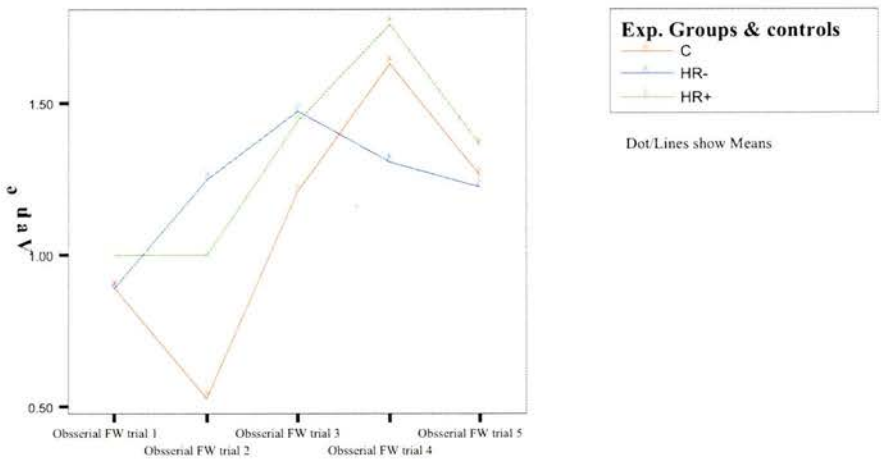
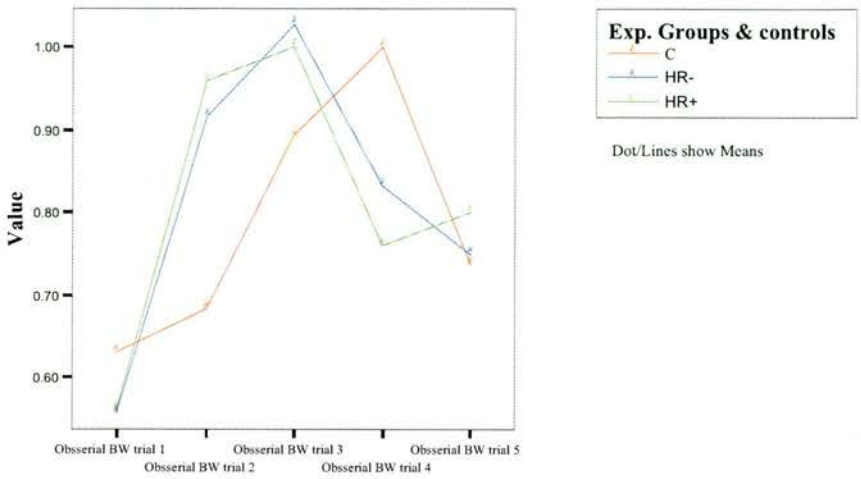


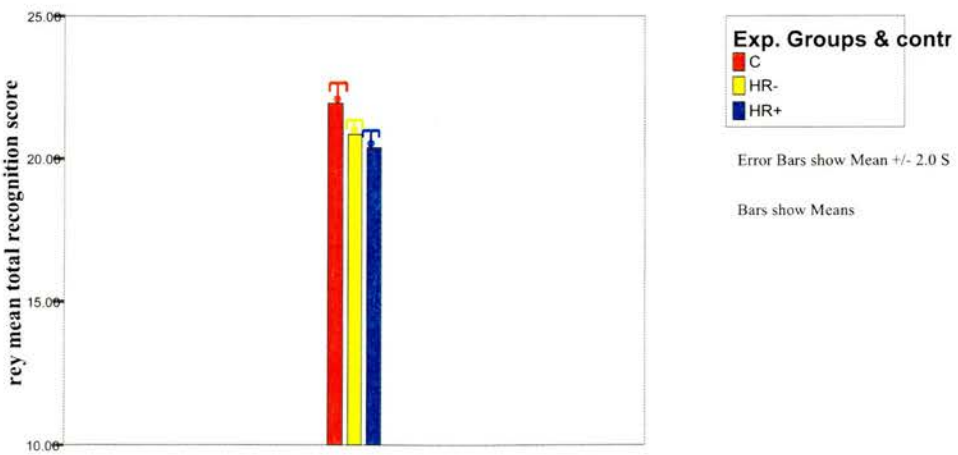
Figure 4.5: Observed serial clustering backwards across five trials of the CVLT in HR+, HR- and C



4.2.2 RCFT results

Levene's test of homogeneity of variance showed homogeneity of variance for all groups on all measures. The Kolmogorov-Smirnov test showed a number of measures in some groups, which were not normally distributed (see Appendix 3: Table 3A & 3B). Means, standard deviations, medians, quartile splits and results of univariate analyses are presented in Appendix 3: Table 3D. Results of the ANOVAs showed that on the RCFT there was a significant main effect of group for correct recognition only (i.e. $F_{(2, 95)} = 5.2$, $p = 0.007$) (see figure 4.6). Contrasts showed greater correct recognition in controls relative to the high-risk group (i.e. $t = 3.1$ (d.f. = 93), $p = 0.002$). There were no other significant main effects of group for this test. Analysis of the individual aspects of recognition response showed a significant main effect of group for true positives (and therefore also false negatives) (i.e. $F_{(2, 95)} = 5.4$, $p = 0.006$). Controls made more true positive (and therefore less false negative) responses than the high-risk group (i.e. est.diff = 1.11(s.e. = 0.38), $p<0.005$) while HR- showed a trend for significantly greater true positive responses than HR+ (i.e. est.diff =0.69 (s.e. = 0.38) p=0.071). Kruskal-Wallis non-parametric tests showed significant differences between groups on the same measures as shown using the parametric ANOVA (See Appendix 3: Table 3D).

Figure 4.6: Rey-Osterrieth Complex Figure Test correct recognition means and standard errors in the HR+, HR- and C



Chapter 5: Discussion of investigation 4

5.1 CVLT

Our results overall show a poorer performance of the high-risk group relative to controls on aspects the CVLT. This difference was nearly significant for three measures of recall, namely immediate recall of List B, delayed cued recall of List A, and immediate recall of list B minus list A. There was also a significant group effect on one measure of retention, long delay free recall minus short delay free recall.

Both list A and list B immediate recall trials are measures of short-term retention and auditory attention. Controls showed a trend for a significantly greater recall of list B, compared to the high-risk group. However, high-risk participants showed no significant within group difference between the recall of list B and recall of list A, suggesting that impaired auditory attention was not responsible for the recall deficit on list B relative to the control group. Indeed, given that list B presentation follows the five recall trials of list A, it is likely due to the interference of previously learned list A material. Pro-active interference on this trial is not unexpected and is considered a normal phenomenon. However, the significant difference between groups on the number of words recalled on list B minus list A, suggests that controls exhibit less susceptibility to pro-active interference than do the high-risk participants. In fact, a paired t-test shows a significantly superior recall on list B relative to list A in the control participants, possibly due to familiarity with the test format and awareness of the implicit semantic cues available. This further suggests that the main effect of group on recall of list B and list B minus list A exaggerates the extent of susceptibility to proactive interference in the high-risk group, due to the significantly better performance of the controls on list B recall relative to list A.

The retention of words between short and long delay free recall trials was greater in controls than in the high-risk group. However, this is not evidence of a storage deficit, because all groups recalled more words after a long delay than after a short delay. This implies that information was not lost over the extended delay period, and may in fact have been reinforced following the intervening short delay cued recall task. Paired t-tests showed controls to remember significantly more after the long delay

than previously after the short delay, whereas there was no significant increase in the number of words remembered by the high-risk participants. We can infer that, given that the high-risk group's recall was not significantly worse than the controls at the short delay recall trial or at the long delay recall trial, this measure reflects the additional learning occurring between these two trials.

The control group's greater delayed cued recall (the trial which followed delayed free recall) relative to the high-risk participants is therefore not surprising, despite being no differences on the measure of free recall after a delay. Indeed, while all groups appeared to improve scores between free and cued recall, this finding suggests controls derived greater benefit from the presence of semantic cues than the high-risk participants. This is likely attributable to the controls increased awareness of this facility at the short delay cued recall trial, but may also be due to their non-significantly greater usage of semantic cues than the high-risk participants during the encoding of list A. Nonetheless, despite the implication that encoding organisation may be impaired, and the pattern of means showing more semantic clustering in the controls relative to the high-risk group, these differences in clustering were not significant.

Previous studies of the CVLT in schizophrenic patients have revealed a slightly different pattern of performance when compared with a control group. Paulsen et al (1995) and Van Oostrum et al (2003) reported a significantly poorer recall and recognition in schizophrenic patients when compared to controls, suggestive of an encoding deficit. However, Paulsen et al (1995) also noted a disproportionate improvement on recognition discrimination relative to long delay free recall in schizophrenia patients, additionally indicative of a retrieval deficit. Their discriminant function analysis also revealed diversity in aspects of function affected on the CVLT, within the patient group. 50% exhibited similar deficits to those in Huntington's disease patients, or so-called 'sub-cortical' memory profiles (verbal learning over 5 trials), 15% were categorised as cortical profile patients, with similar encoding and storage deficits as those apparent in Alzheimer's disease and the remaining 35% evinced normal memory profiles (Paulsen et al 1995). Nathaniel James et al (1996) showed poorer learning over five trials, but equivalent levels of retention between short and long delay free recall in schizophrenia patients relative to controls. Interestingly, impairments on aspects of executive function

correlated significantly with CVLT performance, suggesting that frontal deficits may be more prevalent and/or exert more of an influence over verbal learning than medial-temporal lobe deficits. Heinrichs et al (1994) showed impairments on trial 1 recall and recognition discriminability only, in a comparison of schizophrenic, personality disorder and Korsakoff patients (Korsakoff's reputedly involving structural abnormalities in the basal forebrain, mammillary bodies and medial thalamus). Schizophrenic patients showed no difference in performance from the personality disorder patients and were generally superior in performance to the Korsakoff patients (Heinrichs 1994; Nathaniel-James et al 1996). Finally, Van Oostrum et al (2003) and Kareken et al (1996) both showed less semantic and greater serial clustering in patients relative to controls, while Hill (2003) showed a slight improvement in patient performance when made aware of semantic cues. This suggests cues are used, but less effectively than in controls. Reduced susceptibility to proactive interference in the schizophrenic group could be attributed to poor semantic clustering, although Kareken et al (1996) found no correlation between the two. These findings suggest that medial-temporal lobe function (i.e. hippocampal function) is relatively preserved in relatives of schizophrenic patients, while the general encoding and retrieval deficits could be attributed to impaired frontal function. Alternatively, given the evidence for volumetric abnormalities in both the frontal and medial-temporal lobes in schizophrenic patients and to a lesser extent in their relatives, perhaps hippocampal abnormalities are not severe enough to confer an extreme dysfunction on tests of declarative memory. A third possibility is that patients with severe medial-temporal lobe deficits represent a sub-group of schizophrenics (Heinrichs 1994).

5.2 RCFT

While recognition was unimpaired on the CVLT, this was the only aspect of the RCFT that significantly discriminated between the high-risk and control groups. Interestingly, this was predominantly attributable to the greater level of true positive responses in the controls relative to the high-risk participants. Difficulties in correctly identifying previously presented items from among similar competing alternatives may arise because of poor discrimination between items presented. Moreover, given that recall was unimpaired and only features of the complex figure were re-presented at recognition, deficits may be due to ineffective memory for the component aspects of the visual

event rather than poor recall of the visual figure as a whole. Perhaps tentatively related to this finding, is the previous result of better performance on a Block Design task in high-risk participants with two or more 1st degree relatives. It is possible that successful replication of a design using component blocks could be achieved with a 'gestalt' perspective, that is by viewing the design as a whole rather than as individual facets of a picture. Non-verbal memory has been less extensively studied in schizophrenia than verbal memory, and has often been shown to be less impaired. Holtahusen et al (2003) showed worse performance on the CVLT than RCFT in schizophrenic patients. However, Tracy et al (2001) showed both recognition and retrieval deficits in non-verbal learning, but only retrieval deficits in CVLT, suggesting an equivalent, if not worse impairment in the former test. In such instances, without matching for task difficulty, the true differences in performances between tests cannot be measured.

5.3 Limitations

This analysis was designed to allow for a more in depth investigation of the nature of verbal and non-verbal memory processing in those participants who underwent at least one functional MRI scan. Bearing in mind the reflections on differential deficits in chapter 1, it is appreciated that no conclusions can presently be drawn about material specific domain deficits, because these tasks have not been matched for difficulty. Similarly, while normative scores are available for both tests (Delis et al 2000; Lezak et al 1995), these scores have not been included in this investigation. An interesting additional investigation might therefore involve the direct comparison of performance on both tests using available normative score conversions. Similarly, without the in vivo imaging of participants during the tasks, we cannot be sure whether performance on these tests is reflective of the same underlying neural substrates. Furthermore, the participants included in this investigation were selected based on their additional inclusion in investigation 5, the functional MRI study of verbal encoding and retrieval. Perhaps given larger numbers in this investigation, differences that are more robust might have emerged on our measures of verbal and non-verbal memory.

5.4 Conclusions

Our results suggest subtle deficits in verbal recall, partly due to proactive interference and partly attributable to lower levels of semantic encoding in the high-risk relative to control group. This also suggests a less effective usage of cues at both encoding and retrieval. Visual memory recall appears relatively intact. However, compared to controls, the high-risk participants' inferior recognition of the complex figure features previously presented implies that feature level aspects of the visual learning event were poorly encoded. Both tests may reflect difficulties in the 'bottom-up' processing stage of memory, perhaps during the accessing of stored representations of visual and semantic information. Although unlikely a reflection of medial temporal dysfunction specifically, less effective executive control during encoding and retrieval, may indicate frontal dysfunction in this group.

Chapter 6: Literature review- Structural and functional neuroimaging in schizophrenia

6.1 Structural imaging in schizophrenia

As discussed in chapter 1, Kraepelin's understanding of schizophrenia was perhaps limited by the diverse prognosis of his patients and the lack of anatomical evidence to indicate an organic basis. However, in spite of this, Kraepelin believed schizophrenia to be a pathological brain disorder (Johnstone 1999). The advancement of neuroimaging techniques has enabled the in vivo three-dimensional visualisation and measurement of the anatomical structures of the brain during life and has greatly informed our understanding of aberrant brain structure and function in schizophrenia. Appendix 4: Tables 4A and B list studies of structural integrity in biological relatives, and functional neuroimaging of memory and language function in schizophrenia, respectively.

Computerised Tomography (CT) was the earliest technique applied, using the detection of attenuated x-rays transmitted through the body to distinguish between cerebro-spinal fluid, brain tissue, and the skull. More recently, Magnetic Resonance Imaging (MRI) was introduced, and utilises the detection of a signal derived from the application of a radio frequency pulse, which disrupts the magnetic field alignment of the hydrogen atoms in the water of the body. MRI is superior in resolution to CT and can distinguish between grey and white matter in the brain, as well as permitting the imaging of midline and sub cortical structures such as the corpus callosum, thalamus and caudate, which are considered important structures in schizophrenia (Sharma and Chitnis 2000).

Attempts to unravel the aetiology of structural and functional brain deficits in schizophrenia have been embraced by two theories of abnormal brain development in schizophrenia, -the neurodevelopmental, and the neurodegenerative. Weinberger's neurodevelopmental theory postulates that schizophrenia is a result of a brain lesion or maturational defect early in life (i.e. early lesion hypothesis), manifesting itself when it interacts with normal biological and behavioural events (and the general environmental stresses of life). Evidence in support of this includes higher incidence of obstetric complications, soft neurological signs and minor physical abnormalities in patients with schizophrenia and their relatives (Niemi et al 2003). Further sources of support for the neurodevelopmental hypothesis arise from the

structural imaging of brain regions vulnerable to peri-natal insult and linked to increased genetic risk for the disorder. Other neurodevelopmental theorists (i.e. Feinberg 1982) have suggested normal childhood development, followed by a late brain insult such as aberrant synaptic pruning coinciding with the onset of psychotic symptoms (i.e. late lesion hypothesis). Volumetric deficits in first episode patients and in individuals at high-risk for psychosis, imply that structural aberrations may indeed predate the onset of psychosis.

6.1.1 Structural deficits in schizophrenic patients and their relatives

Two meta-analyses have reported whole brain reductions in schizophrenic patients relative to controls (Lawrie and Abukmiel 1998; Wright et al 2000). Although significantly greater whole brain volumes have been shown in unaffected siblings of schizophrenic patients compared to their schizophrenic relatives (Steel et al 2002), smaller whole brain volumes relative to controls have also been reported (Keshavan et al 1997; Lawrie 1999), while others show no differences (Seidman et al 2003). Whole brain volume is also reported as positively correlated with cognitive function, but is more likely associated with general intellectual than specific cognitive ability (Antonova et al 2004)

Johnstone et al (1976) were the first to provide evidence for cerebro ventricular enlargement in the brains of schizophrenic patients from the CT scans of elderly patients. This implied a reduction in brain tissue volume associated with schizophrenia and has since been described across several studies using structural MRI (Chua and McKenna 1995). Chua and McKenna (1995) assert that lateral ventricular enlargement remains the most reliable structural aberration in schizophrenia, and this assertion is supported by evidence from meta-analyses (Lawrie and Abukmiel 1998; Wright et al 2000). Ventricular abnormalities which are less severe than those apparent in schizophrenia, but greater than in controls, have also been reported in unaffected relatives of patients (Cannon and Marco 1994; Cannon et al 1993; Cannon et al 1998; Keshavan et al 1997; McDonald et al 2002). The relationship between cognitive function and ventricular aberrations in both schizophrenics and in controls is unclear, with larger left ventricles in females and smaller left ventricles in males, associated with better overall cognitive function (Antonova et al 2004).

Bilateral frontal lobe volume reductions have been demonstrated, though less consistently, in schizophrenic patients relative to controls. Reductions are attributed to gray matter rather than white matter loss, and are potentially larger in the right than left hemisphere (Wright et al 2000) (Lawrie and Abukmiel 1998). However, the complex structure of the frontal lobes, and the functional heterogeneity of its sub-regions may have obfuscated consistent findings of volume differences between groups (Szesko et al 1999). In unaffected relatives of schizophrenics, Lawrie et al (2001) showed a non-significant reduction in frontal brain volume relative to controls (Lawrie et al 2001). Antonova (2004) summarises that total frontal lobe volume is related to executive function (e.g. contextual organisation), verbal fluency, working memory, and immediate memory in schizophrenia.

Several meta-analyses also report bilateral temporal lobe volume reductions in schizophrenic patients relative to controls (although slightly greater reductions on the right), attributed in part to limbic structure abnormalities (i.e. smaller hippocampus, parahippocampus and amygdala) (Chua and McKenna 1995; Lawrie and Abukmiel 1998; Nelson et al 1998; Wright et al 2000). Bilateral temporal lobe deficits and limbic lobe abnormalities are also apparent in unaffected adult relatives of schizophrenia patients compared to controls (see table 3.1)(Harris et al 2002; Lawrie et al 2002b; O'Driscoll et al 2001; Rajarethinam et al 2004; Seidman et al 1999; Staal et al 1998; Tepest et al 2003; Toulopoulou et al 2004; Van Erp et al 2002), and in unaffected adolescent relatives of patients with schizophrenia relative to controls (Keshavan et al 1997; Lawrie 1999; Schreiber et al 1999). Seidman et al (2002) indicated that reduced left hippocampal volume might be a potential vulnerability indicator for schizophrenia in individuals at genetic risk for development of the disorder (Seidman et al 2002a). Moreover, the same authors have additionally shown significantly smaller right anterior parahippocampal gyrus volumes (and a trend for the left) in unaffected relatives from multiplex, but not simplex families and schizophrenic patients, compared to controls, while unaffected relatives from simplex families showed greater posterior parahippocampal gyrus volumes relative to controls. While the implications of the latter result are unclear, the former may support the multifactorial genetic model of schizophrenia, such that increased structural deficits are consistent with increased genetic loading for the disorder. However, this does not rule out the possibility of other factors impacting on structural integrity in multiply affected families (i.e. pregnancy and birth complications).

Verbal memory deficits have been associated with amygdala-hippocampal volume reductions in schizophrenia (Goldberg et al 1994; Gur et al 2000; Weiss et al 2004a) and in unaffected relatives of schizophrenics, beyond the age of maximum risk for the disorder (O'Driscoll et al 2001; Seidman et al 2003; Toulopoulou et al 2004). However, several studies have equally failed to find any relationship between immediate or delayed memory and hippocampal volume in schizophrenia (Colombo et al 1993; Torres et al 1997). Parahippocampal gyrus (PHG) volume has also been positively correlated with verbal IQ in first episode and chronic schizophrenia patients (Delisi et al 1991 as cited in Antonova 2004), although this is not a consistent finding across studies (Seidman et al 2003).

Bilateral enlargements of the putamen, globus pallidus (lenticular nuclei) and the left caudate (with reduction in the right) have also been reported in schizophrenics (Wright et al 2000) and relatives of schizophrenics (Lawrie et al 2001). However, the smaller lenticular nuclei in high-risk participants lends support to the view that enlargement in this area in patients may be attributable to medication effects (Gur et al 1998; Lawrie et al 2001). Indeed, clozapine induced reductions in putamen and caudate volume have been shown in schizophrenic patients switched from typical anti-psychotics, and attributed to the higher D2 receptor antagonism in typical anti-psychotic medication compared to clozapine (Corson et al 1999)(Frazier et al1996 as cited (Niznikiewicz et al 2003)).

Finally, MRI studies of cerebellar volume in schizophrenia have shown mixed results, with some reporting no total volumetric differences between patients and controls (Nopoulos et al 1999; Staal et al 2000b), enlarged cerebellar vermis in patients relative to controls (Levitt et al 1999), or smaller total cerebellar tissue volume in patients who had at least 1 of 6 cerebellar signs (e.g. intention tremor, heel-knee-shin test, flaccid muscle tone, tandem gait test) relative to those without any cerebellar signs (Ho et al 2003). This suggests that cerebellar volume differences may vary within patient sub-groups. Only one study, using whole brain voxel based morphometry, demonstrated reduced cerebellar volume in unaffected relatives of patients compared to controls (Marcelis et al 2003). In Beng-Choon Ho (2004) patients with cerebellar signs showed more severe cognitive deficits, poorer premorbid function and worse negative symptoms than those without (Ho et al 2004), while Levitt et al (1999)

showed cerebellar white matter volume to be correlated with severity of positive symptoms and impaired performance in verbal prose recall (Levitt et al 1999). Toulopoulou et al (2004) recently showed positive correlations between delayed visual memory (WMS Visual Reproductions) and cerebellar volume in unaffected adult relatives of schizophrenia patients, who had performed significantly worse than controls on measures of memory, although there were no volume differences between groups. In addition, cerebellar volume in the study's combined sample was significantly positively correlated with delayed verbal recall (WMS Logical Stories) (Toulopoulou et al 2004). This would support more contemporary evidence for a link between higher cognitive functions, in particular memory, and the function of the cerebellum (Cabeza et al 2002). Indeed, Desmond (2001), proposed a superior cerebellar circuitry linked to the frontal lobes for articulatory control and an inferior cerebellar circuitry projecting to the temporo-parietal lobes for the phonological store, in verbal working memory processes (Desmond 2001).

Existing evidence for neuropsychological deficits in unaffected children at genetic risk for schizophrenia (Asarnow et al 2002; Kremen et al 1994), and unaffected high-risk children who later develop the illness (Erlenmeyer-Kimling et al 2000), is therefore complemented by the presence of structural abnormalities in unaffected relatives, which are milder than but consistent with those apparent in schizophrenia patients. This further suggests that structural and cognitive deficits may predate the illness, be present from an early stage in development, and are at least partly genetic in origin (Lawrie 1999). However, given that not all relatives develop schizophrenia, and deficits appear to be worse in those with the illness, the lesion itself may not be sufficient to induce the development of the disorder. It may therefore be a combination of genetic and non-genetic factors which lead to illness (Weinberger 1995). Indeed, Cannon et al (2002) showed foetal hypoxia to predict reduced cortical and sub-cortical grey matter, specifically in the temporal lobes, of schizophrenia patients and their relatives (Cannon et al 2002). Both lines of evidence provide support for a neurodevelopmental model of schizophrenia i.e. abnormal brain structure development. However, additional evidence for or against the course of these deficits after illness onset is crucial in order to elucidate the stability of brain pathology in schizophrenia.

6.1.2 Cross sectional and longitudinal studies of structural deficits in schizophrenics and people at high-risk of psychosis

Cross sectional studies show structural volume differences across patient age groups in gray matter and frontal lobe volume (Hulshoff Pol et al 2002) (Convit et al 2002 as cited in (Niznikiewicz et al 2003)), between first episode and chronic patients, and first episode patients and controls bilaterally in the hippocampus (Velakoulis et al 1999), between first episode patients and unaffected relatives in the amygdala-hippocampus (Lawrie 1999), and between ultra high-risk participants who had and had not developed psychosis. Copolov et al (2000) reported smaller bilateral hippocampal volumes in first-episode schizophrenic patients medicated for a maximum of 6 weeks, relative to participants at high-risk of developing psychosis (i.e. first degree relatives of patients, individuals with frequent attenuated psychotic symptoms or individuals with transient psychotic symptoms). However, the preliminary analysis reported volumes in high-risk subjects to be similar to those in a control group. The authors suggest this may implicate a time period very close to psychosis onset during which hippocampal volume reduction is accelerated (Copolov et al 2000). Lawrie et al (1999) demonstrated slightly smaller amygdala-hippocampal complex volumes in high-risk participants (1^{st} and 2^{nd} degree relatives of schizophrenics) relative to controls (Lawrie 1999). These two studies may differ due to the nature of the respective high-risk groups, and brain structure aberration may be more trait than state related. Pantelis et al (2003) compared structural MRI scans between ultra high-risk participants (i.e. a mixture of 1^{st} degree relatives of people with psychotic disorder and individuals with transient and attenuated psychotic symptoms) who had and had not developed psychosis within 12 months of a baseline scan. Those with psychosis showed smaller volumes in the right medial temporal lobe, right lateral and superior temporal lobe, right inferior frontal gyrus, insula, basal ganglia and cingulate gyrus (Pantelis et al 2003).

Previous longitudinal studies of brain pathology in schizophrenia have suggested that abnormalities are not neurodegenerative and evidence from post mortem studies has revealed an absence of gliosis (a feature which normally accompanies neurodegeneration) (Jaskiw et al 1994). However, these findings have been contradicted by more recent fMRI studies, which suggest widespread volume changes in both first episode and previously treated schizophrenic patients. (Cahn et al 2002; DeLisi

et al 1997; Gur et al 1998; Ho et al 2003; Kasai et al 2003; Mathalon et al 2001; Wood et al 2001). Longitudinal changes measured just prior to the onset of schizophrenia have also been reported. Pantelis et al (2003) compared longitudinal structural MRI scans over 1 year between 11 ultra high-risk participants who subsequently developed psychosis (within 2 years) and 10 who did not. The 10 individuals who had developed psychosis had grey matter increases in the cuneus, but grey matter reductions bilaterally in the cingulate gyrus, the left parahippocampal gyrus, left fusiform gyrus, left orbitofrontal cortex and left cerebellum, relative to the 11 who did not develop psychosis. Of the latter group, a reduction in left cerebellar volume was also apparent over time. Although the latter study's findings are important, and the first of their kind, the small sample size at follow up suggests they should be considered carefully until additional and more robust evidence is provided in support.

The possibility of structural changes occurring during the course of the illness further implies that these are not static aberrations. The neurodegenerative model suggests in fact that brain pathology is progressive with the course of the illness and would explain the increasing evidence for differences in severity of brain deficits in chronic and first episode schizophrenia patients. Currently however, it is accepted that these two apparently divergent hypotheses may both in fact be relevant to the increasing literature reporting diverse structural and functional abnormalities in schizophrenia patients (both first episode and chronic) and in unaffected relatives of schizophrenics. Furthermore, the diversity of implicated brain areas and their correlations with impairments in several cognitive domains, specifically memory, executive and intellectual function, suggests a more complex relationship between structure and function than functional localisation would permit.

6.2 Introduction to functional neuroimaging of memory in schizophrenia

The literature suggests impairments in memory, executive and intellectual ability in schizophrenia patients, and their relatives, with coincident deficits in brain regions such as the frontal and temporal lobes, which are correlated with these aspects of function. The exact nature of the impairment is however unclear. While the diversity of affected cognition implies a global impairment, the prevalent and often superficially more severe deficits in verbal memory suggests that these tasks place greater demands on function or that there is a differential deficit in general memory processing. Functional

neuroimaging of memory in schizophrenics and their relatives allows for a more direct examination of the collective brain regions and networks which may be functionally defective and impinge upon aspects of function such as verbal memory.

Brain energy is derived mainly from the oxidation of glucose. Blood flow in the brain may be locally increased in order to meet demands for oxygen and glucose supply for action potentials or neuronal inhibition, and is therefore taken as an indication of increased synaptic energy utilisation to drive neuronal response. However, the specific relationship between the haemodynamic response and neuronal activity is not yet clear, and it is appreciated that the relationship between the two may be far more complex than is currently understood (Jezzard and Clare 2001). Nonetheless, functional neuroimaging utilises the relationship between brain blood flow and neuronal activation, in order to correlate localised brain activations with aspects of cognitive function.

In vivo structural neuroimaging is complemented by functional imaging techniques such as single photon emission tomography (SPECT), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), which enable the visualisation of the brain' s neuronal response to cognitive engagement. SPECT uses the detection of radionuclide tracers introduced to the blood, which emit single gamma-ray photons. These photons interact with a sodium crystal to produce a detectable signal. PET similarly uses a radionuclide exogenous tracer (e.g. H_20^{15} for regional cerebral blood flow and F^{18} fluoro-deoxy-glucose for regional cerebral glucose metabolism), which is injected into the blood stream to diffuse across the blood brain barrier, accumulate, and circulate within the tissue. The decay of the tracer results in the emission of positrons, which interact with electrons producing two separate gamma rays, the detection of which gives rise to a measurable signal. By far the most sensitive technique of the three is fMRI, which provides greater temporal (i.e. one image per second) and spatial resolution (i.e. 1-2 mm), although temporal resolution is lost in BOLD fMRI due to the time it takes for oxygenated blood to accumulate (Seminowicz, 2001-http://www.uoguelph.ca/, accessed 18/07/01). Unlike PET and SPECT, blood oxygen level dependent (BOLD) fMRI uses an endogenous tracer in the form of the brain's blood response to neuronal activity. BOLD fMRI depends on the ratio of the diamagnetic oxyhaemoglobin (i.e. which has little magnetic effect on the

surroundings) to the paramagnetic deoxyhaemoglobin (i.e. which has a significant magnetic effect on the surroundings). In areas of increased neuronal activity, an increase in local blood flow and volume results in an increase in oxygen. However, due to a slower uptake of oxygen into the cells, there is an increase in the diamagnetic oxyhaemoglobin resulting in an increase in the MR signal (T2* value) (Jezzard and Clare 2001).

Task related functional activations should be considered meaningful within the context of the task administered, and the psychological process it purports to measure. In order to enable correlation between neuronal activation and aspects of cognitive processing, functional MRI traditionally employs the categorical, subtractive, block paradigm design, which enables the examination of levels of a category in separate blocks of trials in order to evoke a response to a specific cognitive process of interest. 'Experimental' blocks, designed to evoke the cognitive process of interest, will be flanked by 'control' blocks, which ideally will evoke all cognitive processes except the process of interest. The contrasting of conditions relies on cognitive subtraction, matching equally and hence holding constant all other variables in the experiment except for the variable under scrutiny. Any ensuing differences in brain activity can then be attributed to the process under investigation. Although this conveys the advantage of a robust response to the cognitive process of interest, in that neural activity is measured and averaged across a block of trials, it does not allow for discrete event analysis. This means that participants could be unduly affected by the predictability of trial presentation both during the experimental blocks and during the following blocks of rest.

In addition to this, cognitive subtraction relies on the theory of 'pure insertion', which posits that a cognitive process of interest can be added to other cognitive processes without impacting on the ensuing responses associated with them. Unfortunately, without a measure of the original processes both with and without the addition of the process of interest, we cannot be sure we have extrapolated the responses attributed to those processes independently, or whether these responses are mediated by the existence of the additional process during the experimental task (Aguirre and D'Eposito 2000). With these issues in mind, a categorical blocked design is advisable only where the effect of interest is an isolated phenomenon, where it can be separated easily from other cognitive processes, where the

effect is elicited as only one type of response and where it cannot be manipulated using a parametric design.

The need for application of the principle of 'pure insertion' is obviated in conjunction, factorial and parametric designs, which can be used in both event-related and blocked experiments. Conjunction designs involve the conduction of a number of categorical cognitive subtraction experiments, varying the additional cognitive processes while maintaining the same cognitive process of interest. This allows investigation of the process of interest in the presence of different additional cognitive processes to isolate areas of activation solely associated with the process of interest. Alternatively, factorial designs explore the interaction between two cognitive processes of interest, with the evoking of these processes independently, together, and not at all, when substituted with a condition that does not evoke either process of interest. Finally, parametric designs explore the response associated with only one parameter and its varying levels of difficulty (Aguirre and D'Esposito 2000).

Studies of the functional neuroimaging of verbal memory in schizophrenics, and to a limited extent in their unaffected families, have been reviewed. Additionally included is a review of functional neuroimaging of the same processes in healthy volunteers. Given that the neural correlates of verbal memory in the normal brain are also still under investigation, this was considered crucial to informing the discussion of neuroimaging of verbal memory in schizophrenia. Moreover, although the primary focus of this thesis lies in the elucidation of any differences in the neural correlates of memory processing between relatives of schizophrenics and controls, it is appreciated that the same implicated areas may also be involved in other aspects of affected cognition in the disorder (i.e. executive function). Where relevant, studies investigating these processes have also been discussed (see Appendix 4: table 4B).

6.2.1 Functional imaging of verbal working memory

Working memory is a limited capacity system enabling the brief maintenance and manipulation of material. Baddeley's (1992) traditional three component model of working memory comprises a hypothetical phonological loop for articulatory rehearsal and acoustic and verbal storage, and a visuo-

spatial sketchpad for the brief maintenance and manipulation of verbal and non-verbal information, both controlled by a central executive which allocates attentional processes during performance (Baddeley 1992). Fronto-parietal activations are considered an important part of a brain network sub serving verbal working memory processing, and the reciprocal connections between the two enable their parallel activation. The cerebellum has additionally been implicated as an important contributor to this network, with inferior and superior cerebellar projections to the parietal lobes and prefrontal cortex (PFC) respectively (Desmond 2001).

6.2.1.1 Functional imaging of verbal working memory in healthy volunteers

6.2.1.1.1 Frontal lobes

Evidence supports the role of the left dorsolateral prefrontal cortex (DLPFC; BA9/46) as the central executive, controlling attentional processes during rehearsal and storage of material during working memory performance (Callicott et al 1999; Jonides et al 1998a). Evidence also suggests the DLPFC is necessary for both manipulation and maintenance processes during working memory tasks, although it is reported as more active for the former than the latter tasks (Manoach et al 2003). This area is also commonly bilaterally activated during episodic retrieval tasks, and may therefore be responsible for the control of transient information, or material generated from a search (Cabeza and Nyberg 2000). The limited capacity of working memory is reflected in the activation of the DLPFC during working memory tasks, with an increase in activation analogous to increasing task demands, but a reduction in activation as capacity is breached. It is possible that this indicates a disengagement from the task due to limitations in the attentional reserves of the central executive (Callicott et al 1999).

The left inferior frontal cortex (IFC; BA44), or Broca's area, is hypothesised as integral to the articulatory sub-vocal rehearsal component of the phonological loop (Baddeley 2000; Fiez et al 1996). Paulesu et al (1993) and Awh et al (1996) used the Sternberg item recognition task to investigate verbal working memory processes. Participants were briefly presented with sets of 3-9 letters, followed by a probe, and asked to decide whether or not the probe was one of the original set (Fletcher and Henson 2001). Both studies showed activation in the right cerebellum and left lateralised activations in the parietal, dorsal premotor and importantly, the left IFC (Fletcher and Henson 2001).

Paulesu et al (1993) compared the Sternberg memory condition to a control task (i.e. judging the rhyming of letters with a target letter, thus isolating articulatory processes) in order to investigate verbal maintenance and rehearsal activations separately. This contrast showed left inferior parietal but no left IFC activation, suggesting that the latter was responsible for verbal rehearsal, and the former for verbal maintenance processes (Fletcher and Henson 2001).

6.2.1.1.2 Parietal lobes

The bilateral inferior (IPL) and posterior parietal lobes (PPL) have been consistently implicated in the phonological storage or buffer component of working memory. Deficits in the phonological loop have been demonstrated in inferior and posterior parietal lesion patients, while mainly right lateral posterior parietal (BA40) activation during the storage of verbal material (non-words) in a verbal working memory task (although left hemisphere activation was present to a lesser degree) has been shown in healthy volunteers (Honey et al 2000; Jonides et al 1998a). Awh et al (1996) used two paradigms (i.e. 2-back task using letters and a continuous sub-vocal verbal repetition task) to manipulate verbal storage and rehearsal respectively. While both PPL and IFC activations were observed across tasks, when comparing verbal storage to verbal rehearsal, only PPL activations remained. This suggests PPL activations may be integral to the phonological buffer or storage component of verbal working memory. Fiez et al (1996) failed to show the same PPL activation during a PET study of retention during a verbal working memory task (i.e. scanned during the 40 second retention period of five word or non-word items). However, it is thought that their participants may have used semantic as opposed to phonological coding, because words are likely coded both semantically and phonologically, whereas non-words are coded only phonologically (Fiez et al 1996). Jonides et al (1998) also asserted that this loci of activation could be important for attentional processes in the shifting from the internal representation of one item to another during rehearsal (Jonides et al 1998a). However, Honey et al (2000) matched stimulus frequency and duration across the experimental (i.e. n-back task with letters) and control tasks (i.e. viewing letters and pressing a button on seeing X), so that attentional shifts would not be expected. Bilateral PPL activation was still evident and positively correlated with response time, thus supporting the involvement of this region in the phonological storage of verbal material (Honey et al 2000). More recently Logie et al

(2003) attempted to isolate the encoding strategy employed during a verbal maintenance fMRI study, by explicitly asking participants to sub-vocally rehearse aurally 5 alphabetically presented letters, followed by recall and compared this to the sub-vocal rehearsal of several sequences of 5 randomly presented consonants (Logie et al 2003). Participants showed greater activation in the left IPL (BA40), left IFC (BA6) and left middle frontal gyrus (BA8) during the random sequence relative to the alphabetical sequence. Having removed the effects of verbal rehearsal, this suggests that these specific activations may be associated with verbal storage.

6.2.1.1.3 Cerebellum

Desmond et al (1997) assert that the cerebellum increases rehearsal effectiveness during working memory, by comparing output from frontal and temporo-parietal regions and based on this, sending 'feed-forward' output to aid in rehearsal processing (Desmond et al 1997). Desmond et al (2001) used the Sternberg item recognition task with a high and low load condition and compared this with a rehearsal control task in healthy volunteers. Consistent with their hypothesis, the analysis revealed a high versus low load memory effect in the superior vermis of the cerebellum, while the right inferior cerebellum demonstrated a load by task interaction. Several other studies of verbal working memory also report cerebellar activation along with contralateral activation in the frontal and parietal lobes (Awh et al 1995; Paulesu et al 1993).

6.2.1.2 Functional imaging of verbal working memory in schizophrenia

6.2.1.2.1 Behavioural performance

The N-back task is a reliable test of working memory function, requiring the monitoring and maintenance of a sequence of increasing numbers of visually presented stimuli and the updating of these stimuli as a new one is presented. The n value is often viewed as proportional to the load of working memory (i.e. n = 2 back requires recall of the stimulus presented 2 trials previously). N-back has been shown to induce prefrontal activation in healthy controls and for this reason is used consistently in functional imaging studies of working memory in schizophrenia (Callicott et al 1998). Several studies have shown behavioural differences between schizophrenic patients and controls with increasing difficulty on the n-back task (i.e. equivalent on 0 back, but worsening by 2 back) (Callicott

et al 1998; Menon et al 2001; Wencel et al 2002). In low load n-back tasks, both groups have performed equivalently, but patients have shown slower response times or more errors relative to controls (Honey et al 2002; Weinberger et al 1996).

6.2.1.2.2 Frontal lobes

A number of studies have also shown normal DLPFC activation at low levels of n-back, but deficient activation of the same area (frequently in the right hemisphere) with increasing difficulty on this task, which is suggestive of patients achieving peak activation in this area before controls (Callicott et al 1998; Jansma et al 2004; Menon et al 2001; Perlstein et al 2001). Stevens et al (1998) showed no differences between controls and patients in the DLPFC during a word and tone serial position task, but the authors attributed this to the robust sub-vocal rehearsal component to this task (Stevens et al 1998). Similar deficits have also been demonstrated on visuo-spatial working memory for happy and sad faces task and a digit recognition task (Manoach et al 2000; Manoach et al 1999; Quintana et al 2003), while increased DLPFC activation in patients has also been inversely correlated with task performance (Manoach et al 2000; Manoach et al 1999). These findings suggest that the increased recruitment of the DLPFC in patients reflects greater effort to perform the working memory task equivalently to controls, albeit often in slower time and with greater errors. However, as load and hence difficulty increases, DLPFC recruitment declines. This could reflect the exceeding of working memory capacity. Indeed, matching the performance of patients and controls (i.e. comparing controls at 3-back to patients at 2-back) has in some instances resulted in a loss of the DLPFC difference (Jansma et al 2004; Perlstein et al 2001), suggesting that this is a normal response to increasing task demand. Callicott et al (2003) showed frontal areas of both increased and decreased activation in schizophrenics with normal n-back performance, whereas poor patient performance was characterised by frontal decreases alone (Callicott 2003). More recently, Thermenos et al (2004) demonstrated increased right BA10 and left BA46 activity in schizophrenic patients relative to controls during a 2-back working memory task, after co-varying for IQ and task accuracy. IFC activation has also been demonstrated as defective in patients relative to controls during a word serial position task, suggesting that the articulatory processing aspect of verbal working memory may be deficient in schizophrenia (Stevens et al 1998; Wexler et al 2000). This is especially interesting given that the same language

related area is not impaired in patients relative to controls during verbal fluency tasks (Fletcher et al 1996; Frith et al 1995). Therefore, the rehearsal but not the generation of verbal material may result in reduced activation at this location. However, Wexler et al (2001) demonstrated that this response impairment was reversible in schizophrenia patients who received training on the Word Serial Position Task over 10 weeks. This implies that familiarity with a task improves performance and thus normalises frontal response (Wexler et al 2000). In an analysis of n-back performance in schizophrenic patients over time, Mendrek et al (2004) showed an over-activation of several regions including the DLPFC at baseline scanning in the 0-back versus rest contrast compared to controls, but a reduced activation relative to controls in the 2-back versus 0-back contrast. At the second scanning session, patients also showed increased response relative to controls in the LDLPFC during 0 back, but less during the 2-back condition. Moreover, while the difference in activation of regions during 2-back relative to 0-back was marked, and reflected the response to increased load, patients showed equivalent activation in both conditions (though still less than controls during 2-back). This pattern characterises well the hypothesised non-linear inverted U shaped response of the DLPFC. This may be shifted slightly leftwards in schizophrenics, leading to the breach of capacity limits at an earlier stage than in healthy controls (Mendrek et al 2004).

6.2.1.2.3 Parietal lobes

Along with deficient DLPFC response with increasing working memory load in patients, evidence also supports an over activation of the parietal lobes, with increased IPL sulcus response (BA40) (Callicott et al 2000; Callicott et al 1998; Jansma et al 2004; Thermenos et al 2004a) and greater bilateral PPL activation correlated positively with response time (Honey et al 2002). This corresponds with the notion that this area is critical for phonological storage, and increased effort through enhanced phonological processing may be required in patients as task demands rise. Moreover, Menon et al (2001) showed deficient DLPFC, IPL and superior parietal activation during the n-back task in schizophrenics. This implies that both areas are capacity constrained, and the IPL also deactivates when the working memory load limit is reached (Menon et al 2001). Quintana et al (2003) also demonstrated greater bilateral PPL activity in schizophrenic patients relative to controls during the anticipatory condition of a working memory task, which demanded retention and anticipation of

visuo-spatial cues (i.e. line faces and coloured circles) for successful identification of targets. Given the additional decreased DLPFC activation in this condition, PPL activation was described as compensatory to reduced frontal cortex function. The lack of evidence for structural deficits in the posterior parietal lobes in schizophrenia, suggests that hyper activity may reflect compensation to frontal lobe deficiencies (Quintana et al 2003).

6.2.1.2.4 Cerebellum

Mendrek et al (2004) showed more persistent abnormalities of function in the left cerebral hemisphere and right cerebellum, but more transient abnormalities associated with the acute psychotic state in the right cerebral hemisphere and left cerebellum in schizophrenics (i.e. normalised over time with medication and remittance of symptoms), across two fMRI n-back task sessions. This reflects the contralateral connections between the prefrontal cortex and cerebellum mediated by the thalamus. The additional evidence for thalamic dysfunction in this patient sample supports evidence for cognitive dysmetria in schizophrenia, which describes the dysconnectivity in the fronto-thalamic-cerebellar network (Andreasen et al 1996; Crespo-Facorro et al 1999; Mendrek et al 2004).

6.2.2 Functional imaging of verbal encoding

Verbal episodic encoding tasks demand the intentional memorisation of material in order to facilitate later recall. Superficial encoding is the processing of words based on their perceptual properties (i.e. counting number of T letters in words). Deep processing is learning based on meaningful associations, will normally facilitate better recall and will often be self initiated during encoding tasks as a strategy for more effective recall. Levels of processing paradigms manipulate encoding processes to allow for (1) elucidation of brain areas recruited during the encoding task itself, (2) a comparison of activations associated with recall following specific forms of encoding (i.e. semantic or repetitious versus superficial encoding, such as perceptual word judgements), or (3) a comparison of successful (i.e. recalled correctly) versus unsuccessful (i.e. recalled incorrectly) encoding (Cabeza and Nyberg 2000; Demb et al 1995; Gabrieli 1998). Semantic processing is also apparent in incidental or unintentional learning tasks (i.e. tasks where material is processed without explicit request for later recall, e.g. word classification tasks).

6.2.2.1 Functional imaging of verbal encoding in healthy volunteers

6.2.2.1.1 Frontal lobes

Increased left ventrolateral prefrontal cortex (VLFC; BA45/47) activation, unrelated to task difficulty, during deep relative to superficial verbal encoding, has previously been demonstrated in healthy volunteers (Demb et al 1995; Fletcher and Henson 2001; Gabrieli 1998; Pilgrim et al 2002). Moreover, this left hemisphere activation is coincident with a left lateralisation for language (Gabrieli 1998). Left VLFC activation has also been shown to decrease during retrieval following semantic repetition priming, or repeated word presentation at encoding and may represent an experience induced plasticity resulting in the updating of semantic knowledge (Demb et al 1995; Gabrieli 1998). Shallice et al (1994) showed that reduction in left anterior VLFC rCBF occurred during verbal learning in the presence of a motor distractor task, which resulted in poor cued recall (Shallice et al 1994). Wagner et al (1998) showed greater left posterior VLFC activation during the encoding of words that were recalled with confidence relative to those that were subsequently forgotten (Wagner et al 1998). This implies a role for this area in successful verbal encoding and others have hypothesised that this may relate to the generation of semantic or contextual attributes of an item during learning, thus facilitating successful recall (Fletcher and Henson 2001; Simons and Spiers 2003). Fletcher and Henson (2001) describe the anterior VLFC as important in semantic memory retrieval (i.e. word generation tasks). The more posterior VLFC areas, including Broca's area (BA44) may be involved in the online holding of verbal material (sub-vocal rehearsal), while selection of responses, especially in tasks with high levels of competition (i.e. similar distractors, proactive interference), may involve both VLFC and additional recruitment of the DLPFC (Fletcher and Henson 2001).

Retrieval following deep relative to shallow processing has been shown to induce more accurate recall (Gabrieli 1998). In a blocked fMRI experiment, Buckner et al (1998a) used deep processing to induce high levels of success and low levels of effort, and shallow processing to induce low levels of success and high levels of effort, at recognition. Bilateral anterior insula and left DLPFC activations were apparent during retrieval following shallow encoding, whereas activation in the right anterior

prefrontal cortex (APFC; BA10), a fronto-polar area anterior to the IFC, was apparent during retrieval, post deep processing. The authors tentatively suggested that right APFC might therefore be specific to retrieval success, although equally this could reflect the conscious recollection of deeply processed words (Buckner and Koutstaal 1998). Grasby et al (2001) also showed right APFC activation during retrieval, but following both semantic and non-semantic encoding of pictures and words (Grasby et al 2001). The lack of impact of encoding style in this instance may be due to the fact that items were re-presented in the same format as during encoding, minimalising the extent of search required, or reflective of effortful conscious recollection.

6.2.2.1.2 Temporal lobes

The left medial temporal lobe (MTL) is involved in a network of left lateralised brain regions activated during verbal encoding, but shows bilateral activation during non-verbal encoding. Evidence suggests MTL recruitment is particularly prominent during the detection of new information. In a blocked fMRI picture encoding and retrieval task, both Gabrieli et al (1997) and Stern et al (1996) demonstrated increased bilateral posterior MTL activation (i.e. parahippocampal gyrus (PHG)), in relation to novel pictures relative to familiar pictures (Schacter and Wagner 1999). Conversely, Ranganath et al (2001) showed mainly right anterior hippocampus activation during the maintenance (i.e. delay period prior to retrieval condition) of novel relative to familiar faces (Ranganath and D'Esposito 2001), while Saykin et al (1999) showed increased left anterior hippocampal activation during the processing of novel relative to familiar words (Saykin et al 1999). Daselaar et al (2004) demonstrated activation of the left MTL (i.e. PHG and hippocampal formation), during both successful word encoding and recognition of the same words. However, the left anterior MTL (i.e. entorhinal cortex) was only activated during encoding (Daselaar et al 2004b). The PHG is thought to sub-serve memory formation and reactivation of memory traces, and several other studies have also shown left parahippocampal activation during successful retrieval of context (Dobbins et al 2003). The entorhinal cortex may be exclusively involved in the detection of novel stimuli. This is supported by evidence from studies in monkeys, which identified a group of cells in the entorhinal cortex region of the monkey brain to be sensitive to stimuli novelty (Xiang and Brown 1998 as cited in (Daselaar et al 2004b)). A number of studies reported by Henson et al (2003) show a smaller

response elicited in the anterior MTL during old relative to new word discrimination (Henson et al 2003). Similarly, Dolan and Fletcher (1997) showed a stepwise increase in the left MTL response (i.e. PHG and hippocampal formation) with category-exemplar word pair associates (i.e. dog-boxer) of increasing novelty (i.e. old-old; old-new; new-old; new-new), also suggesting sensitivity to contextual novelty (Dolan and Fletcher 1997; Schacter and Wagner 1999).

Other evidence suggests the MTL response extends beyond basic novelty detection. Saykin et al (1999) showed increased left posterior PHG activation during the processing of familiar relative to novel words, although greater left anterior MTL activation has been demonstrated in deep relative to shallow word processing in both intentional and incidental verbal encoding tasks (Demb et al 1995; Martin 1999; Otten et al 2001; Saykin et al 1999; Wagner et al 1998). In a PET study during an encoding task, strength of left MTL activity was shown to vary as a function of meaning, and subsequent memory for an item was directly related to the strength of MTL activation during encoding (Martin 1999; Schacter and Wagner 1999; Wagner et al 1998). Similarly, Davachi et al (2003) showed hippocampus and posterior PHG activity during encoding to be predictive of later source recollection (i.e. consciously recalling the context surrounding the item) (Davachi et al 2003). The impact of MTL activation during encoding, on the later recollection of aspects of context for items learned, suggests the posterior MTL may also have a role in the binding together of attributes of a learning event during the formation of an episodic memory (Desranges et al 1998). Furthermore, the interconnection between the MTL and PFC suggests that these regions might act in concert to receive and maintain information during verbal processing. It is clear that the MTL has a complex involvement in the process of learning, exacerbated by the likely functional dissociation within limbic structures such as the hippocampus and parahippocampal gyrus, and the varied recruitment identified by PET and fMRI across cognitive tasks.

6.2.2.1.3 Cerebellum

Although the cerebellum receives less attention than other brain regions commonly activated during memory tasks, a small number of studies do show cerebellar response during verbal encoding in healthy volunteers. Lidaka et al (2000) showed right cerebellar coincident with left prefrontal BOLD

response, while Busatto et al (1997) showed left cerebellar activity and Fernandez et al (1998) bilateral cerebellar activation during word encoding (Busatto and Fernandez as cited by (Cabeza and Nyberg 2000; Iidaka et al 2000). This may again be a reflection of the contralateral interconnections between the cerebellum and the prefrontal, temporal and parietal lobes.

6.2.2.2 Functional imaging of verbal encoding in schizophrenia

6.2.2.2.1 Behavioural performance

Several functional imaging studies have shown that schizophrenic patients benefit from deep processing (i.e. semantic encoding). Crespo Faccoro et al (2001) showed no differences between groups in recognition performance of well learned (i.e. one week prior to experiment) and novel words, Hofer et al (2003) showed high recognition performance in both acute and remitted schizophrenic patients and controls following a semantic encoding task relative to rest (i.e. like versus dislike & rest), while Kubicki et al (2003) (i.e. abstract versus concrete & upper versus lower case) and Heckers et al (1998) (i.e. counting word meanings & counting word T junctions) showed better performance following deep relative to shallow encoding in both patients and controls (Crespo-Facorro et al 2001; Heckers et al 1998; Hofer et al 2003a; Hofer et al 2003b; Kubicki et al 2003). However, usage of information during encoding may be different between patients and controls. Jennings et al (1998) showed equivalent performance in patients and controls during a perceptual judgement task, but a significant difference between groups in accuracy on a category judgement task, while Ragland et al (2004) noted that patients subjectively reported using fewer associations than controls during an intentional verbal encoding task (Jennings et al 1998; Ragland et al 2004). During a verbal list learning task, Nohara et al (2000) presented participants with three word lists of varying inherent semantic organisation, of which participants were not informed: random (i.e. no relationship between words); blocked (i.e. words fit into 1 of 4 possible exemplar categories); and semi-blocked (i.e. contains some words from previous exemplar categories randomly intermixed). Patients recalled fewer words across all three lists than controls. However, although controls showed recall improvement from random to semi-blocked to blocked lists, the performance of the patients on the random and semi-blocked lists did not differ. This suggests that the majority of schizophrenic patients did not spontaneously utilise the implicit semantic structure of the semi-blocked list to the same extent

as controls (Nohara et al 2000). Similarly, Hazlett et al (2000) showed patients to exhibit less semantic clustering, greater serial ordering and more intrusions than controls during list learning across five trials in schizophrenic patients (Hazlett et al 2000). These findings are consistent with the previously reviewed neuropsychological evidence for encoding deficits in schizophrenia.

6.2.2.2.2 Frontal lobes

In patients compared to controls, differences in prefrontal (PFC) activation during deep encoding, between recall following deep and shallow processing or during intentional encoding without strategy instruction, imply that patients may be acquiring information differently from or less effectively than controls. During a semantic encoding condition, Jennings et al (1998) and Hofer et al (2003) showed decreased right APFC (BA9/10) response in patients relative to controls. This is surprising given that the hemispheric encoding/retrieval asymmetry model (HERA) implicates left lateralised PFC activation during verbal encoding and right PFC activation during retrieval. However, this may be due to words that induce high levels of imagery or to material that is already familiar to participants, and more speculatively could be indicative of the usage of a different encoding strategy in the control group relative to the patients (Hofer et al 2003a; Hofer et al 2003b; Jennings et al 1998). Kubicki et al (2003) showed decreased bilateral BA45 response in patients relative to controls, suggestive of reduced semantic processing during the encoding of words in the patient group (Hofer et al 2003b; Jennings et al 1998; Kubicki et al 2003). While Kubicki et al (2003) showed increased cingulate gyrus activation in patients during semantic relative to perceptual processing, Hofer et al (2003) showed reduced AC (BA32) response in patients relative to controls during their semantic encoding relative to rest condition, and Nohara et al (2000) showed reduced AC rCBF during the encoding of lists of different semantic structure relative to verbal repetition. The levels of cingulate activity in the groups during the different control conditions, could possibly explain these differences. Hazlett et al (2000) showed increased serial ordering during list learning to be associated with decreased rGMR in the left middle and left inferior frontal gyrus, and left and right precentral gyrus (Hazlett et al 2000; Kubicki et al 2003).

During recall following deep processing (minus recall following shallow processing), Heckers et al (1998) showed increased rCBF in the right prefrontal cortex (RPFC; BA10) in patients relative to controls. Greater RPFC activation may reflect effort, especially when the patients showed greater accuracy for shallow than for deeply processed words. Similarly, impaired hippocampal activation for the same contrast implies difficulties in conscious recollection of words that should have been deeply encoded (Heckers et al 1998). Interestingly, Ino et al (2004) showed RPFC activation to be negatively correlated with correct recall in healthy participants during an auditory verbal encoding and retrieval task (Ino et al 2004).

During encoding of word lists of varying semantic structure, Nohara et al (2000) showed less rCBF in the left IFC, whilst during the control verbal repetition task patients showed decreased rCBF in the right middle frontal gyrus. This suggests that the impaired semantic processing (apparent from the behavioural results), may be correlated with reduced left IFC activation, compared to the controls (Nohara et al 2000). The application of semantic structure to a list will facilitate later recall, and has previously been associated with left IFC activation in healthy controls (Fletcher et al 1998 as cited in (Nohara et al 2000). During a PET encoding and retrieval task, Ragland et al (2001) asked participants to look at words as they were individually presented, try to remember them and then press a button. During encoding, patients showed reduced left IFC (BA45) and superior frontal gyrus (BA8 and 9) rCBF relative to controls. Ragland et al (2001) suggest that patients have used working memory to maintain words online in order to perform the recognition task to the same level as controls. However, again, reduced left BA45 activation may reflect a lack of semantic processing relative to that which may have been self initiated by the controls (Ragland et al 2001). More generally, both Hofer et al (2003) and Ragland et al (2001) suggest that less prefrontal activation in the patient groups relative to controls during deep encoding, may be evidence for impaired executive control (Hofer et al 2003b; Ragland et al 2001).

6.2.2.2.3 Temporal lobes

Temporal lobe recruitment also appears to be abnormal in schizophrenic patients compared to controls. During a comparison of deep encoding, Hofer et al (2003) (i.e. like or dislike word decision

task) showed less lateral temporal (BA21) activation in acute patients (Hofer et al 2003a; Hofer et al 2003b). Reduced lateral temporal (BA21) activity, which was attributed to impaired semantic processing, was also shown by Ganguli et al (1997) in an auditory verbal suprapspan task, and considered consistent with frontal cortex failed executive control (Fletcher et al 1998; Ganguli et al 1997; Kubicki et al 2003). During an intentional encoding task (i.e. explicitly asking participants to try and remember words), Ragland et al (2001) showed reduced superior temporal gyrus (STG)(BA38) activation, while Jennings et al (1998) showed reduced right middle temporal lobe (BA22) activation, but greater right STG activation (BA22) during a living versus non-living word classification task in patients relative to controls. There were no differences between groups in the left STG. However, the functional interactions between the STG and the left IFC (BA45) and left AC (BA32) showed negative correlations, compared to positive associations in the control group. The authors suggest that despite not impacting negatively on performance in this instance, the poor functional connectivity between these networks may be reflected as an inability to flexibly respond to increasing task demands during tasks that are more difficult. During a semantic encoding task (i.e. abstract or concrete word classification task) Kubicki et al (2003) showed increased STG activation concomitant with reduced left IFC activation (Hofer et al 2003b; Jennings et al 1998; Kubicki et al 2003; Ragland et al 2001). A failure of STG deactivation in schizophrenic patients was previously shown in a PET study of graded word list recall (Fletcher et al 1998). Fletcher et al (1998) suggest that 'over-elaboration of verbal information', or hyper-activation of semantic representations may be due to an over activation of the STG in schizophrenia, coincident with a failure of PFC executive mediation (Fletcher et al 1998).

6.2.2.2.4 Medial temporal lobes

Several studies also show an abnormal response of the hippocampus during encoding or during recall following encoding in patients relative to controls. Heckers et al (1998) showed less right anterior hippocampal activation in patients during recall following deep processing, but the opposite for recall following shallow processing, and no difference between deficit and non-deficit patient groups. Jessen et al (2003) showed less left anterior hippocampus activation during deep encoding, and increased right anterior hippocampal activation following the presentation of novel words, while

Barch et al (2002) showed impaired left anterior hippocampus and PHG activation during both an intentional encoding and working memory task (i.e. 2-back) in schizophrenic patients relative to controls. This pattern of results suggests a lateralisation in the hippocampus during encoding and retrieval (left for encoding and right for retrieval) along with reduced anterior hippocampus activation in patients in instances of encoding which requires 'semantic processing' or the retrieval of the semantic properties of items. With respect to the literature in healthy volunteers, this region may be linked to temporary maintenance of verbal information, the initial process of feature binding during a learning event or novelty detection (Barch and al 2002; Heckers et al 1998; Jessen et al 2003).

6.2.2.2.5 Parietal lobes

There is little evidence to suggest dysfunctional parietal response during encoding in schizophrenia. However, during the semantic encoding relative to baseline condition, Kubicki et al (2003) showed hyper-activation in patients relative to controls in a cluster extending from the left STG to the left inferior parietal lobes. This left parietal response was active in patients during both the non-semantic and semantic encoding condition, suggesting it was not specifically related to the accessing of semantic information (Kubick et al 2003). In addition to the increased activation in the frontal and temporal areas in patients during these conditions, Kubicki et al (2003) asserted that the accessing and storage of semantic and non semantic information was supported by the network of these regions, and a hyper-activation of this network may well reflect a disturbance in semantic memory. Ragland et al (2004) showed no differential activation in the left inferior parietal lobe (BA40) in patients relative to controls during encoding. However, patients did show left inferior parietal activation in the patient within group maps for the encoding of correctly recognised words, a region not activated for the same contrast in controls.

6.2.3 Functional imaging of verbal retrieval

The Burgess and Shallice (1996) model of episodic retrieval describes it as a two stage process: (1) identification and specification of retrieval cues and (2) monitoring of information retrieved with the aid of those cues. Functional imaging of episodic retrieval tasks typically involves the active recall of information that has been intentionally learned (i.e. word list learning task) when represented among

similar novel distractor items (i.e. old words versus new words) or following a cue (i.e. stem completion). This is normally through forced choice recognition tasks in order to minimise speech and movement during scanning. Investigation of the neural correlates underlying retrieval success and effort are fundamental issues in the cognitive neuroscience of memory. Furthermore, an understanding of these neural correlates can aid in informing investigations of similar processes in the brains of schizophrenic patients

6.2.3.1 Functional imaging of verbal retrieval in healthy volunteers

6.2.3.1.1 Frontal lobes

In healthy participants, a large number of studies demonstrate an increased response in the right APFC (BA10) during verbal episodic retrieval tasks. Using an event-related fMRI encoding and retrieval task, Buckner et al (1998a) showed activation in the right APFC for correctly recalled items (correct recognition and rejection), while Cabeza et al (2000) showed right APFC activation during a verbal retrieval task shortly before the presentation of a retrieval cue. Henson et al (1999) and (2000) showed a late bilateral anterior PFC activation during old versus new word recollection, while LDLPFC showed greater activation during correct low relative to correct high confidence recollection judgements (Buckner et al 1998a; Cabeza and Nyberg 2000; Henson et al 2000; Henson et al 1999a). Although right APFC activation during retrieval has since been characterised as an indicator of retrieval mode, where novel items are used to cue information about studied items, Henson et al (1999) also suggested that increased activation in this area might be analogous to a failure to consciously recollect the learning event associated with an item, prior to making a response based on familiarity. The recruitment of the right APFC later in time than other regions may additionally reflect it's involvement in a 'post' retrieval verification and monitoring of recovered items (Buckner et al 1998a; Rugg et al 1999; Rugg et al 1998) (Lepage 2000 as cited in (Dobbins et al 2003). Henson et al (2000) have also proposed a functional dissociation in the dorsolateral (DLPFC; BA 9/46), ventrolateral (VLFC; BA44/45/47) and anterior (APFC; BA10) frontal lobe sub-regions during verbal episodic retrieval (Henson et al 1999a). The DLPFC, which has previously been linked to the process of monitoring during working memory, may also be involved in the monitoring and maintenance of recently retrieved information, while the VLFC is described as responsible for response organisation,

based on the explicit retrieval of information from posterior association cortices. In order to demonstrate support for this theory, Henson et al (1999) used a verbal encoding and retrieval task manipulating types of encoding and retrieval. During encoding participants were instructed to remember the orientation or temporal position of some words presented in one of two lists. During retrieval, the 'inclusion' condition required recognition of whether or not a word had appeared previously, whereas the 'exclusion' condition required identification of the context in which the word had been encoded (i.e. spatial or temporal). Both DLPFC and VLFC were active during the 'exclusion' and 'inclusion' retrieval conditions. However, while the VLFC response was of equal magnitude in both conditions (and therefore insensitive to task instructions), the DLPFC response was greatest in the exclusion condition, reflective of a demand related recruitment (Henson et al 1999b).

6.2.3.1.2 Parietal lobes

Fletcher et al (1995) were among the first authors to identify activation in the posterior medial parietal lobe (at or near the precuneus) during episodic retrieval. While additional anterior medial parietal areas have also been reported during retrieval (Buckner et al 1996), the specific role of either of these regions was previously unclear, although authors did suggest they may be imagery related. Activation of the precuneus during retrieval of both auditory and visual, and both imaginable and abstract material, also suggests it may be a multimodal association area (Krause et al 1999). Coincident with LAPFC activation, Konishi et al (2000) showed left lateral and medial parietal activations in volunteers during correct recognition versus correct rejection of a verbal encoding and retrieval task (Konishi et al 2000). Henson et al (1999) and Dobbins et al (2003) both showed activation of a similar lateral parietal area during conscious source recollection (on the lateral border of the precuneus (BA19) in the former study, and including the supramarginal and angular gyrus in the latter study) (Dobbins et al 2003; Henson et al 1999a). Saykin et al (1999) showed activation of the left PPL during recognition of familiar relative to novel words, while Grady et al (2001) showed increased response in the bilateral IPL, an area normally recruited during short-term verbal working memory tasks (Grady et al 2001; Saykin et al 1999).

6.2.3.1.3 Temporal lobes

Medial temporal lobe (MTL) activation has previously been inconsistently demonstrated in functional imaging memory studies. This is perhaps due to the more likely MTL response during learning tasks that emphasise complex and meaningful associations between items, and in which the MTL have been shown to be critical to both encoding and retrieval processes. Daselaar et al (2004) demonstrated activation of the left MTL, including the PHG and hippocampal formation, during both successful word encoding and recognition of the same words (Daselaar et al 2004b). Similarly, Cabeza et al (2001) showed hippocampal activation during verbal true and false recognition and greater PHG activation for true than for false information (Cabeza et al 2001). This implicates the hippocampus in the activation of semantic information, and suggests a PHG involvement in the accessing of perceptual information (i.e. original features of a learned event). The PHG is thought to sub-serve memory formation and reactivation of memory traces, and several other studies have also shown left PHG (Dobbins et al 2003) and right PHG activation during successful retrieval of episode context (Eldridge et al 2000). Similarly, in a contrast of correct recognition and correct rejection during a verbal encoding and recognition task, Eldridge et al (2001) showed activation in the left fusiform/PHG (Daselaar et al 2001). This further supports the notion that the posterior MTL may be responsible for the reinstatement of the contextual features comprising a learned event, while the anterior MTL may act as a temporary store for retrieved semantic information.

6.2.3.1.4 Cerebellum

The cerebellum has been more consistently associated with verbal retrieval than encoding tasks in healthy volunteers. Schacter et al (1996) showed left cerebellar activation in both high and low cued recall conditions (high based on deeply encoded words, and low based on superficially encoded words) relative to baseline, in healthy volunteers (Schacter et al 1996a). Grasby et al (1993) showed cerebellar activity in healthy volunteers during both a sub-span (5 word lists heard in scanner) and supra-span recall task (15 word list heard in scanner) (Grasby et al 1993). Several other cued recall tasks (i.e. Petrides et al 1995, Backman et al 1997 as cited by(Desranges et al 1998)) have shown left cerebellar activation in healthy volunteers, while free recall tasks have shown mainly bilateral responses in this area (Desranges et al 1998). Conversely, Andreasen et al (1999) showed right lateral

cerebellar activity concomitant with left thalamic, frontal and parietal rCBF increase during the conscious free retrieval of an episodic memory in healthy volunteers (Desranges et al 1998). Desmond et al (1997) has hypothesised that superior cerebellar activation represents input from the articulatory control system in the frontal lobes, whereas posterior vermis activation may be associated with input from the phonological store in temporo-parietal areas. The cerebellum may be actively involved in the feed forward loop of information in the monitoring and retrieval of memories (Desmond et al 1997).

6.2.3.2 Functional imaging of verbal retrieval in schizophrenics

6.2.3.2.1 Behavioural performance

Behavioural performance on word recall tasks in schizophrenia is often mixed. This is understandable given the differences in encoding conditions, length, and nature of delay between encoding and retrieval, form of retrieval (i.e. free recall, cued recall or recognition) and the amounts of material to be recalled. Performance differences are therefore often due to differences in the levels of task difficulty. However, in functional imaging studies it is generally preferential to equate performance between patients and controls in order that ensuing response differences might be attributed to brain dysfunction, rather than poorer task performance, or unequal levels of perceived task difficulty. Several studies have demonstrated no differences in task performance between groups during imaging. Hofer et al (2003) showed high recognition performance during the presentation of 25 targets and 25 similar foils, in both acute and remitted schizophrenic patients and controls following a 50 item deep encoding task (Hofer et al 2003a; Hofer et al 2003b). Crespo-Faccoro et al (1999) showed no differences in a 15-word list free recall task of practiced or novel words (novel words presented 1 minute prior to spoken recall), and Ragland et al (2001) showed equivalent performance (although increased guesses in patients) in patients and controls during a 20-word recognition task (words were presented twice at least 15 minutes prior to recognition among 20 foils) (Crespo-Facorro et al 1999; Ragland et al 2001). However, several tasks show a reduction in the performance of patients with increasing task difficulty. Ragland et al (2004) altered their original task by increasing words by ten and placing a distractor task (i.e. n-back) between the encoding and recognition conditions, thus preventing word maintenance and rehearsal (Ragland et al 2004). Consequently,

patients showed greater difficulty than controls in correctly recognising than correctly rejecting items. Gur et al (1994) and Weiss et al (2004) also showed poorer recognition specificity (i.e. ability to reject word as novel) relative to sensitivity (i.e. ability to recognise word as familiar) in patients relative to controls. However, in Gur et al (1994), despite only 20 target words, their presentation among 80 similar foils may have made rejection of foils more difficult. This may be due to patients basing their recognition judgements on word familiarity, rather than explicit recollection. Weiss et al (2004) presented 80 targets among 80 foils (a larger number than in other studies), and encoding and recognition conditions were separated by a 15 minute delay period, both of which may have made the task more demanding (Gur et al 1994; Weiss et al 2004a). Similarly, in a graded word list recall task (varying from 1-12 items), Fletcher et al (1998) showed normal recall up to four words in patients, after which performance deteriorated relative to controls (Fletcher et al 1998). Barch et al (2002) showed poorer and slower recognition of words and faces in patients relative to controls, although both groups showed superior recall for verbal over non-verbal material (Barch and al 2002). Ganguli et al (1997) showed poorer free recall for the most recent words on a 12 word list relative to controls, but intact memory for words at the start of the list, suggesting intact long-term but poorer short-term verbal memory than controls (Ganguli et al 1997). Reduced spontaneous recall of information was also demonstrated by Andreasen et al (1996), who showed significantly poorer spoken recall of a novel story (administered 1 minute prior to scan) but no differences in memory for a practiced story (learned 1 week prior to scan and refreshed prior to entering scanner), in patients relative to controls (Andreasen et al 1997).

6.2.3.2.2 Frontal lobes

Several studies of word recall and recognition have shown reduced DLPFC, IFC and AC activation in schizophrenia patients relative to controls. In Hofer et al (2003) acute and remitted patients showed significantly less BOLD response in the bilateral DLPFC (BA9 & BA46) and right cingulate gyrus (BA32) when compared to controls (Hofer et al 2003a; Hofer et al 2003b). Crespo-Faccoro et al (1999) showed decreased rCBF in the left DLPFC and bilateral medial frontal cortex during practiced word recall and in the left IFC and right AC during novel word recall (Crespo-Facorro et al 1999). Fletcher et al (1998) showed the left DLPFC (BA46) to be continually activated in controls

throughout a graded list recall task, and patients with and without memory impairment showed similar activation in the recall of up to 4 words, beyond which point this area showed a decrease in activation in patients, presumably associated with task difficulty (Fletcher et al 1998). Barch et al (2002) reported reduced right DLPFC (BA9) activation in patients relative to controls during both a working memory (i.e. 2-back task) and recognition task. Barch et al (2002) suggest that although the left DLPFC is normally associated with monitoring and maintenance, the right DLPFC may have a similar role in this instance, by guiding the selection of strategy for the task. However, left DLPFC may be more common in verbal tasks due to the left lateralisation for language. This right hemisphere activation was specific to the working memory and recognition conditions, irrespective of material type. As such, the visuo-spatial nature of the n-back working memory task and the combination of words and faces for the recognition tasks may have resulted in greater right hemisphere activity. Interestingly, unlike controls, patients also failed to show significantly greater activation in the left IFC for word relative to face recognition, despite being an area typically associated with verbal recall (Barch and al 2002). Ganguli et al (1997) also showed smaller rCBF increases in patients relative to controls in the bilateral DLPFC and right AC during supra-span list recall versus fixation, while Ragland et al (2001) showed decreased rCBF in the left IFC (BA45), left middle frontal gyrus (BA8/9), and right AC (BA32) during recognition in patients relative to controls (patients minus controls contrasts were not computed) (Ganguli et al 1997; Ragland et al 2001). During an event-related fMRI encoding and recognition task, Ragland et al (2004) showed less right DLPFC (BA 9) in patients relative to controls during correct recognition relative to correct rejection, while patients exhibited a greater bilateral response in the OFC (BA 11) and left SFC (BA 8). An absence of right DLPFC (BA9) on the within group maps of patients during correct recognition suggests that poor correct rejection may in part be attributable to a failure in retrieval monitoring normally ascribed to this brain region. These findings also differ from the previous study (2001) in that the left middle frontal gyrus (BA8/9) activity appears normal, and the previous reduced activation in the mesial temporal cortex appears greater in patients than controls (Ragland et al 2004). These differences may be indicative of differences in neuroimaging techniques. Alternatively, the latter paradigm's inclusion of a distractor task and increased time between encoding and retrieval may have altered the demands of the memory task and ensuing activations. Interestingly, Hofer et al (2003) showed increased

bilateral APFC (BA10) and left sensorimotor cortex (BA6) activation in acute schizophrenic patients relative to controls during word recognition following a deep encoding task. Given the small intervening period between encoding and recognition conditions, patients may have held the semantically processed information in working memory briefly before engaging retrieval processes. The authors therefore attribute the greater right APFC activation in patients to retrieval success. However, this activation may also be due to response uncertainty, and enhanced monitoring processes prior to selection (Hofer et al 2003b). Andreasen et al (1996) showed reduced rCBF in patients relative to controls, in the left anterior and right medial frontal lobes during the practiced story recall task (on which performance in both groups was not significantly different). During the novel story recall task frontal rCBF deficits were only apparent in the left frontal operculum and AC (Andreasen et al 1996).

6.2.3.2.3 Temporal lobes

Andreasen et al (1996) showed no temporal lobe rCBF deficits in patients relative to controls during a practiced story recall task. However, during the novel story recall task, patients showed less rCBF in the bilateral anterior temporal lobes and AC (Andreasen et al 1996). Both Hofer et al (2003) and Ganguli et al (1997) showed reduced lateral temporal cortex (BA21/22) activation in patients relative to controls during recognition and recall respectively. This temporal region may be linked to semantic processing, given that Wernicke's area (BA21/22) is reportedly the loci of stored information relating to the meanings and semantic properties of words (Ganguli et al 1997; Hofer et al 2003a; Hofer et al 2003b). Barch et al (2002) showed no significant difference between left temporal activation for word recognition relative to face recognition, despite a significantly greater activation for this region in this contrast for controls. This is possibly evidence for a diminished laterality for language in the patient group. In the same way, it may also reflect greater dysfunction in the left hemisphere brain networks supporting verbal processing (Barch and al 2002; Gur et al 1994). In Fletcher et al (1998) the STG showed a task related decrease in controls, unlike the linear increase in activation in this area in patients, which was unrelated to the performance of the task (Fletcher et al 1998). Furthermore, in the same task, Fletcher et al (1999) showed PFC and AC activity to significantly predict STG activation decrease in controls, although this pattern was not apparent in the patients. The authors suggest that

the interaction between the PFC and AC might modify activity in the STG. The functional deficits demonstrated in schizophrenia may be related to the failed interaction or connectivity between frontal and temporal regions and the AC (Fletcher et al 1999). This corresponds to a finding in Jennings et al (1998), showing negative effective functional connectivity between the left IFC, left AC and left STG in patients, the opposite pattern to that shown in controls. This further supports the notion that schizophrenia is characterised by abnormal fronto-temporal connectivity, mediated in part by AC activity (Jennings et al 1998).

6.2.3.2.4 Medial temporal lobes

Ragland et al (2001) showed reduced mesial-temporal activation in patients relative to controls during recognition, while in Ragland et al (2004) patients showed increased PHG activation compared to controls during correct recognition relative to correct rejection. This is an unexpected finding, given that PHG involvement in retrieval in healthy volunteers is normally associated with retrieval of contextual features of a learning event. This region was not apparent in either of the within group maps for this contrast, suggesting that it is the result of an interaction effect (Ragland et al 2001; Ragland et al 2004). Jessen et al (2003) showed less bilateral hippocampal activation during word recognition in patients relative to controls, and Weiss et al (2004) demonstrated bilateral hippocampal activation in both old and new events relative to baseline in both groups. However, there was greater right posterior hippocampal response in patients during old relative to new events, a response not apparent in controls. Conversely, controls, but not patients showed increased right anterior hippocampal response during new relative to old events. Weiss et al (2004) suggest that the correlation in patients only, between false alarm rate and right hippocampal activation, implies impaired novelty detection in this patient group (Jessen et al 2003; Weiss et al 2004a).

6.2.3.2.5 Parietal lobes

Ragland et al (2004) reported reduced left IPL and superior parietal activation (BA7) in patients relative to controls during correct recognition, although patients showed enhanced activation relative to controls in a proximal cluster (precuneus, BA7) (Ragland et al 2004). Weiss et al (2003) also reported increased activation in the precuneus in patients relative to controls during new events at

retrieval (Weiss et al 2003). Fletcher et al (1998) showed parietal differences between controls and patients who were both impaired and unimpaired on the graded recall task. Specifically, unimpaired patients and controls showed increased activity in the PPL, whereas impaired patients did not. Moreover, the task related decrease apparent in the IPL in controls was not demonstrated in the patient groups, similar to the effect apparent in the STG (Fletcher et al 1998). This is perhaps consistent with findings in the verbal working memory tasks, which show a linear increase in these areas during tasks of increasing difficulty, with an eventual reduction in activity when capacity is breached. It is possible that activation in the IPL is compensatory for the failed recruitment of the left DLPFC, while at the same time being capacity dependent, and therefore sensitive to increases in memory load. Barch et al (2002) showed no significant difference between left parietal (BA7) activation for word recognition relative to face recognition, despite a significantly greater activation in this region for the same contrast in controls (Barch and al 2002). Finally, Hofer et al (2003) showed left inferior parietal (BA40) activation in the within group contrast map of schizophrenic patients in remission and in a separate study in acute schizophrenic patients, during verbal recognition relative to baseline. Although this area was not apparent in the within group maps of controls, it did not emerge as an area of significant differential activation between the groups (Hofer et al 2003a; Hofer et al 2003b). The evidence therefore, seems to indicate a general compensatory hyper activation of the parietal lobes in schizophrenic patients during verbal retrieval.

6.2.3.2.6 Cerebellum and thalamus

Few of the recall tasks report cerebellar activation differences, while the thalamus is consistently implicated. Barch et al (2002) showed significantly greater right thalamus activation in controls relative to patients during both a working memory and recognition task, while Ganguli et al (1997) identified greater left thalamus activation in controls relative to patients during supra-span verbal recall. Evidence suggests the thalamus may act as a filter to 'online' sensory information, by mediating between the cerebellum and frontal regions (Andreasen et al 1999; Barch and al 2002; Ganguli et al 1997). Crespo-Faccoro et al (1999) showed decreased rCBF in the left thalamus and left cerebellum during practiced word recall and in the right thalamus and bilateral cerebellum during novel word recall (Crespo-Facorro et al 1999). Andreasen et al (1996) showed the same pattern of

fronto-thalamic-cerebellar rCBF in both patients and controls, but rCBF was reduced in the thalamus and bilateral cerebellum in patients relative to controls during the practiced story recall task (on which performance in both groups was not significantly different). During the novel story recall task, rCBF deficits were apparent in the right thalamus, bilateral lenticular nuclei and bilateral cerebellum (Andreasen et al 1996). This group have since proposed that a fundamental deficit in schizophrenia is a failure in the meta-process of monitoring and coordination of cognition or 'cognitive dysmetria' due to defective circuitry in the fronto-thalamic-cerebellar network. This model has been borrowed from neurology, where dysmetria normally refers to the failed synchrony of motor movement (i.e. the rapid updating of input and output to guide motor actions), controlled by a multiple nodal feedback loop, the cortico-cerebellar-thalamic-cortical circuit (Andreasen et al 1999).

6.2.4 Functional imaging of word generation

Word generation or verbal fluency tasks require the covert or overt generation of words from auditory or visual letter or exemplar cues. Due to the planning, search, and retrieval aspect to these tasks, they are often classed as tests of both executive function and semantic memory retrieval.

6.2.4.1 Functional imaging of word generation and classification in healthy volunteers

6.2.4.1.1 Frontal lobes

In healthy volunteers, semantic memory retrieval tasks (regardless of stimulus modality) elicit mainly left lateralised activations in the PFC. The left dorsal, posterior and inferior frontal activations (BA44, BA46, BA9) predominantly associated with generation tasks, are possibly reflective of language processing, covert articulation and working memory maintenance operations (McCarthy et al 1993) and up until recently were considered to guide access to information relevant to the task and permit evaluation of this information. This is reflected in evidence for decreases in left IFC activity associated with repeated access to information pertinent to the task in hand (Demb et al 1995; Kapur et al 1994). Thompson-Shill et al (1997), on the other hand, suggest that left IFC activation (in both classification and generation tasks) does not mediate access to information for semantic processing, but instead mediates the response/semantic knowledge *selection* in the presence of competing knowledge, necessitated by the demands of the task (Tempini et al 1998; Thompson-Schill et al 1997).

By varying selection demands in a semantic decision task, the authors showed LIFC activation in conditions of high selection, where items were compared on one semantic feature of similarity, as opposed to conditions of low selection, where items were compared on global features of semantic similarity (Thompson-Schill et al 1997). In a similar vein, Wagner et al (2001) proposed that the LIFC was responsible for the 'controlled' retrieval from semantic memory in instances where automatic retrieval is precluded. This might occur in situations where semantic association between encoded items is weak and recovery of target information is not immediately facilitated by the presence of an associate, or when competition from irrelevant information places a greater load on top-down processes (Wagner 2001). More generally, the functional heterogeneity of the left IFC is important. VLFC activations (BA45/46/47) have been shown to be common to both generation and classification, while the left dorsal-lateral IFC (BA 44) has been shown in studies of inhibition and selection resolution (Jonides et al 1998b; Thompson-Schill et al 1997) or in tasks requiring forms of phonological control (Fiez et al 1996). Conversely, ventro-medial frontal activations (BA 11, 32) appear to be specific to classification tasks only and may be associated with decision making processes (Cabeza and Nyberg 2000; Pilgrim et al 2002; Thompson-Schill et al 1997). The distinction between types of word generation tasks is also an important one. Mummery et al (1996) showed rCBF to be greater in left temporal regions during semantic relative to letter fluency, whereas the left IFC (BA44/6) showed greater response for the reverse contrast (Mummery et al 1996). Paulesu et al (1997) showed overlapping as well as differential areas of activation in the left IFC during an fMRI study of letter and category fluency. In the letter fluency condition only, there was an activation in the posterior opercular portion of the left IFC, but in the category fluency condition only, a response was shown in the left retrospleniel area (Paulesu et al). Drager et al (2004) showed the typical left IFC (BA 45/47) and middle frontal gyrus (BA 6/8/9) and AC (BA32) activation, along with activation of the left IPL, caudate and right cerebellum, during the retrieval of as many words as possible following the cue of a word beginning. However, only the right IPL (BA40) and right superior parietal lobe (BA7) showed increased activation with increased difficulty (i.e. easy, moderate, and difficult to complete word stems). Otherwise, there were no changes in activation or reduction in laterality in these language related areas concomitant with moderated task difficulty. Fu et al (2002) reported similar areas of activation during an fMRI verbal fluency task, using sets of both 'easy' (e.g. T, L and

S) and 'hard' letter cues (e.g. O, A and G). During the hard relative to easy letter cue conditions however, volunteers showed an enhanced response in the left AC (BA32), and during easy relative to hard, in the right cerebellum and occipital areas (BA18) (Fu et al 2002). This provides additional evidence for the recruitment of the dorsal anterior cingulate in tasks requiring increased attention due to elevated difficulty (Paus et al 1998).

6.2.4.1.2 Temporal lobes

Coincident with increased prefrontal activation are decreases in activation of the right or bilateral STG during word generation tasks, with in some instances a noted negative correlation between the left DLPFC and the right STG (Frith et al 1991; Warburton et al 1996). Frith et al (1991) postulate that the STG may be an area involved in the storage of word representations which is mediated and controlled by the left PFC (Frith et al 1991). Pihlajamaki et al (2000) showed activations in the left MTL, including the hippocampus and PHG during semantic word generation in volunteers. Given that most word generation tasks do not require semantic association, this MTL activation may be specific to semantic fluency tasks only. Authors suggest the fusiform gyrus, PHG and hippocampus may act in concert to retrieve semantically associated words (Pihlajamaki M et al 2000). Mummery et al (1996) provide additional evidence of the specific fronto-temporal activations during semantic relative to letter fluency tasks, providing support for the suggestion that temporal areas important for word 'meaning' are accessed during the former task only.

6.2.4.1.3 Parietal

Left lateral parietal activation (BA39/40) has been commonly demonstrated in word generation tasks (i.e. Frith et al 1991 and Warburton et al 1996 as cited in (Cabeza and Nyberg 2000)). However, a number of categorisation tasks also show left lateral parietal response (i.e. Price et al 1997 as cited in Cabeza and Nyberg 2000). This suggests that this area is probably involved in the accessing or holding of meaning based information about items. This is interesting given the hypothesised role of this region in phonological storage during the retention component of verbal working memory, but considered unlikely to be associated with the semantic coding of words (Jonides et al 1998a). Thompson-Schill et al (1997) showed a left parietal activation (BA7) during a high versus low

semantic word and picture memory selection condition, which may reflect the usage of imagery during the high selection condition (Thompson-Schill et al 1997). Drager et al (2004) allows for a more prosaic interpretation of IPL activity during word generation tasks. While left IFC, left middle frontal and left IPL language related areas showed similar activation during both 'easy', 'moderate' and 'difficult' stem cue conditions, the right IPL (BA40) and right superior parietal lobe (BA7) showed an enhanced response during the retrieval of words in the hard relative to easy cue conditions. The authors suggest IPL activation reflects the maintenance of more difficult word stem representations in the phonological store for a longer duration than those stems for which words would be retrieved quickly. This implies that right lateralised parietal activations support performance response to increased task difficulty. This interpretation is compatible with fMRI studies of selective attention, which show an increased response of the IPL with increased demands on auditory selective attention (Pugh et al 1996; Shaywitz et al 2001)

6.2.4.2 Functional imaging of word generation and classification in schizophrenics

Functional MRI during word generation/verbal fluency experiments in patients with schizophrenia were traditionally employed as a means of exploring frontal lobe integrity, given this task's considerable executive component (Artiges et al 2000). Ingvar and Franzen's reportage of reduced frontal activation relative to posterior activation in a schizophrenic group was the first indication in this population of what has now been termed hypofrontality (Bullmore et al 1999). Word classification tasks have been used most often as a form of deep or 'incidental episodic encoding' to facilitate later episodic recall in studies comparing patients with schizophrenia and controls.

6.2.4.2.1 Behavioural performance

Behavioural measures of fluency in neuroimaging tasks are often conducted prior to scanning due to the paced nature of the tasks administered during imaging, or the additional component of sub-vocal articulation (i.e. to reduce head motion) precluding behavioural measurement. In a phonological fluency task, participants are cued by a letter (e.g. F, A or S) and asked to generate as many words as possible beginning with that letter. Curtis et al (1998) and Weiss et al (2004) both showed equivalent performance on a verbal fluency task in patients and controls, prior to scanning (Curtis et al 1998;

Weiss et al 2004b). During a paced phonological fluency task, Fletcher et al (1996) showed patients to produce non-significantly fewer and slower responses and more passes than controls, while Yurgelun-Todd et al (1996) showed equivalent performance and Spence et al (2000) reported satisfactory performance of all groups (Fletcher et al 1996; Spence et al 2000; Yurgelun-Todd et al 1996). In a verbal initiation task adapted from the Hayling Sentence Completion Test, participants were required to covertly generate a word, which sensibly completed a sentence with the last word missing. Lawrie et al (2002) showed increasing response time and word inappropriateness with increasing sentence constraint (i.e. ambiguity of sentence) across both groups, although schizophrenic patients were significantly slower to respond and produced significantly less appropriate words relative to controls (Lawrie et al 2002a). Similarly, in a verb-generation task, Sommer et al (2003) showed equivalent performance between patients and controls. However, in the additional reverse-read task, participants were required to read words spelled from right to left, vocalise that word, and press a button if considered an animal. This places an emphasis on phonological encoding, thus avoiding direct orthographic word recognition. Patients showed worse performance on reverse read relative to controls (Sommer et al 2003a).

6.2.4.2.2 Frontal lobes

Although some studies employing word generation tasks have shown attenuated frontal activation in schizophrenics relative to controls (Artiges et al 2000; Curtis et al 1998; Yurgelun-Todd et al 1996) others have shown equivalent levels of left frontal activation in both groups (Lawrie et al 2002a)or increased right frontal activation in patients relative to controls (Sommer et al 2003b; Weiss et al 2004b). Curtis et al (1998) showed increased rCBF in controls relative to patients in the left IFC and left DLPFC. Spence et al (2000) showed no differences in functional connectivity between the left DLPFC and STG, but reduced connectivity between the left DLPFC and the AC (Curtis et al 1998). Dye et al (1999) showed no differences in frontal response in asymptomatic schizophrenic patients, remitted bipolar patients and controls during a verbal fluency task (Dye 1999). Similarly, Lawrie et al (2002) showed equivalent levels of bilateral DLPFC, but in the functional connectivity analysis lower correlation between the left DLPFC and left middle/STG in patients than in controls. This correlation was also lower in those patients with auditory hallucinations relative to those without, possible

evidence for increased fronto-temporal connectivity in schizophrenia, which may be related to the disease state (Lawrie et al 2002a). Spence et al (2000) might have failed to demonstrate a similar relationship due to the smaller number of hallucinating patients in their sample. Weiss et al (2004) showed patients to bilaterally activate the frontal cortex, unlike control participants who typically show left lateralised activations during verbal fluency (Weiss et al 2004b). Artiges et al (2000) also reported reduced left and greater right hemisphere rCBF in patients relative to controls. This parallel right hemisphere activation was also associated with reduced verbal fluency performance in the patient group, and may therefore reflect attempts at compensation for lower left hemisphere activation (Artiges et al 2000). In both studies this was posited as an indication of diminished language lateralisation in patients with schizophrenia, a hypothesis endorsed by Crow and others (Crow 2000; Weiss et al 2004b). However, this could equally reflect a failure to inhibit areas not involved in language processing (Sommer et al 2003a) or as discussed, an effort based recruitment of additional areas of the prefrontal cortex.

6.2.4.2.3 Temporal lobes

Other evidence supports the notion that patients with schizophrenia (both medicated and unmedicated (Fletcher et al 1996) fail to 'deactivate' the STG in the manner apparent in healthy controls during word fluency tasks, and that this may reflect a dysconnectivity between the left DLPFC and STG, or a failure of one area to suppress the activity of the other during this task (Fletcher et al 1996; Frith et al 1995; Spence et al 2000; Yurgelun-Todd et al 1996). However, this has not been consistently demonstrated. Spence et al (2000) showed only a failure to 'deactivate' the precuneus in patients with schizophrenia relative to controls, while Dye et al (1999) showed bilateral decreases in the STG during verbal fluency in both schizophrenic and bipolar patients (Dye 1999). Conversely, Fletcher et al (1996) showed both a failure to 'deactivate' the STG and AC in patients compared to controls in a paced verbal fluency task (Fletcher et al 1996; Spence et al 2000). This is supported by a study by Dolan et al (1996) which showed decreased AC activation in patients during a verbal fluency versus word repetition task, but which was consequently modulated by apomorphine. The latter finding was interpreted as apomorphine's modification of brain activity through normalisation of AC activity, due to the dopaminergic antagonistic effects of the drug (Fletcher et al 1996).

Curtis et al (1998) also compared activations between patients and controls in a semantic decision (living versus non-living classification) task. Although the patients were shown to activate all areas to a greater extent than controls, the attenuated frontal response was evident only in the verbal fluency task, while ventro-occipital-temporal areas were more greatly activated in patients during the semantic decision task. The authors assert that the convergent frontal activation results may reflect differences in task difficulty (where verbal generation is more taxing than classification), whereas non-dominant language area activation may be a compensatory recruitment to meet the demands of the task (Curtis et al 1998). In a similar classification task when compared with a basic letter-scanning task, Jennings et al, (1998) showed greater rCBF in patients relative to controls in bilateral STG (BA21) and the left APC (BA10), but less in right BA 10, right precuneus (BA 7), left thalamus and left occipital cortex (Jennings et al 1998). Path analysis (i.e. effective connectivity, which demonstrates the correlations between regions within a brain network) showed negative reciprocal connections in schizophrenic patients between the right and left frontal cortex (BA 10, 45) and the between the former regions and the temporal cortex (BA 22, 32), the opposite pattern to that shown in healthy controls (Jennings et al 1998). This again suggests a possible fronto-temporal network functional dysconnectivity in the brains of patients with schizophrenia.

6.3 Functional Imaging of cognition in people at genetically enhanced risk for schizophrenia

There are only a few extant functional neuroimaging studies, which have investigated functional brain activation differences in relatives of patients with schizophrenia, compared to controls. Spence et al (2000) reported no differences in rCBF in ten unaffected obligates (mean age 55.4 years) (i.e. unaffected middle aged carriers of a predisposition for schizophrenia with an affected parent and child) relative to ten matched controls during a PET study of paced phonological verbal fluency (Spence et al 2000). The mean age of the obligate sample placed most members of the group out-with their period of maximum risk for development of the disorder. Moreover, the obligates were an exclusive group, who in spite of their multiply affected first-degree relatives are highly unlikely to develop the disorder. This, combined with the ease of the task (paced phonological fluency is unlikely

to challenge this group) may explain the lack of functional differences between the obligates and controls.

Several studies have in fact reported hypofrontality in unaffected relatives across memory and executive function tasks. Keshavan et al (2002) showed decreased DLPFC (BA9/46) and IPL (BA40) activation in four young (mean age 13.25 years) offspring of schizophrenics (two males and two females) relative to four age and gender matched controls during a spatial working memory task (i.e. memory guided saccades task) (Keshavan MS et al 2002). This particular study should however be considered with caution, given the small number of participants scanned and the fact that two of the four high-risk participants were diagnosed with Attention Deficit Hyperactivity Disorder, and one with major depression. Macdonald et al (2003) also reported (in abstract format only) reduced left DLPFC activity in first episode schizophrenic patients and their relatives during attempted inhibition of response in a spatial variant of the Stroop task. The age of these participants and further study details were however not available due to the abstract format, thus precluding a definitive criticism of this study (MacDonald et al 2003a). Blackwood et al (1999) used SPECT to compare brain perfusion maps between high-risk participants and controls. They revealed reduced perfusion in the left IFC (BA47) and AC, and bilaterally increased perfusion in the internal capsule (sub-cortical region) in high-risk participants and schizophrenic patients relative to controls. However, neuropsychological performance on verbal and visual memory tasks and a verbal fluency task did not correlate significantly with perfusion in any brain regions, unlike in the schizophrenic patient group (Blackwood et al 1999).

In the EHRS, Whalley et al (2004) compared first and second-degree relatives of schizophrenics and controls during an fMRI study of covert word generation in a task adapted from the Hayling Sentence Completion Test. This requires the covert generation of words to sensibly complete sentences presented with the last word missing. During a parametric contrast controls showed greater increases with increasing task difficulty in the right medial prefrontal cortex (BA6), AC, thalamus and left posterior cerebellum. Furthermore, high-risk participants who had experienced isolated psychotic symptoms showed greater activation than controls and those without symptoms during sentence

completion relative to rest in the left intraparietal sulcus (BA40) (Whalley et al 2004). This is an important study given that most participants are not yet out-with their period of maximum risk for development of the disorder. Moreover, a proportion of this high-risk group has subsequently developed schizophrenia. It is plausible therefore that some response differences are precursors to the development of schizophrenia in these individuals.

Hyperfrontality has also been demonstrated in unaffected relative groups. Callicott et al (2003) showed an exaggerated response in the right DLPFC in siblings of schizophrenics (mean age 38 years) relative to controls during a working memory task (i.e. n-back) (Callicott et al 2003). Thermenos et al (2004) used two versions of an auditory continuous performance test (baseline low load vigilance task and high load auditory working memory task) during fMRI in non-psychotic first-degree relatives of schizophrenics (mean age 35.5 years) and controls. Relatives showed equivalent performance to controls on the low load working memory task (respond to A following Q), but significantly poorer performance on the high-load condition (respond to A only when preceded by Q separated by 3 other letters). Relatives showed a greater response in the left DLPFC and anterior and dorso-medial thalamus relative to controls during the high load working memory task relative to the baseline vigilance task. However, after controlling for task performance, response differences were apparent only in the AC (Thermenos et al 2004b). Both studies highlight the more limited capacity of the working memory system in relatives of schizophrenics compared to controls and the deficient task performance due to increasing working memory demand analogous to the increasing DLPFC response.

Although these individual studies manipulate different aspects of cognition, consistent areas of aberrant activation relative to healthy controls have emerged, and reflect a similar profile to patients of fronto-temporal and fronto-thalamic-cerebellar network dysfunction, as well as an inferior parietal lobe hyperactivity in one study, which is possibly specific to at risk subjects predisposed to psychotic symptoms, and some of which may be in the early stages of psychosis onset. Moreover, results from parametric tasks (Callicott et al 1999), suggest that the non-linear inverted U shaped profile of DLPFC response may be shifted slightly leftwards in both schizophrenic patients and their unaffected

biological relatives, compared to controls. This implicates deficiency of response in the DLPFC as a putative indicator of genetic liability to schizophrenia

6.4 Summary of the functional neuroimaging of memory in people with schizophrenia and their unaffected relatives

Imaging results suggest a clear overlap in recruited and aberrant brain regions across verbal working memory, verbal episodic encoding and retrieval, semantic retrieval and verbal phonological fluency tasks. This implies dysfunction in shared brain networks responsible for higher general cognitive processing. Findings of frontal lobe abnormality in schizophrenics and to some extent in their unaffected relatives during tests of verbal memory may implicate the aberrant function of the DLPFC as a potential indicator of genetic vulnerability to schizophrenia. The DLPFC, hypothesised as responsible for the monitoring and control of 'online' transient material, shows the normal increased activation with tasks of increasing load or difficulty in patients, but a deficiency at lower capacity loads than controls. This suggests the breaching of capacity limits earlier in time than controls. Most studies report predominantly left DLPFC activation differences, possibly due to the verbal nature of the tasks, although right DLPFC deficiencies have also been reported. Structural studies suggest the left may be important in executive tasks and the right in the allocation of attention. Bilateral DLPFC response in patients relative to left lateralised DLPFC response in controls may additionally be an indication of reduced laterality in schizophrenia.

While the dorsal areas are loosely linked to general executive control, ventral areas are considered important in memory ability. Left IFC (BA44/45) reductions in patients during verbal working/immediate memory tasks may be indicative of poor articulatory control or verbal rehearsal in the hypothetical phonological loop (Broca's area). However, the left VLFC (BA45/47), an area anterior to Broca's area (BA44), has also been identified as deficient in schizophrenia, particularly during verbal encoding tasks. Evidence from the literature in healthy volunteers suggests this area may be involved in the semantic processing of verbal material, the accessing of online information related to word meaning and the strategic organisation of material, enabling successful contextual recall. This is likely, given this area's strong reciprocal connections with the STG (BA22), also

known as Wernicke's area and related to stored semantic information about words. Usually the left IFC (e.g. BA44/45) appears normal in schizophrenia during word generation tasks. This may be attributable to the phonological nature of the paced verbal fluency tasks, which are unlikely to require the generation of semantic information.

One study (i.e. verbal retrieval) showed reduced right APFC (BA10) activation, and another increased right APFC activation in patients relative to controls. However, this may be due to the focus on correct recognition events versus correct rejection events in the former study, and successful retrieval following deep encoding and brief delay to recall in the latter. This area is hypothesised as responsible for supervision of the switching between specifications of search parameters (i.e. cues-VLFC) and monitoring of retrieved information from the search (i.e. DLPFC). This may therefore reflect an enhanced monitoring of material prior to responding.

Verbal memory tasks placing an emphasis on the online maintenance and storage of verbal information show enhanced IPL (BA40) and PPL (precuneus, BA7) activations in patients relative to controls. This is often accompanied by hypofrontality, though equally hyperfrontality is apparent when the demands of the task require integration of both areas. It is thought these areas may therefore be recruited to compensate for failed frontal integrity, especially in verbal tasks of increasing difficulty.

The temporal lobes have integral connections to the PFC. Reduced lateral temporal (BA21) activation during semantic encoding in schizophrenia may reflect poor semantic processing. The increased STG (BA22) activations are often concomitant with reduced PFC response during verbal memory tasks in schizophrenia, although the opposite pattern is also reported. This may be a reflection of abnormal connectivity between these regions. Winterer et al (2003) suggest the relationship between the two may be reduced during general information processing (negative connectivity), but enhanced rather than inhibited (as in controls) during maximum activation (positive connectivity). The consistent implication of the cingulate gyrus, suggests this area may also play a role (possibly modulatory/attention related) in this network.

Impaired hippocampal activity during both verbal encoding and retrieval processes in schizophrenia are consistent with the literature on structural deficits in the MTL in schizophrenia. However, hippocampal activation across PET and fMRI studies of memory is not always consistent. This is possibly due to the lower temporal resolution of PET compared to fMRI, and the differences in tasks administered. The small intervening period between most encoding and retrieval tasks (in order to reduce time within the scanner) may enable the maintenance online of recently learned material, and therefore may not be 'long-term memory tasks' in the true sense. Indeed, evidence suggests the hippocampus may be more integral to tasks requiring conscious retrieval of contextual features, rather than simple recognition often driven by familiarity based decisions. The PHG on the other hand may be more important for recognition tasks, but is implicated in both familiarity and recollection decisions (Eldridge et al 2000). Finally, Fletcher et al have suggested that the absence of hippocampus involvement in some tasks may be due to the continuous activation of this area throughout (Fletcher et al 1997).

Finally, attention has been less focused on cerebellar activity during cognition in schizophrenia. This is possibly due to a lack of clarity over the role of this area in cognition, given that up until recently it has been considered specific to motor control, and not to higher cognitive processes. Evidence from recent functional imaging studies does suggest an abnormal response in this area in schizophrenia. Moreover, it is suggested this may be part of a network with less connectional integrity than that apparent in controls (i.e. fronto-thalamic cerebellar network). Evidence for reduced thalamic volume in schizophrenia, and aberrant thalamic functional activation during verbal retrieval tasks, further supports this theory. Schlosser et al (2003) explored effective connectivity (i.e. regional correlations) in schizophrenic patients and controls during a verbal working memory task (i.e. n-back). Patients showed a pattern of reduced connectivity in the PFC-cerebellar and cerebellar-thalamic limbs, and increased connectivity in the thalamo-cortical limb of the cortico-cerebellar circuit, which may be an area of compensatory strengthened connections. The lower right VLPFC to right DLPFC, and left parieto-frontal path coefficients in patients treated with atypical anti-psychotic medication relative to those medicated with typical anti-psychotics, may in fact imply enhanced functional efficiency in the former group (i.e. fronto-parietal connectivity was not different between patients and controls, and is a

feature perhaps of differential responses in the two patient groups and hyperactivity in the typical anti-psychotics group to maintain satisfactory performance). Importantly, the cerebellum is now assumed to play a role in the timely relaying of information to the temporo-parietal and frontal lobes to aid in memory search and retrieval.

6.5 Aims and hypotheses of investigation 5

6.5.1 Functional MRI of verbal encoding and retrieval in high-risk participants and controls, using a word classification and recognition task

The brief review of the literature concerning structural brain deficits in schizophrenia details a diversity of volumetric differences between patients and controls, including frontal and medial temporal lobe abnormalities. Functional neuroimaging during verbal memory tasks in schizophrenia has also shown activation deficiencies in fronto-temporal, fronto-parietal and fronto-thalamic-cerebellar regional brain networks. Although similar deficits may also be apparent in individuals at enhanced genetic risk for development of the disorder, there are only a few studies and less still have addressed the functional neuroimaging of unaffected relatives not yet out-with their period of maximum risk for the development of schizophrenia.

Given the results of our four previous experiments, and our systematic review of memory in relatives of schizophrenics, we are able to conclude that there are verbal memory deficits in close relatives of schizophrenic patients, albeit less severe than those apparent in schizophrenia, which could be considered indicators of vulnerability to schizophrenia. It could also be inferred that deficits partly arise from the impaired executive control of strategic encoding processes, and retrieval difficulties precipitated by the impaired reactivation of less efficiently processed material. While there is weak evidence for early state deficits in relatives of schizophrenics, in some instances there may be a pattern of slightly reduced performance relative to those high-risk participants without psychotic symptoms. This suggests that psychotic symptoms do not significantly interfere with neuropsychological performance. However, it is conceded that the sensitivity of fMRI may enable a more effective discrimination between those at genetic risk with and without the experience of psychotic symptoms around the time of scanning.

To investigate more thoroughly the issue of biological vulnerability to schizophrenia, with respect to underlying verbal memory processes, an event related fMRI verbal encoding and retrieval task was used with high-risk participants with one or more first or first and second degree relatives of schizophrenia patients, with or without isolated psychotic symptoms and healthy controls. This allowed the direct comparison of these groups in order to analyse independently any trait effects, and any differential responses which might be attributed to the experience of transient or partial psychotic symptoms at the time of the scan (mild state effects).

The explicit encoding task was a semantic classification task, which has been used consistently in studies of verbal memory, both in schizophrenic patients (Curtis et al 1998; Jennings et al 1998) and in healthy volunteers (Kapur et al 1994). Word processing was therefore additionally facilitated during the semantic classification (living vs. non living decision) of a limited number of words.

The retrieval task involved the recognition among similar lures, of those words previously presented during the classification task. Reliable activation differences between old versus new words were previously shown in blocked design tasks with healthy volunteers, and were interpreted as indicators of retrieval success (Buckner et al 1998b; Henson et al 1999b). However, later event related fMRI tasks using the same contrast showed no such differences (Buckner et al 1998a; Schacter et al 1997), and suggested that the increased prefrontal response reported within blocked design tasks, may be due to participant 'expectancy', and the predictability of responses within trial blocks. It was also suggested that differences may be due to a state and not item related effect, or that event related fMRI was less sensitive to differences between event types (Friston et al 1999b). Subsequent event related tasks have since shown activation differences for correct old versus correct new word contrasts. Saykin et al (1999) showed increased right dorsolateral prefrontal cortex response during old relative to new responses, while Henson et al (1999) showed increased right and left frontal response during recollected events in a remember/know memory task (Henson et al 1999a; Saykin et al 1999). Konishi et al (2000) and Kahn et al (2004) also showed increased activation in the left inferior parietal, left anterior frontal, left thalamic and left precuneus during correct old relative to correct new

responding (Kahn et al 2004; Konishi et al 2000). Given the nature of this task, it was firstly hypothesised that all groups would show equivalently high levels of accuracy during both word classification and episodic retrieval. This would mean that any ensuing differences could be attributed to a qualitative group difference in the BOLD fMRI response, rather than the demands of the task.

Within the confines of the task therefore, increased BOLD responses in the frontal, temporal, and parietal lobes and cerebellum, in the high-risk group relative to controls during the word classification and episodic retrieval tasks, were hypothesised. This is based on an understanding of the role of these areas in the support of both encoding and retrieval processing, and previous neuroimaging evidence for their functional deficiency in schizophrenics and to a lesser extent in their biological relatives. Reduced activations in patients, particularly in the frontal cortex, tend to reflect impaired cognitive performance. In this group however, we predicted that enhanced activations might be associated with increased efforts, especially in order to successfully perform the task.

Any BOLD fMRI response differences between groups could therefore be interpreted as follows: (1) a reflection of biological brain differences between people with and without a genetic predisposition for the development of schizophrenia (i.e. trait effect), or between those who are and are not experiencing transient psychotic symptoms (i.e. state effect); (2) in part related to (1), a reflection of compensatory biological brain responses due to a functional brain response deficiency, in order to achieve equivalent performance to the controls, or (3) a reflection of different memory strategy usage between groups (i.e. semantic or phonological encoding, explicit or implicit recollection, or recognition based on familiarity).

Chapter 7: Methodology Investigation 5

7.1 Design

In investigation 5, BOLD functional MRI responses associated with cognitive performance in an event-related verbal encoding (i.e. word classification task) and retrieval (i.e. recognition of old and new words) task were measured during a BOLD functional MRI scan in the first one hundred participants in the EHRS to undergo a scan. Participants were scored on response time and accuracy during the encoding and retrieval task and scores compared within and between the three groups (C, HR- & HR+) using one-way ANOVAs and mixed repeated measures ANOVAs. Functional MRI data were analysed in order to address our hypotheses (outlined in full in Chapter 6), using fixed and random effects to identify statistically significant areas of BOLD functional MRI response associated with word classification responses and correct old and new recognition responses within and between participant groups.

7.2 Participants

7.2.1 Participant sample

The details of high-risk sample recruitment were previously outlined in 2.1.2. The Edinburgh High Risk Study (EHRS) initially recruited a potential sample of 162 well individuals with at least one first or second-degree affected relative, all between the ages of sixteen and twenty-five. Of this number, a total of 124 participants have had 1 scan and 70 have had two (at the time of writing, June 2004), of which 96 high risk participants and 28 controls have participated in at least one structural and functional MRI scan and 53 high-risk and 17 controls in at least two. In order to coincide with a preliminary analysis of fMRI data using the Hayling Sentence Completion Task, which used the first one hundred participants to attend for a first fMRI scan, the same first one hundred participants of the EHRS are included in the functional MRI analyses presented in this thesis. Details of exclusions and the final numbers included in the analyses are described in chapter 8.

Prior to entering the scanner, participants were required to undergo a consultation with the on duty Radiographer. Participants were excluded from scanning if they reported a history of head surgery, injury while working with metal that required medical attention, metal fragments lodged in the head or

body, or metal implants. Participants with prescriptions for long sight were given spectacles with lenses approximately equal to their own prescriptions.

7.2.2 Psychopathological assessment

Psychopathological measures were obtained using a 140 item structured psychiatric interview – i.e. the Present State Examination (Wing et al 1974), which was conducted with participants as far as possible on the same day as the scan. On average, the PSE was conducted within 17.2 (s.d.=104.8) days of each scan (range=730 days). This interview was videotaped with permission, and lasted approximately 1 hour. Based on this examination, a score is derived indicating the presence or absence of psychotic symptoms (see table 2.1).

Psychotic symptoms were either definite transient delusions and/or hallucinations, or attenuated psychotic symptoms and/or perceptual distortions, which were questioned and may have been attributed to the imagination, but not an external source. Such psychotic symptoms are common within this group, are often reported in normal populations and are therefore not necessarily an indication of illness (Verdoux and Van Os 2002). Indeed, in the EHRS sample, theses symptoms do not prevent full time employment or study. These data formed the basis for our within high-risk group comparisons, whereby participants are grouped into:

HR+: those manifesting psychotic symptoms around the time of the scan

HR-: those experiencing no psychotic symptoms around the time of the scan

C: none of which experienced psychotic symptoms around the time of the scan

An additional group of six participants in the HR+ group have subsequently developed schizophrenia. However, at the time of scanning all participants were well. Furthermore, during analysis (i.e. March 2004-June 2004) these diagnoses had not been established (i.e. August 2004), so the six participants are included in the HR+ group.

7.3 Materials

7.3.1 Pre-test forms and information

Prior to entering the scanner, participants were asked to read the fMRI study information sheet (Appendix 5: Figure 5A) and complete informed consent (Appendix 2: Figure 2A) and medical screening forms (Appendix 5: Figure 5B). Following this, participants were given both verbal and written instructions (Appendix 5: Figure 5C) for the two behavioural tasks, which would be administered during scanning.

7.4 Paradigm design

This investigation employed an event related fMRI design to a verbal encoding and retrieval task. One advantage of this type of experimental design is that it allows for the measurement of neural activity associated with a specific event, such as individual word presentation, which is afforded by the fact that separate stimulus events can give rise to a detectable signal (Wilding 2001). This type of design is conceptually similar to event related potentials, in that the signals evoked by temporally separate behavioural trials are recorded and then analysed, revealing information about neural activity associated with a specific event. Event-related or trial based designs therefore mirror the fMRI signal associated with individual trials, as opposed to trial blocks. Event–related fMRI enables discrete event analysis and allows for the detection of underlying neural activity associated with inter trial variance or specific trial based behaviour, such as the accuracy of recognition, or trial type (i.e. living words versus non-living words). This is a facility not available to block design experiments, due to the fact that the fMRI signal is averaged across trial blocks, thereby reducing any variance (Jezzard et al 2001).

7.4.1 Averaged response

Event-related fMRI measures the signal evoked by individual behavioural trials combined together over time, and each individual event is therefore responsible for a fluctuation in the BOLD signal. The BOLD haemodynamic responses to discrete stimulus events spaced only a few seconds apart (short inter-stimulus intervals) will overlap, but will remain stable and sum linearly, producing one combined complex waveform (Donaldson and Buckner 2001). The fMRI signal measured is therefore

the linear summation of each individual stimulus response. The individual haemodynamic responses to the same trial types are therefore averaged to produce a representative response for those trials. As a result it is normally desirable to have at least thirty trials for each event or condition type, in order that the averaged response is truly reflective of the responses associated with individual trials (Wilding 2001). Unfortunately, the latency of a signal may vary from one trial to the next, reducing the amount of information available, or, above all in cases with variable latency across trials, signal amplitude may vary not due to differences in condition, but because of the variable stimulus presentation rate. Finally, response averaging could be misleading where responses made on similar trials are qualitatively different. This is especially pertinent with regard to inaccurate responding in recognition memory tasks, which in the absence of subjective accounts of the basis for error commission, could be due to guessing. The average response from incorrect trials may therefore be attributed in part to the signal associated with guesses and not a failed retrieval attempt (Wilding 2001). It some cases recognition discriminability measures are applied in order to assess the proportion of inaccurate responses that could be attributed to guessing (Ragland et al 2004). This artefact could also be controlled by introducing an additional response of 'don't know' in forced choice paradigms, a continuum of confidence judgement decisions, or by removing incorrect response events from the analysis (Wilding 2001).

7.4.2 Inter Stimulus Interval (ISI)

The overlap of responses in designs using short inter stimulus intervals prevents the haemodynamic response from returning fully to baseline between trials, reducing signal modulation and variance. In addition, the lack of an algorithm enabling identification of the separate contributions to one complex haemodynamic response means that it is advisable to extend the length of inter stimulus intervals so that they are greater than the blood flow response time associated with each event (i.e. 7-12 seconds)(Wilding 2001). This therefore optimises the signal to noise ratio by increasing the variance in the signal. However, conversely, long intervals between stimuli can often lead to low power due to the reduced number of events that can be presented in that time. Accordingly, inter stimulus intervals are preferentially variable as opposed to fixed. This means that as the inter stimulus interval fluctuates across trials, so too does the level of overlap between the BOLD haemodynamic response,

thus increasing signal variance and the amount of information available for each trial type. Variable ISIs do engender problems however, especially where participants may not attend to the task at all times, and where the number of trials which can be presented within a session, will still be reduced due to time constraints (Wilding 2001). The encoding and retrieval task described in this thesis, employed a variable ISI (2-10 seconds).

7.4.3 Stimulus Onset Asynchrony (SOA)

Random SOAs remove the confounding effects of anticipation and predictability and have the additional effect of maintaining the attention of the participant throughout the task. The SOA and the events it separates will determine at which point on the activation curve the scan will sample. With random SOAs the ensuing waveform will be irregular (Friston et al 1999b).

7.4.4 Randomisation of trials

Event–related fMRI permits the randomisation of trials within an experiment, unlike blocked designs, which require the grouping of the same behavioural trials (blocked by experimental condition or type) (Zarahn E 1997). Trials in this verbal encoding (word classification) and retrieval paradigm were randomised across participants, i.e. during the word classification task the living word trials were mixed with non-living word trials, while during word recognition, old word trials were mixed with new word trials (Dale and Buckner 1997). Event-related fMRI therefore removes the confounding effect of adaptation, where participants may adopt specific strategies and develop expectations in response to a predictable grouping of stimulus events, both during and between (in the inter stimulus interval) trials, in blocked designs. An optimisation programme called Optseq was used to generate event sequences and fixation durations between each event (Flett 2000). This is a specific tool responsible for optimising rapid presentation event related stimulus sequences by counterbalancing trial conditions using the time window and temporal resolution to determine the order (http://surfer.nmr.mgh.harvard.edu/optseq/, accessed 24th of May 2004). This program is based on Dale and Buckner's selective averaging procedure, which permitted the estimation of individual contributions of different trial types overlapping over time (Dale and Buckner 1997). By counterbalancing trial presentation, all trial types will follow one another equally often. As a result,

the overlap, which occurs between different yet adjacent trial type responses, will be cancelled out by subtraction.

7.4.5 Verbal Encoding and Retrieval Task

The encoding and retrieval task was programmed and generated using a program called E-prime (Copyright 2000 Psychology Software Tools http://pstnet.com) and is developed to include the Integrated Functional Imaging System (IFIS) software tool, that is responsible for synchronising the data presentation and recording with the MRI scanner timing. The version of the verbal memory paradigm that was employed in this investigation was originally designed and piloted in 1999 by Enrico Simmonotto, Susanna Flett and colleagues (Flett 2000). Pilot data based on a preliminary analysis of 27 high-risk and 6 control participants can be found in detail elsewhere (Human Brain Mapping 2001 poster & MSC thesis).

7.4.6 Experimental stimuli

The stimuli that were used in the verbal memory paradigm presented in the scanner were eighty three different words (i.e. eleven words were used for practice sessions and seventy two for the experimental tasks) of high imageability (at least 590 on a scale of 100-700) (Flett 2000), matched across categories for word length (number of letters), concreteness (i.e. on a scale of 100-700), syntactic category (i.e. nouns) and frequency in the English language (based on Celex written frequency) and could be classified as either living or non-living objects

(MRC Psycholinguistics database: http://www.psy.uwa.edu.au/mrcdatabase/mrc2.html). No ambiguous word categories, such as fruit or body parts were included. Stimuli were presented for two seconds in thirty-six pt Times New Roman font, black on white screen. A list of stimuli used is presented in Table 7.1.

Table 7.1: Task Stimuli

Classification words		**Distractor words**	
Living	Non-living	Living	Non-living
Chicken (PRACTICE 1)	Computer (PRACTICE 1)	Deer (PRACTICE 2)	Lamp (PRACTICE 2)
Ostrich (PRACTICE 1)	Fence (PRACTICE 1)	Shark (PRACTICE 2)	Piano (PRACTICE 2)
Wolf (PRACTICE 1)	Pram (PRACTICE 1)		Tent (PRACTICE 2)
Ant	Balloon	Bee	Axe
Cat	Barrel	Butterfly	Brush
Caterpillar	Bus	Camel	Button
Cow	Chisel	Dog	Candle
Crab	Desk	Donkey	Cup
Fox	Flag	Fish	Drum
Giraffe	Flute	Goat	Key
Hamster	Glove	Kangaroo	Needle
Horse	Jug	Lobster	Pliers
Lion	Kettle	Owl	Shawl
Monkey	Peg	Peacock	Stool
Mouse	Plug	Pig	Tie
Penguin	Purse	Rabbit	Toaster
Racoon	Rocket	Seahorse	Torch
Snake	Spanner	Sheep	Towel
Spider	Spoon	Snail	Tractor
Tiger	Sword	Swan	Vase
Zebra	Trumpet	Whale	Waistcoat
36 studied words		36 unstudied words	

Note: 36 classification words presented at encoding and recognition; 36 distractor words only presented at recognition

7.5 Procedure

7.5.1 Pre-test briefing

As described in 7.3.1, prior to entering the scanner, participants were asked to complete consent and medical screening forms and given verbal and written instructions for the two behavioural tasks (the Verbal Encoding and Retrieval Task and the Hayling Sentence Completion Test) which would be administered during scanning. Participants were asked to minimise movement and not to speak during scanning. They were also informed that in the event of wanting to leave the scanner, they should press all five buttons on their keypad and scanning would be aborted.

7.5.2 Scanning protocol

Participants lay on the scanner bed and a five-button keypad (with a button corresponding to each finger) was strapped to the dominant hand. Earphones were placed over their ears and a 15x15 centimetre computer screen was positioned approximately thirty centimetres above their heads. Radiographers obtained T1 and T2 weighted structural images followed by a functional pre-scan, which lasted approximately 2 minutes, prior to the presentation of the first behavioural task instructions on the screen (Appendix 5: Figure 5C). After completion of the first functional MRI Hayling Sentence Completion task (approximately 13 minutes), instructions were presented for the verbal memory task and a functional pre-scan was run during the first practise task for verbal memory word classification/encoding task. A third functional pre-scan was also run during the second practice task for the verbal memory retrieval task.

7.5.3 Task procedure

7.5.3.1 Hayling Sentence Completion Task

While in the scanner, participants were shown a series of sentences with the last word missing and asked to silently think of an appropriate word to complete the sentence and then press a button on the handset once they had done so. This was a blocked parametric paradigm design, with four blocks of sentences, each block differing from the other in level of difficulty/constraint and flanked by rest periods consisting of a black screen with white circles.

7.5.3.2 Verbal Encoding and Retrieval Task: Practice task 1

Following the on-screen instructions participants were presented with 6 words (see table 7.1). A fixation cross hair was presented for 1.5 seconds (i.e. inter stimulus interval) following presentation of each word for 2 seconds (i.e. stimulus duration). Responses could be made at any time during the presentation of the stimuli and the subsequent fixation, by pressing a button on a keypad strapped to participants' dominant hand. Participants were asked to classify words as either living or non-living, by pressing the thumb or index finger button on their keypad. Performance feedback was visually presented for 1.5 seconds, 'correct' in blue font and 'incorrect' in red font, after each response. This

feedback was restricted to the practice tasks only, to ensure participants had understood the instructions and were pressing the correct buttons.

7.5.3.3 Task 1: Encoding (Living/Non-living word classification task)

Immediately following the practice task 1, participants were presented with instructions again, for the actual task. The 36 words were presented randomly, with 18 words referring to living things and 18 to non-living things (see table 7.1). A fixation cross hair was presented for a variable duration of 2-10 seconds following the presentation of each word for 2 seconds. Responses could be made at any time during the presentation of the stimuli and the subsequent fixation, by pressing a button on a keypad. Participants were required to group words as either living or non-living objects by pressing a button and could respond at any time during the presentation of the stimuli and the subsequent fixation. The Task duration was 3.3 minutes/200 seconds. There was a brief delay of approximately a minute while the second practice task was set up with IFIS.

7.5.3.4 Practice task 2

Following instructions, participants were presented with 10 words, 5 of which had been presented in the previous practice task (old words) and 5 matched lures (new words). A fixation cross hair was presented for 1.5 seconds following presentation of each word for 2 seconds. Responses could be made at any time during the presentation of the stimuli and the subsequent fixation period by pressing a button on the keypad. Participants were asked to make an old/ new recognition decision based on whether or not they believed they had viewed the word in practice task 1, by pressing the thumb/index finger button on their keypad. Performance feedback was presented again as in practice task. This lasted approximately 1 minute.

7.5.3.5 Task 2: Recognition task

Immediately following the practice, participants were presented with instructions for the actual task. In the actual task, lasting 6.6 minutes/ 400 seconds, participants were presented with 72 words; the same 36 words presented in Task 1 (i.e. old words), intermixed with 36 matched lures (i.e. new words). Again, a fixation cross hair was presented for a variable duration of 2-10 seconds following

the presentation of each word for 2 seconds. Responses could be made at any time during the presentation of the stimuli and the subsequent fixation period, by pressing a button on the keypad. Participants were required to make an old/new recognition decision based on whether or not they had previously viewed the word in the classification task, by pressing a button. Participants could respond at any time during the presentation of the stimuli and the subsequent fixation.

7.5.3.6 Post test Briefing

Following scanning, participants were given a seat and asked to complete a post-test briefing form. This was to ensure that participants had understood the task and to ascertain their subjective perception of performance during the task. It also enabled us to immediately identify any sources of problems with individual behavioural results or within scanner artefact (i.e. movement) (Appendix 5: Figure 5D).

7.6 Data Acquisition

7.6.1 Structural Scans

MRI data was acquired on a 1.5 Tesla Magnetom Signa General Electric (GE) scanner at the Brain Imaging Research Centre (BIRC) for Scotland at the Western General Infirmary in Edinburgh. Following a localiser scan and T2 (spin echo sequence) weighted structural scan, structural data were also acquired using the Magnetisation Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence, consisting of a 180 degree inversion pulse with a Fast low angle shot (FLASH) collection (i.e. *flip angle=15 degrees, TR=10ms, TE=4ms, TI=600ms, relaxation delay=200ms, field of view=22cm, matrix=256x192*). The ensuing 128 contiguous coronal slices were 3 dimensional with a slice thickness of 1.7mm and an in plane resolution of 1 mm. The gradients had a maximum strength of 23mT/m, and a slew rate of 120T/m/s. This lasted for approximately 7 minutes 15 seconds.

7.6.2 Functional Scans

Functional images were collected using a Gradient Echo Planar Imaging sequence (EPI), a fast acquisition allowing activation response to short stimuli to be detected (i.e. flip angle 90 degrees, TR=2s, TE=40ms, field of view=22x22cm, matrix=64x64 pixels, pixel size=3.4x3.4mm, slice

thickness=5mm with no gap between slices, single shot). Twenty-four contiguous axial (horizontal) slices were collected at an oblique (slanting) angle aligned with the anterior commissure (AC) /posterior commissure (PC) line, moving from the bottom of the brain and up (ascending) (per volume/image). This slant was originally incorporated in order to allow for the imaging of the hippocampus, because the medial temporal lobes are considered important for verbal memory processing.

Data were acquired during 2 sessions (encoding and retrieval), consisting of 100 volumes for the first session and 200 volumes for the second session (repetition time (TR) 2seconds/volume). To allow for equilibration effects, the first 4 image acquisitions were discarded, resulting in an onset delay of 8 seconds.

7.7 Data Analysis

7.7.1 Behavioural Data Analysis

Behavioural responses and associated parameters were logged in a data file using E-Data Aid (Edat) function within the Eprime suite of programmes (E-Prime 2000). Ensuing Edat files for each participant were then exported to 'Excel' for further analysis. Parameters, which were relevant to the event related analysis (i.e. radio frequency pulse start time, disacquisition time, stimulus onset time, correct response (i.e. 1=correct and 2=incorrect), response given (i.e. 1=yes or 2=no) and stimulus reaction time (msecs)), were copied into a separate text file in Excel for each participant. Behavioural data were then analysed using SPSS (version 11). All data was analysed using the Statistical Package for the Social Sciences (SPSS, version 11). Normailty of distributions was assessed using the Kolmogorov-Smirnov test, and homogeneity of variance using the Levene's test (see Appendix 6: Tables 6K and 6L). Mean response accuracy and reaction time for encoding and retrieval were compared between participant groups using one-way ANOVAs. Differences between participant groups in the number of and reaction time for discrete response events were investigated using mixed repeated measures ANOVAs (Note: p values presented with 1 decimal place were rounded up to the nearest whole number).

7.7.1.1 Terminology

For the purposes of future discussion, 'encoding' refers to the word classification task, during which words to be re-presented in the recognition task were processed. 'Old' and 'recognition' refer to the classification of words as having been seen before, while 'New' and 'rejection' refer to words that are classified as not having been seen before. 'Correct recognition', 'true positives' and 'correct old' refer to words correctly identified as having been seen before, while 'Correct new', 'true negatives' and 'correct rejections' refer to words correctly identified as not having been seen before. 'Incorrect recognition', 'false positives' and 'incorrect old' refer to words wrongly identified as having been seen before, while 'Incorrect new', 'false negatives' and 'incorrect rejections' refer to words wrongly identified as not having been seen before.

7.7.2 Imaging Data Reconstruction

Raw EPI images were reconstructed offline to ANALYZE format (Mayo Foundation, Rochester, MN, USA, The Mayo Clinic http://www.mayo.edu/bir/). Origins were set at the AC-PC basal brain line passing through the superior edge of the anterior commissure and the inferior edge of the posterior commissure, dividing the thalamic from the sub-thalamic region (Talairach and Tournoux 1988).

7.7.3 Imaging Data Analysis

Imaging data was analysed using the software package Statistical Parametric Mapping (http://www.fil.ion.ucl.ac.uk/spm/) (Friston 1995), running in matlab 6.5.1 (The Math Works, Natick, MA, USA)(Gourovitch et al 1996). All analyses were performed in SPM'99 (pre-processing, 1st and 2nd level analysis fixed effects model) and SPM2 (2nd level analysis random effects model).

7.7.3.1 Pre-processing

Pre-processing was carried out using prepared batch scripts on SPM'99 (Enrico Simmonotto). Data pre-processed using SPM99 can be analysed in SPM2, because image files are compatible with both SPM versions (Gitelman, D; SPM@JISCMAIL.AC.UK; 12th March 2003). Pre-processing involves temporal and spatial realignment, spatial normalisation, and smoothing, which are described in more detail below.

7.7.3.2 Temporal & Spatial Realignment

To correct for different acquisition times between slices, a slice timing procedure was applied and the signal measured in each slice was shifted relative to the acquisition of the first slice using a Fast Fourier Transform interpolation. Additionally, for each participant, all EPI volumes were realigned to the first scan in the series using rigid body transformations. This estimates a set of six parameters of rigid body transformation, with three translations and three rotations about orthogonal axes, which minimise the mean squared difference between each scan and the first scan (Jezzard et al 2001). This was necessary to co-register images of the same subject together and to correct for individual participant movement during acquisition. Participants were excluded if movement in either x, y or z exceeded 3mm.

7.7.3.3 Spatial Normalisation

Each volume was then normalised to a standard SPM'99 EPI template volume using linear affine transformations (registering images into the same co-ordinate system) followed by non-linear deformations (to correct for gross differences in head shapes).

7.7.3.4 Smoothing

After normalisation, volumes were spatially smoothed with an 8x8x8 cubic mm full width half maximum (FWHM) gaussian filter, to reduce spatial noise (homologous regions in different brains are not registered fully in spatial normalisation and smoothing further reduces inter-participant discrepancy). Finally, a high pass filter with a cut off of 150 seconds was applied to the data to remove low frequency drift in the signal (during statistical analysis).

7.8 Image analysis

7.8.1 Fixed and Random effects

A fixed effects analysis is traditionally associated with case studies in individual participants or in groups with less than twelve participants, in order that an effect observed can be repeated in another participant. This type of analysis permits you to infer typical responses for that group. A fixed effects

analysis however, assumes that all participants within a group activate to the same extent and the effect size is averaged across participants. It therefore considers only within session variability (i.e. the error related to the task sessions) and statistical inferences are drawn from the effect size relative to the within participant variability. Results are therefore normally highly significant because the degrees of freedom are related to the number of scans across all participants. However, it is a limiting method in that the effect size may be driven by the activations of only a few participants and results can therefore be generalised only to that sample and not to the population as a whole. Fixed effects form the basis of the 1st level of the group analyses (Friston et al 1999a; Jezzard et al 2001; Penny and Holmes 2003).

A random (mixed) effects (or 'second level') analysis, on the other hand, takes into consideration both within (scan to scan) and between (participant to participant) session variance, where the expression of variability in activation between participants is modelled as a random factor (Friston et al 1999a). Individual t values for individual participant contrasts are reduced in value where the underlying variance across the participant's scans is high. One observation per participant per condition or individual contrast of parameter estimates from the first level analysis is entered into the second level analysis. Contrast images for each participant represent 'spatially distributed images of the weighted sum of parameter estimates for a specific contrast. This type of model makes fewer assumptions about the data therefore allowing the generalisation of the results from a single experimental sample to the population from which it was derived. The compromise is found in the more conservative, less sensitive results derived from a random effects analysis, because the error of the effect is calculated from the independent sessions, reducing the degrees of freedom. More participants therefore increase the chances of more robust statistical results (Friston et al 1999a; Jezzard et al 2001; Penny and Holmes 2003). Subsequently, differences in both the size and the pattern of BOLD fMRI responses between fixed and random effects analyses were expected.

7.8.2 General Linear Model

Using the General Linear statistical model, variability in the data is explained by the linear (additive or gaussian) combination of the predictor variables plus an error term (Y is the data, j represents

individual observations, Beta is the slope of the line, x is the predictor variable, c is the line intercept and E is the remaining error): Y (j) = beta*x (j) + c + E (j)

This formula can be expressed in the design matrix (**X**), where data from multiple subjects (for fixed effects) or single subjects (for random effects) is combined into a single column vector **Y** (response variable/data matrix), with each row representing an independent observation. Individual columns of the design matrix represent each model parameter (**B**) (predictor variable/parameter matrix) and error (**E**) (Error matrix), which may have an effect on the response variable: $\mathbf{Y} = \mathbf{X} * \mathbf{B} + \mathbf{E}$

Using the F test (ANOVA), one can test the null hypothesis that all estimates are zero or for a contrast test the null hypothesis that there is no linear relationship using the SPM 'T' statistic (i.e. assume a linear relationship between voxel value and effect of interest). This divides the contrast of parameter estimates by the standard error of that contrast to address the question whether given the error in these observations; the estimate of the slope would have arisen by chance (http://www.mrc-cbu.cam.ac.uk/Imaging/Common/ accessed June 10th 2004).

7.8.3 SPM

Single subject first level and random effects second level analyses for encoding and retrieval were computed in SPM'99 and repeated in SPM2, in order to remain up to date with changes in the software.

SPM2 is an updated version of SPM software with structural, theoretical, and algorithmic improvements on the previous versions. For example, for the estimation of model parameters, SPM2 now uses restricted maximum likelihood (ReML) estimates of variance components, instead of ordinary least squares estimators, allowing for i.i.d (identically and independently distributed errors) assumption departures (i.e. non-sphericity). Non-sphericiy estimates are then used to create maximum likelihood (ML) estimates using weighted least squares (WLS) (http://fil.ion.ucl.ac.uk/spm). Non-sphericity can be attributable to serial correlations in fMRI data, or hereoscedasticity. For parameter inference in SPM2, p values are adjusted to protect against family wise false positives across the search volume using a gaussian field correction. P values are also provided based on the false discovery rate (FDR), that for a given threshold, a proportion of supra-threshold voxels will be false

positives. For the computation of ANOVAs in SPM2, the following selections were made: yes to non-sphericity correction; yes to replication across three groups; no to correlated repeated measures.

Given that the data analysis differs in SPM2 from that in SPM'99 (e.g. filtering in time is computed differently between the two versions), it was not considered appropriate to correct for multiple comparisons. An additional advantage of this re-analysis however, was the increased sensitivity of SPM2, which could improve detection of BOLD fMRI response differences between groups. There is currently a deficit in the literature comparing large data samples on SPM2 and SPM'99. However, Keihl and colleagues at Yale University reported that a comparison of the analyses of 20 participants on an fMRI auditory oddball task, between SPM'99 and SPM2, showed a 10-15% increase in individual and group T scores on SPM2 (Kiehl, K.A; SPM@JISCMAIL.AC.UK; 14th March, 2003).

7.8.3.1 First level and second level analyses

Using SPM'99, both encoding and retrieval single subject first level analyses and multiple subject second level fixed effects analyses were run by means of batch scripts adapted from Friston (1999) by Enrico Simonotto. Random effects within and between group analyses were then calculated by manually entering individual contrast images (representing the weighted sum of the parameter estimates) into one sample t-tests and one-way ANOVAs, followed by post-hoc between group comparisons.

In order to achieve consistency, it was considered pertinent to additionally rerun the multiple subject fixed effects analysis on SPM2. However, given the size of this data set (89 participants) and the magnitude of a multiple subject fixed effects analysis, this was not successfully recomputed for the encoding or retrieval analyses. Only the results of the random effects analyses calculated using SPM2 have been presented in this thesis (Note: data from the fixed effects analyses as calculated using SPM'99 is also available on request, and where pertinent to our results interpretation, we have referred to the results of the between groups fixed effects analysis).

7.8.4 Encoding

The main factor of interest during the word classification task was the BOLD fMRI response associated with the processing of the words presented. Given that this was a word classification task, word processing would also be accompanied by the retrieval of semantic information associated with the words presented, in order to aid in the selection of an appropriate response (i.e. is this living or non-living?). Due to a high level of accuracy on this task, all events were included and all items were treated as equal and entered into a single regressor model. The single regressor was obtained by convolving a canonical haemodynamic response function with a vector of the onset times. Head movement was introduced as a further regressor, in order to model movement related residual variance. First level contrast parameter estimate images for each individual participant (encoding > baseline experimental activation; baseline experimental activation > encoding) were computed and manually entered into a second level random effects analysis to examine activations within groups (one sample t-tests) and activation differences between groups (one-way ANOVAs). ANOVAs were followed by post hoc t-tests, to examine differences between each of the three groups (i.e. HR+, HR- and C). In order to address our apriori hypotheses, the maximum number of post-hoc two sample t-tests was computed. This allowed us to compare the control group with the high-risk group to determine possible 'trait' effects (i.e. HR (as a whole), and HR- and HR+ independently > or < C, but HR- = HR+), and the control group and high-risk participants without symptoms to those with psychotic symptoms to elucidate any response differences which could be attributed to the presence of psychotic symptoms or 'state' effects (i.e. C & HR- > or < HR+).

7.8.5 Retrieval

7.8.5.1 Old vs. new

Our first contrast of interest was the comparison of retrieval events (both correct and incorrect) where words were identified as old (recognition) with events where words were identified as new (rejection). Three classes of events (i.e. old, new and no responses) were entered into a three-regressor model, with head movement as an additional regressor to model movement related residual variance. First level contrast parameter estimate images for each individual participant (old > new; new > old) were computed and manually entered into a second level random effects analysis to calculate activations

within groups (one sample t-test) and activation differences between groups (one-way ANOVAs). Post-hoc two sample t-tests were computed to explore activation differences between each of the three groups (i.e. HR+, HR- and Controls). It would have been of interest to look at the difference in response between successfully and unsuccessfully encoded items by computing the contrast of correct old versus incorrect new items. However, there were too few false negative responses to allow for computation of this contrast.

7.8.5.2 Correct old and correct new

Incorrect responses were not investigated separately in these analyses. This was partly due to the number of incorrect events, which precluded analysis following a division of events into false positives and false negatives. This also had the added advantage of removing any confound which could be associated with differences in behavioural task performance, e.g. unknown reasons for error commission and guessing. Similarly, some evidence suggests that the neural correlates associated with true and false recognition activate the same or overlapping areas of the brain (Heun et al 2004; Schacter et al 1997). Although Heun et al (2004) showed overlapping activations for true and false recognition, they also reported greater medial parieto-occipital activation for hits, and greater lateral parieto-occipital activation for false alarms. The analysis therefore focused on those activations associated with correct responses only. Three classes of events (i.e. correct old, correct new and errors (incorrect and no responses)) were entered into a three-regressor model. Head movement was again included as an additional regressor. First level contrast parameter estimate images for each individual participant (correct old events vs. baseline experimental activation, correct new events vs. baseline experimental activation, and correct old events vs. correct new events) were also computed and manually entered into a second level random effects analysis to examine within group activations (one sample t-tests) and activation differences between groups (one-way ANOVAs). In the same way as above, one-way ANOVAs were followed by post hoc two sample t-tests, to explore differences between each of the three groups (i.e. HR+, HR- and Controls).

7.8.6 Localisation of functional activation

SPM generates statistical output, which maps activations with respect to Montreal Neurological Institute (MNI) coordinate system. As with other atlases of the human brain this system maps regions of the brain with respect to their locations in 3D space (i.e. x,y,z dimensions). The MNI output coordinates were converted to standard Talairach space, using a non-linear conversion (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html). The relevant coordinates were entered into the Talairach daemon database and were also checked manually on the Talairach/Tournoux Co-Planar Stereotaxic Atlas of the Human Brain (Talairach and Tournoux 1988). MNI & Talairach coordinates estimated brain regions and Brodmann areas have been included in the results tables.

7.8.7 Presentation of results

The results of the random effects analysis for within and between group contrasts are presented in Appendix 6: Tables 6A-6.J. Where the between group contrasts have shown a clear difference between fixed and random effects results, the fixed effects between group results have also been discussed. Height thresholds of $p<0.001$ (uncorrected for multiple comparisons) were applied to statistical parametric maps for fixed and random effects results. The Brodmann area of significant cluster activation (i.e. BA), the number of voxels within clusters of significant activation (i.e. K_E), the Z statistic for that cluster (i.e. Z), and the cluster level p values (i.e. corrected or uncorrected for multiple comparisons), are noted within the text and in the tables (Appendix 6: Tables 6A-6J). Peak maxima for clusters reported are detailed in the tables. P values noted within the text are corrected for multiple comparisons unless otherwise stated. However, given that results presented are based on a conservative random effects analysis (with a low number of events), and a threshold of $p<0.001$, uncorrected values have also been presented where corrected values in regions predicted to be of interest, did not achieve significance. Where uncorrected p values are presented in the text, they are preceded by the corrected p value for that cluster.

For within group comparisons, increases describe areas of significantly greater activation in one condition (i.e. A) relative to another (i.e. B). For the same contrast, decreases describe areas of significantly less activation in condition A relative to B (or alternatively, greater activation in the latter

B condition relative to the former condition A). For between group contrasts, it is appreciated that, for example, group C > group D, in condition A > condition B, will be the same for the reverse contrast (i.e. group D > group C, in condition B > condition A) (Laurienti, P.; SPM@JISCMAIL.AC.UK; 24th June 2004). The reverse contrasts were also computed, but have not been presented. Due to the number of two-sample post-hoc t-tests, for ease of reporting, C >HR, C > HR- & C > HR+ will be reported under 'C vs. HR'. HR > C, HR- > C & HR+ > C will be reported under 'HR vs. C'. HR- > HR+ & HR+ > HR- will be reported under 'HR- vs. HR+'.

Chapter 8: Results of Investigation 5

8.1 Participant demographic characteristics

Twenty-seven high-risk participants presented with transient or isolated psychotic symptoms at the time of the first scan (HR+). Of this group, there were 13 males and 14 females with a mean age of 25.1 years (s.d. = 3.1). 41 participants exhibited no psychotic symptoms (HR-) and in this group there were 17 males and 24 females with a mean age of 26.6 years (s.d. = 3.3). There were 21 healthy controls (C), of which 13 were male and 8 were female, with a mean age of 26.8 years (s.d. = 2.7). There was a trend for a significant difference in mean age between groups ($F_{(2, 88)} = 2.5$, $p=0.09$). However, age was not controlled for in this sample for either the behavioural or functional MRI data analysis. It was thought a reasonable course of action not to control for participant age given that age related memory deficits are not generally apparent in this age group and are more common in individuals over the age of forty-five years (Parkin 1993). With the exception of the trend towards a significant difference in mean age, the participant groups were suitably balanced for handedness, gender, WAIS- R full scale IQ and NART estimated full scale IQ (Table 8.1).

Table 8.1: Participant demographic characteristics

		C (N=21)	HR- (N=41)	HR+ (N=27)	Test Statistic	P
Mean age at scan: (SD)		26.8 (2.7)	26.6 (3.3)	25.1 (3.1)	F = 2.5 [a]	0.09
Gender		13M: 8F	18M: 23F	13M: 14F	χ^2 = 2.3 [b]	0.30
Hand- L: R: M*		2: 17: 1	3: 37: 1	3: 22: 2	χ^2=1.30 [c]	0.85
WAIS-RFSIQ: (SD)		107.5 (12.5)	103.5 (14.5)	99.4 (12.7)	F = 2.0 [a]	0.14
NART FSIQ: (SD)		102.8 (9.4)	102.1 (8.4)	97.9(10.8)	F = 1.9 [a]	0.19

[a] One-way ANOVA, [b] Pearson's Chi Squared [c] Kruskal Wallis
* Annett Handedness Inventory

8.1.1.1 Excluded participants

Eleven participants were excluded from the overall analysis, for a number of reasons. Five of the first one hundred participants who attended declined to be scanned. A further six participants were

excluded from the image analysis, two were excluded due to loss of behavioural data, two due to minor vascular abnormalities and two due to excessive movement (i.e. >3mm spike in either x, y or z). Scanning data are therefore presented on 89 participants (68 high risk participants and 21 controls).

8.2 Behavioural performance

The performance of the 3 groups on the encoding and retrieval task is shown in tables 5.2-5.5. For all participant groups more than 97% of responses given during encoding (C: 98.3%, HR-: 97.7%, HR+: 97.2%), and over 70% of responses given during retrieval (C: 71.3%, HR-: 74%, HR+: 71.6%) were correct. A series of one-way ANOVAs revealed no significant main effects of group in the number of correct classification responses ($F_{(2, 88)} = 0.49$, $p = 0.61$) or reaction times ($F_{(2, 88)} = 0.26$ $p = 0.77$) during encoding. While ANOVAs are considered robust enough to deal with any deviations from normality in distributions, especially where there is homogeneity of variance between groups (Miller 1996), Kruskal Wallis non-parametric tests were also used to investigate differences between groups in the word classification data. There were no significant differences between groups in the number of correct classification responses (χ^2 =2.5 (2), p=0.28) or reaction times (χ^2 =3.1 (2), p=0.21). Similarly, there were no significant differences between groups in the number of correct responses ($F_{(2, 88)} = 0.43$, $p = 0.65$) or reaction times ($F_{(2, 88)} = 0.35$, $p = 0.70$) during the recognition task. All groups therefore performed well above chance and were equivalent in both accuracy and speed during the encoding and retrieval tasks (see tables 8.2 & 8.3).

Table 8.2: Mean performance scores and reaction times for the encoding condition

Participants (N=89)	**No Response Recorded**	**Incorrect Response**	**Correct Response**	**Total No.**	**Encoding RT (msecs)**
	Mean (SD)	Mean (SD)	Mean (SD)		Mean (SD)
C	0.1 (0.6)	0.5 (1.2)	35.4 (1.2)	36	928.4 (458.6)
HR -	0.1 (0.8)	0.7 (1.1)	35.2 (1.1)	36	1002.8 (353.4)
HR +	0.1 (0.3)	0.9 (1.4)	35.0 (1.4)	36	1005.5 (420.1)

Table 8.3: Mean performance scores and reaction times for the retrieval condition

Participants (N=89)	No Response Recorded	Incorrect Response	Correct Response	Total No.	Retrieval RT (msec)
	Mean (SD)	Mean (SD)	Mean (SD)		Mean (SD)
C	6.2 (6.9)	14.5 (4.8)	51.3 (10.6)	72	1321.6 (385.1)
HR -	5.1 (6.9)	13.5 (4.6)	53.3 (9.1)	72	1254.1 (338.8)
HR +	5.1 (4.5)	15.2 (5.7)	51.6 (8.5)	72	1313.2 (353.2)

8.2.1 Old versus new responses

The results of the mixed repeated measures ANOVA showed a main effect of response type across groups ($F_{(1, 86)} = 5.5$ $p<0.05$), with groups making more new than old responses. From the means however, this appears mainly attributable to the responding tendency in the high-risk group, rather than the controls (see table 8.4). There was no main effect of group ($F_{(1, 86)} = 0.23$ $p = 0.79$), and no group by response type interaction ($F_{(1, 86)} = 1.66$, $p = 0.19$), suggesting no significant differential number of responses made by any one group. There was a trend for a significant correlation between old and new events for the control group ($r = -0.4$, $p = 0.06$) and a significant correlation between the two in HR- ($r = -0.4$, $p<0.005$) and HR+ groups ($r = -0.8$, $p<0.001$).

Table 8.4: Mean number of old and new responses in the high-risk and control groups

Participants (N=89)	C	HR-	HR+	Main effect response type	Main effect group	Response XX group
	Mean (SD)	Mean (SD)	Mean (SD)	F	F	F
Old Response	32.9 (6.7)	30.5 (6.6)	31.6 (6.6)	5.5*	0.2	1.7
New Response	32.8 (6.2)	36.3 (6.6)	35.3 (8.0)			

* $p < 0.05$

8.2.2 Incorrect old and incorrect new response numbers

Repeated measures mixed ANOVA showed no significant main effect of response type for incorrect events (incorrect old and incorrect new) ($F_{(1, 86)} = 2.39$ $p=0.13$), main effect of group $F_{(1, 86)} = 0.95$, $p=0.39$), or group by response type interaction ($F_{(2, 86)} = 2.09$ $p=0.13$), suggesting that all groups made a similar number of incorrect recognition and rejection responses (see table 8.5). However, interestingly, group means show controls to make slightly more incorrect old than incorrect new responses, the opposite to the pattern seen in the high-risk group. There were no significant correlations between incorrect old and incorrect new responses within groups.

Table 8.5: Mean number of incorrect and correct old and new events

	No. Incorrect old	**No. Incorrect new**	**No. Correct old**	**No. Correct new**
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
C	7.6 (3.2)	6.9 (4.5)	25.3 (6.0)	25.9 (5.7)
HR -	5.5 (3.1)	8.1 (4.1)	25.1 (5.7)	28.2 (6.1)
HR +	7.0 (3.9)	8.2 (4.9)	24.6 (5.5)	27.0 (5.9)

8.2.3 Incorrect and Correct Reaction Times

The results of the mixed repeated measures ANOVA showed there was a main effect of response time for event type across groups ($F_{(1, 86)} = 15.1$, $p<0.001$), and response times for correct events were significantly slower than those for incorrect events (mean diff = 126.4 (s.e. = 32.5), $p<0.001$). There was no significant main effect of group ($F_{(2, 86)} = 0.27$, $p=0.76$), suggesting that overall, participant groups were not significantly different for response times during the retrieval condition. There was also no significant group by response time interaction ($F_{(2, 86)} = 2.4$ $p=0.096$), suggesting that groups did not have differential response times for correct and incorrect retrieval events (see table 8.6).

Table 8.6: Means for correct and incorrect retrieval reaction times and results of mixed repeated measures ANOVA

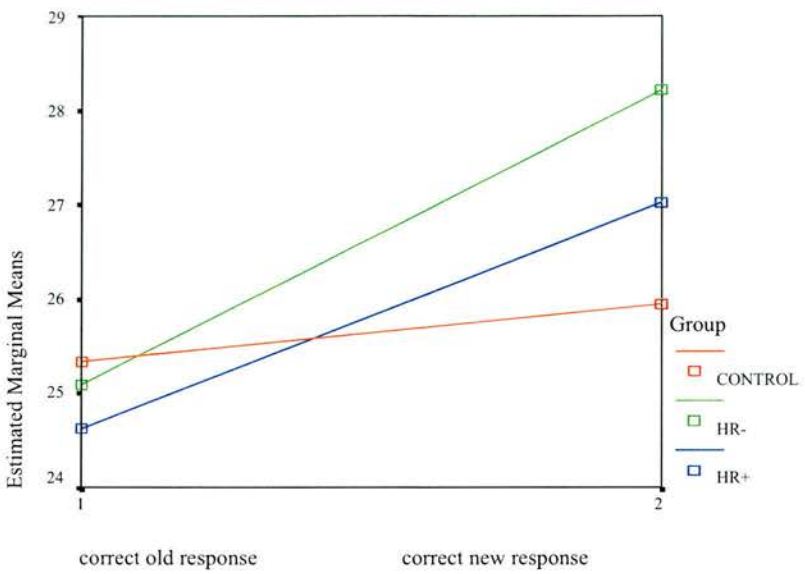
	C	HR-	HR+	Main effect RT	Main effect group	RT type X group
	Mean (SD)	Mean (SD)	Mean (SD)	F	F	F
Correct RT (msecs)	1307.8 (373.5)	1226.9 (344.3)	1245.6 (338.1)	15.1 **	0.3	2.4
Incorrect RT (msecs)	1080.8 (198.9)	1113.6 (379.3)	1206.8 (319.8)			

** p <0.001

8.2.4 Correct old and correct new response numbers

Repeated measures mixed ANOVA showed a significant main effect of response type for correct events (correct old and correct new) ($F_{(1, 86)} = 8.1$ p=0.006), with a greater number of correct new responses than correct old responses made across all participants (mean diff =2.1, s.e. = 0.7). There was however, no significant main effect of group ($F_{(2, 86)} = 0.4$, p=0.65), or group by response type interaction ($F_{(2, 86)} = 1.0$, p=0.36), suggesting that there was no differential number of responses made for either response type in any one group (see table 8.5 and figure 8.1). Correct old and correct new responses were significantly correlated in the control (r = 0.6, p <0.005) and HR- groups (r = 0.3, p <0.05), but not in the HR+ group (r = 0.1, p = 0.6).

Figure 8.1: Number of correct old and correct new events



8.2.5 Correct old and correct new reaction times

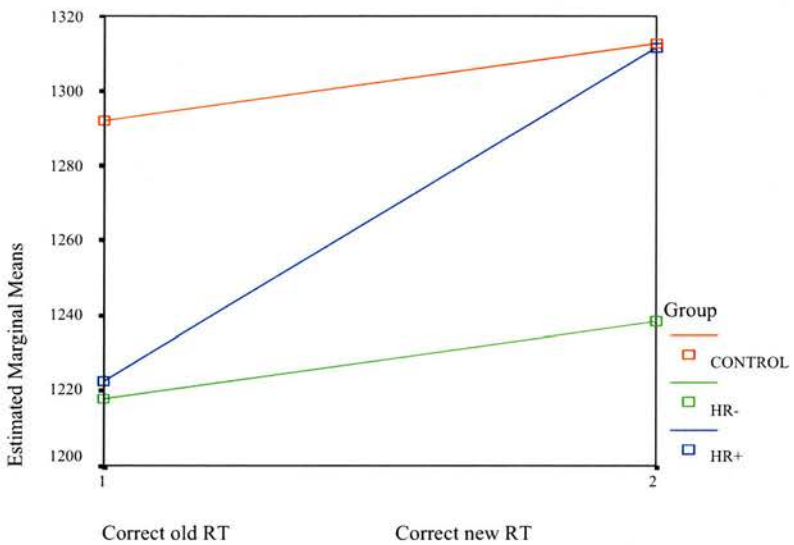
The results of the mixed repeated measures ANOVA showed there was a significant within group effect of reaction time ($F_{(1, 86)} = 5.0$ $p<0.05$), with reaction times for correct old events faster than those for correct new events across participants (mean diff = 43.5, s.e. =19.4). However, there was no significant main effect of group ($F_{(1, 86)} = 0.33$ $p=0.72$), or group by reaction time interaction ($F_{(1, 86)} = 1.4$, $p=0.25$), suggesting that groups were not differential in speed overall or during different event types (see table 8.7). The pattern of means does show there to be a bigger difference between correct old and correct new event reaction times in the HR+ than in either the HR- and controls, although this difference is not statistically significant (figure 8.2).

Table 8.7: Mean correct old and correct new reaction times

	C	HR-	HR+	Main effect RT	Main effect group	RT type X group
	Mean (SD)	Mean (SD)	Mean (SD)	F	F	F
Correct old RT (msecs)	1292.0 (350.5)	1217.9 (363.4)	1222.6 (358.1)	5.0[1]	0.3	1.4
Correct new RT (msecs)	1312.8 (381.7)	1238.6 (338.7)	1311.7 (368.6)			

[1] $p<0.05$

Figure 8.2: Reaction times for correct old and correct new events



8.3 Summary of behavioural results

Importantly all groups performed well above chance and were broadly equivalent in accuracy and in speed during the encoding and retrieval tasks. Observed differences in BOLD fMRI response are therefore unlikely to be attributed to differences in task performance.

Two measures of recognition performance were not computed e.g. recognition discriminability (i.e. recognition accuracy-a high score indicating normal recognition of targets and rejection of distractors, and a low score indicating high recognition of targets plus increased false positives, or low recognition of targets and low false positives) and response bias (reflects bias for yes or no

responding). It was decided that mean performance scores in a task where accuracy was expected to be high, would adequately describe any performance differences between groups.

Although not statistically significant, the means do suggest subtle differences in the numbers of discrete response events and event response times between groups. For example, the high-risk group did not make significantly less correct old responses than controls, so that they are still able to recognise previously presented targets. However, high-risk participants showed a non-significantly greater predilection for new over old responses, which is less pronounced in the control group, a similar pattern to that reported by Ragland et al (2004) in schizophrenics during a functional MRI verbal recognition task (Ragland et al 2004).

Unfortunately, without a subjective account of the basis for participants' responses, we can only tentatively speculate as to the mechanisms underlying these subtle differences. This pattern is somewhat consistent with our investigation of the same group during visual recognition, where a significantly fewer number of true positives were made in the high-risk group relative to the controls, but an equivalent number of true negatives (RCFT results, chapter 4). The high-risk group therefore may find it slightly easier to correctly identify a word that has not been seen before, than a word that has. A parsimonious explanation might be that the criterion for correctly rejecting an item is lower than that for correctly recognising it.

We were precluded from investigating more thoroughly the BOLD response associated with the incorrect old and incorrect new responses, due to there being, in some cases, fewer than twelve events in each discrete incorrect event category (Michael Rugg, personal communication). On average groups made approximately this number of errors overall, and on an individual basis a proportion of participants made considerably less incorrect responses (i.e. 33% of C, and 34.1% of HR- and HR+ made 12 or less incorrect responses). This, coupled with the difficulty in knowing the basis for error commission across groups was a key factor in the decision to omit an analysis of 'incorrect' events from the exploration of differences within and between groups in the functional MRI BOLD response during retrieval.

8.4 Functional magnetic resonance imaging results

See section 7.87 for details on results presentation and see Appendix 6 (Tables 6A-J) for random effects results tables. Please note that all p values reported are corrected for multiple comparisons unless otherwise stated, and only gray matter activations have been presented within the text.

8.4.1 Encoding: within group results

C increases

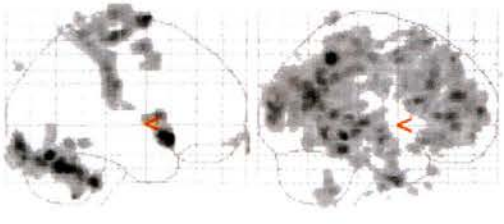
During the processing of words in the word classification task relative to baseline experimental activation, C showed significant increases in BOLD fMRI response in clusters in the left medial frontal lobe (BA 6; $K_E = 222$, $Z = 4.3$, $p<0.001$), bilateral parietal lobe (left pre-central gyrus, BA4; $K_E = 1922$, $Z = 4.7$, $p<0.001$; right post central gyrus, BA 2; $K_E = 199$, $Z = 4.4$, $p=0.006$), left superior temporal lobe (BA 21; $K_E = 243$, $Z = 5.4$, $p=0.002$), and left cerebellum (Declive; $K_E = 1213$, $Z = 5.3$, $p<0.001$).

C decreases

Areas of significantly less response during the processing of words in the word classification task relative to the baseline experimental activation were apparent in right middle temporal gyrus (BA21; $K_E = 75$, $Z = 4.4$, $p=0.32$ and $p=0.011$ *uncorrected*) and again in the left cerebellum (posterior lobe, tonsil; $K_E = 304$, $Z = 4.6$, $p<0.001$) (see figure 8.3).

Figure 8.3: Within group maps (sagittal) of areas of significantly (i) increased and (ii) decreased BOLD response in C during a word classification task relative to the baseline experimental activation

(i) (ii)



HR- increases

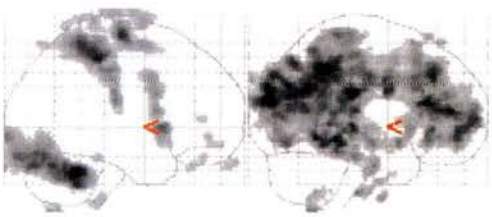
HR- showed activations across both hemispheres, including the bilateral parietal lobes (right post-central, BA 43; K_E = 1282, Z= 5.5, p<0.001 and left post-central gyrus, BA 2; K_E = 7507, Z= 6.8, p<0.001), bilateral superior temporal lobes (BA38; K_E = 444, Z= 4.8, p<0.001; K_E = 672, Z= 4.8, p<0.001), and bilateral cerebellum (left anterior lobe, culmen; K_E = 4408, Z= 7.0, p<0.001; right posterior lobe, tuber; K_E = 6006, Z= 7.0, p<0.001). The greater extent of activation shown in this group may be attributable to the larger group numbers.

HR- decreases

Relative reduced responses during word classification relative to baseline, were apparent in the left frontal lobe (sub-callosal gyrus, BA25; K_E = 518, Z= 4.1, p<0.001), right limbic lobe (cingulate gyrus, BA31; K_E = 73283, Z= 7.5, p<0.001) and right cerebellum (posterior lobe, tonsil; K_E = 1822, Z= 4.8, p<0.001) (see figure 8.4).

Figure 8.4: Within group maps (sagittal) of areas of significantly (i) increased and (ii) decreased BOLD response in HR- during a word classification task relative to a baseline experimental activation

(i) (ii)



HR+ increases

HR+ showed an increased response during word classification relative to baseline in a similar area of the left medial frontal lobe as shown in the control participants (BA6; K_E = 179, Z= 4.3, p<0.01), as well as bilaterally in the inferior parietal lobes (LBA 40; K_E = 2908, Z= 5.8, p<0.001; RBA40; K_E = 483, Z= 5.0, p<0.001), left superior temporal gyrus (BA 22; K_E = 609, Z= 4.5, p<0.001) and bilateral

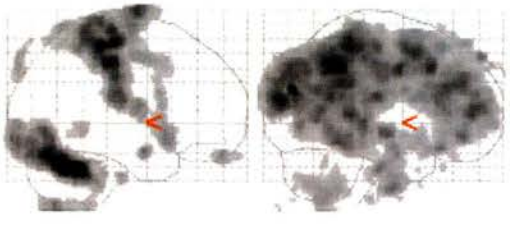
cerebellum (left anterior lobe, culmen; $K_E = 3929$, $Z = 6.4$, $p<0.001$; right posterior lobe, tonsil; $K_E = 4071$, $Z = 5.6$, $p<0.001$).

HR+ decreases

HR+ showed relative reduced responses during word classification relative to baseline in the right thalamus ($K_E = 358$, $Z = 5.5$, $p<0.001$), left cerebellum ($K_E = 265$, $Z = 4.4$, $p<0.001$) and a trend for a reduced response in the right inferior frontal gyrus (BA13; $K_E = 115$, $Z = 4.7$, $p=0.080$) and right inferior temporal gyrus (BA20/38; $K_E = 122$, $Z = 4.6$, $p=0.063$) (see figure 8.5).

Figure 8.5: Within group maps (sagittal) of areas of significantly (i) increased and (ii) decreased BOLD response in HR+ during a word classification task relative to the baseline experimental activation

(i) (ii)



8.4.2 Encoding: between group results

C vs. HR

C showed no areas of significantly greater activation than the HR group.

HR vs. C

During word classification relative to the baseline experimental activation, the HR group as a whole showed a larger BOLD fMRI response in the right inferior frontal gyrus (IFG) relative to C before correction for multiple comparisons (BA45, $K_E = 137$, $Z = 3.8$, $p=0.14$ and $p=0.006$ *uncorrected*) (see figure 8.6a). This IFG area showed a non-significantly greater response in the HR- relative to C (BA45, $K_E = 22$, $Z = 4.0$, $p=0.99$ and $p=0.22$ *uncorrected*) (see figure 8.6b). The HR+ group also showed an increased BOLD response relative to controls in the same right IFG region, befire

correction or multiple comparisons (BA45, K_E = 154, Z= 4.0, p=0.095 and p<0.005 *uncorrected*) (see figure 8.6c) and in the left inferior parietal lobule (BA40, K_E = 111, Z= 4.0, p=0.22 and p=0.01 *uncorrected*) (see figure 8.7).

Figure 8.6 (a): Between group maps of areas of greater BOLD fMRI response during word classification relative to baseline in HR relative to controls C (maxima coordinates noted (52 26 6) are MNI and indicate the inferior frontal gyrus cluster, voxel extent = 0). Sections show peak maxima of cluster overlaid on an average T1 brain

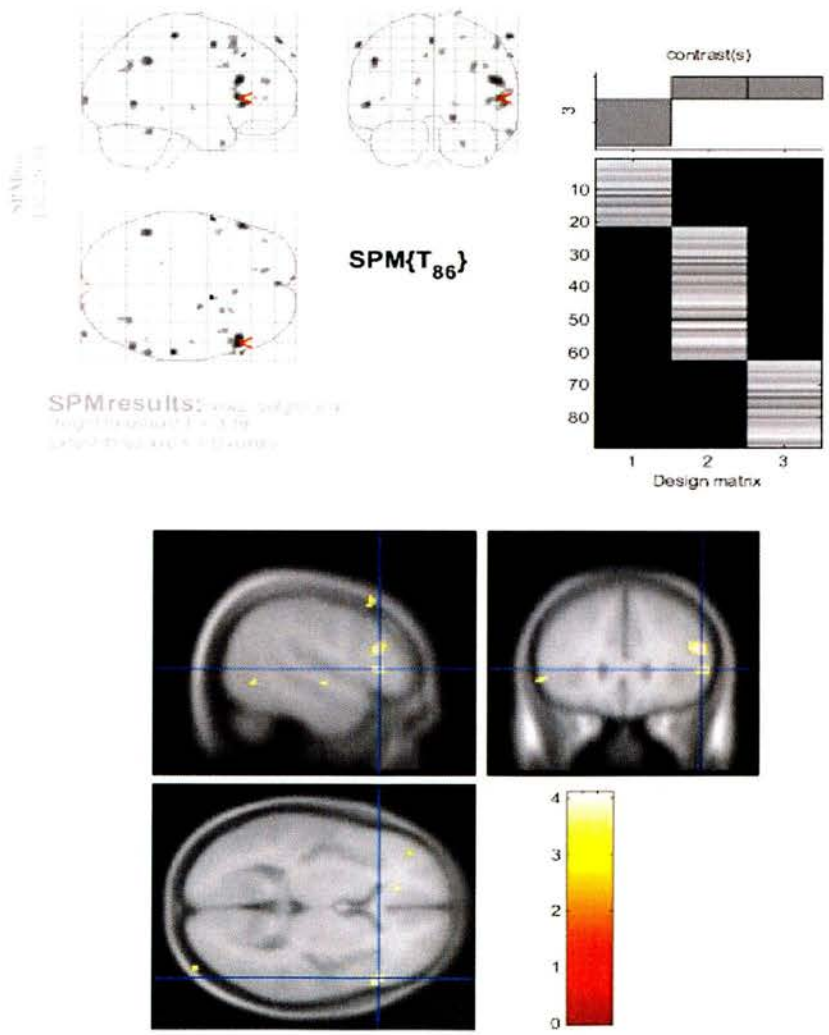


Figure 8.6(b): Between group maps of areas of greater BOLD fMRI response during word classification relative to baseline in the HR- relative to C (maxima coordinates noted (52 26 22) are MNI and indicate the inferior frontal gyrus cluster, voxel extent = 20)

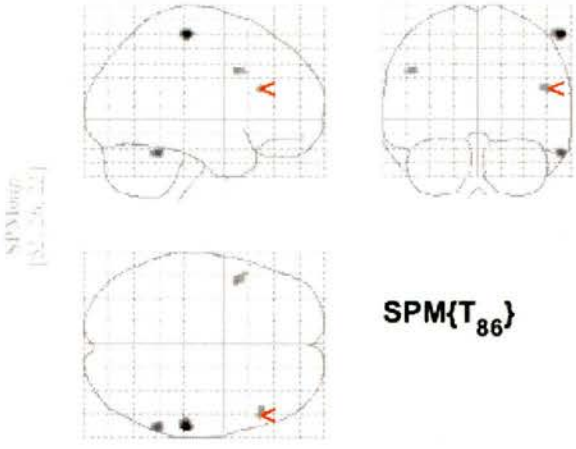


Figure 8.6 (c): Between group maps of areas of greater BOLD fMRI response during word classification relative to baseline in HR+ group relative to C (maxima coordinates noted (52 26 6) are MNI and indicate the inferior frontal gyrus cluster, voxel extent =20 voxels).

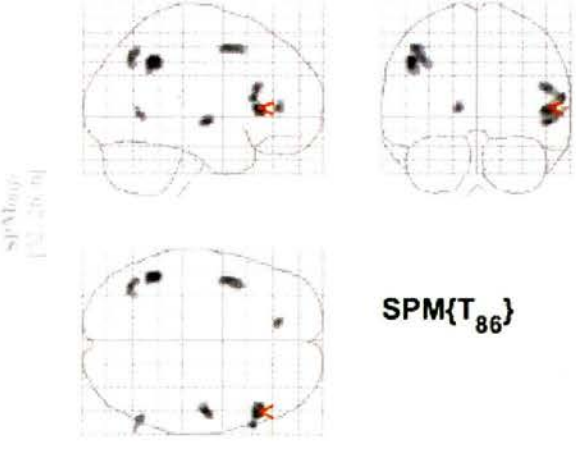
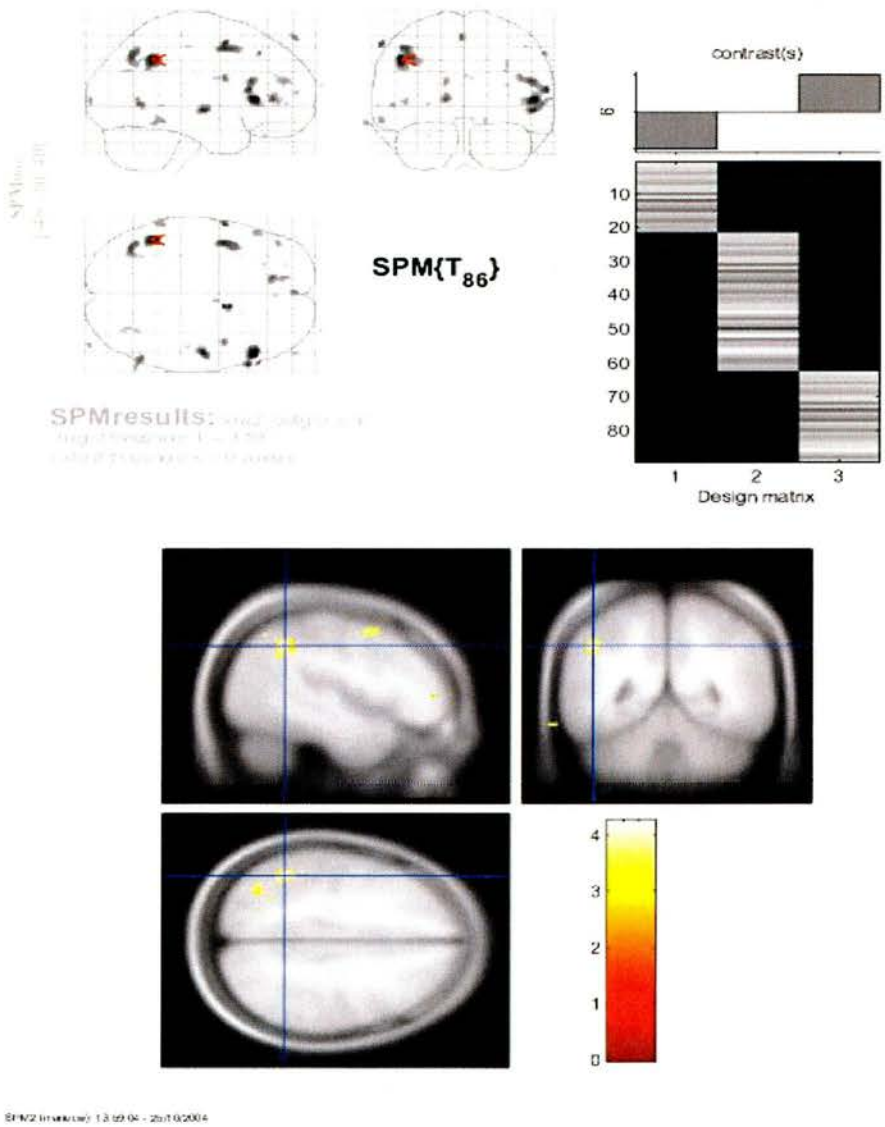


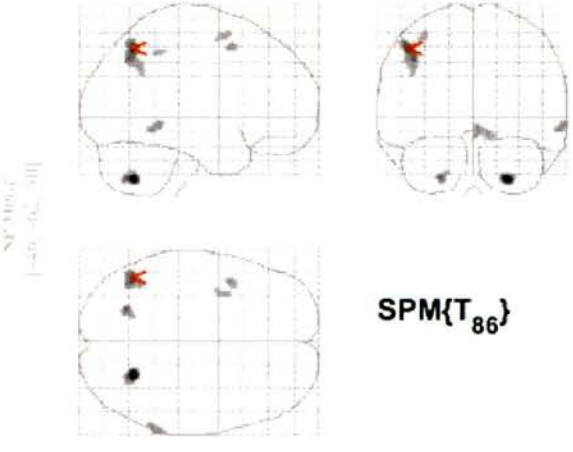
Figure 8.7: Between group maps of areas of greater BOLD fMRI response during word classification relative to baseline in HR+ relative to C (maxima coordinates noted are MNI (-46 -50 40) and indicate the inferior parietal lobe cluster, voxel extent = 0). Sections show peak maxima of cluster overlaid on average T1 brain.



HR+ vs. HR-

HR- showed no significant areas of greater activation relative to HR+ during word classification relative to baseline. However, the HR+ showed a greater fMRI response in the left inferior parietal lobe (BA7/40, $K_E = 168$, $Z = 3.9$, $p=0.069$) when compared to HR- (see figure 8.8).

Figure 8.8: Between group maps of areas of greater BOLD fMRI response during word classification relative to baseline in HR+ relative to HR- (coordinates noted are MNI (-46 –62 50) and indicate maxima of inferior parietal lobe cluster, voxel extent = 20).



8.4.3 Summary of encoding results

C show mainly left lateralised responses during semantic word classification relative to baseline experimental activation in the medial frontal and post-central gyrus, superior temporal lobe and cerebellum. HR-, on the other hand, show both left and right hemisphere responses across similar regions to the control group for this contrast. Furthermore, while HR+ show activation in a similar medial frontal lobe cluster to controls, they additionally activate the inferior parietal lobule bilaterally. Therefore, in the HR+ group, the left inferior parietal lobule (BA40) shows significantly (before correction) greater activation than HR- and C, for this contrast. The BOLD fMRI response in the right IFG (BA45) is also significantly greater (before correction) in the HR group as a whole and in HR+ (and non-significantly in HR-) relative to controls. Analysis of the within group maps suggest that this may be due to a 'deactivation' in this area, particularly in the HR+ group. This suggests a possible state related deficit in the left (and less so in the right inferior parietal lobe), and a trait deficit

as a result of 'reduced' activation during encoding in the right IFG, which is worsened in the psychotic symptom group and therefore additionally influenced by state effects.

8.4.4 Recognition versus rejection: within group results

C increases:

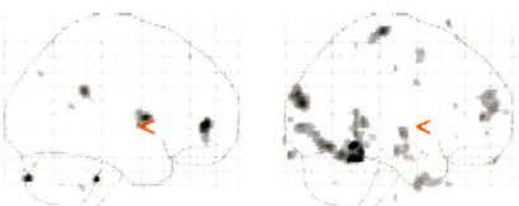
There were no significant areas of increased BOLD fMRI response during recognition responses relative to rejection responses, after correction for multiple comparisons. However, before correction, there was a significantly greater BOLD fMRI response in the left IFG (BA10; K_E = 101, Z= 5.9, p=0.15 and p<0.005 *uncorrected*), and left caudate body (K_E = 68, Z= 4.1, p=0.43 and p<0.05 *uncorrected*).

C decreases:

There were significant areas of increased BOLD fMRI response during rejection relative to recognition responses, in the right medial frontal gyrus (BA10; K_E = 174, Z= 3.7, p=0.016), right fusiform gyrus (BA37; K_E = 223, Z= 4.2, p<0.005), and right cerebellum (culmen; = 393, Z= 4.6, p<0.001), and a trend for significance in the left cuneus (BA18/19; K_E = 129, Z= 4.1, p=0.062) and left fusiform gyrus (BA19; K_E = 118, Z= 4.0, p=0.088) (see figure 8.9).

Figure 8.9: Within group maps (sagittal) of areas of (i) increased and (ii) decreased BOLD fMRI response during recognition relative to rejection in C.

(i) (ii)



HR- increases:

Relative areas of increased BOLD fMRI response during recognition compared to rejection were shown in a cluster in the sub-lobar area (extending to the medial dorsal thalamic nuclei) (BA30; K_E =

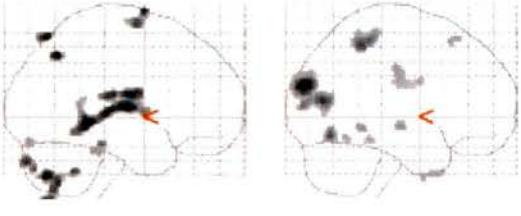
799, Z= 4.1, p<0.001), the right cerebellum (posterior lobe, pyramis; K_E = 308, Z= 4.0, p=<0.005), and the left superior parietal lobe (BA7; K_E = 61, Z= 3.9, p=0.68 and p<0.05 *uncorrected*).

HR- decreases:

Significant areas of increased BOLD fMRI response during rejection relative to recognition were shown in the left frontal, precentral gyrus (BA4; K_E = 168, Z= 3.7, p=0.058), left cuneus (BA18, K_E = 474, Z= 5.7, p<0.001), left middle temporal gyrus (BA19; K_E = 328, Z= 4.8, p<0.005), left precuneus (BA7, K_E = 287, Z= 4.7, p<0.005) and right precuneus (BA19; K_E = 399, Z= 4.3, p=<0.001)(see figure 8.10).

Figure 8.10: Within group maps (sagittal) of areas of (i) increased and (ii) decreased BOLD fMRI response during recognition relative to rejection in HR-.

(i) (ii)



HR+ increases:

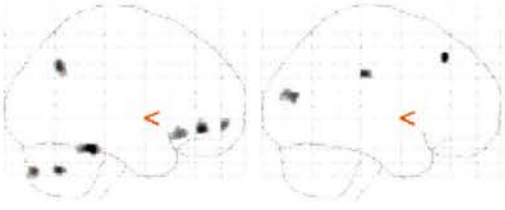
HR+ showed no significant areas of increased activation during recognition relative to rejection after correction for multiple comparisons. Before correction, there were areas of greater BOLD fMRI response in the left middle frontal gyrus (BA11/47; K_E = 52, Z= 4.0, p=0.73 and p<0.05 *uncorrected*), left IFG (BA47;K_E = 58, Z= 3.6, p=0.65 and p<0.05 *uncorrected*), and the left angular gyrus, parietal lobe (K_E = 52, Z= 4.0, p=0.68 and p<0.05 *uncorrected*).

HR+ decreases:

Again, HR+ showed no significant areas of increased activation during rejection relative to recognition after correction for multiple comparisons. However, before correction, there was a greater response in the left middle temporal gyrus (BA19; K_E = 62, Z= 3.5, p=0.59, p<0.05 *uncorrected*) (see figure 8.11).

Figure 8.11: Within group maps (sagittal) of areas of (i) increased and (ii) decreased BOLD fMRI response during recognition relative to rejection in HR+.

(i) (ii)



8.4.5 Recognition versus rejection: between group results

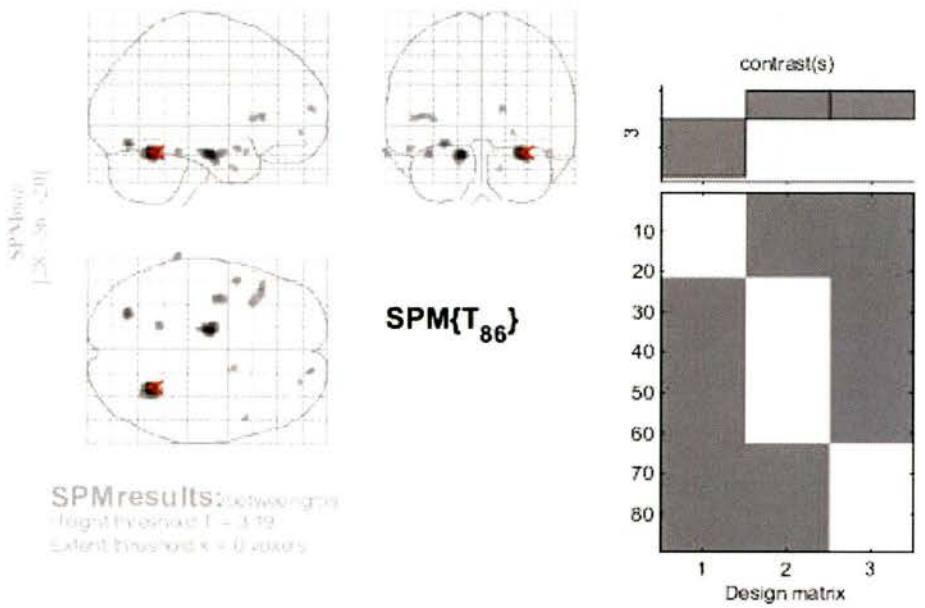
C vs. HR

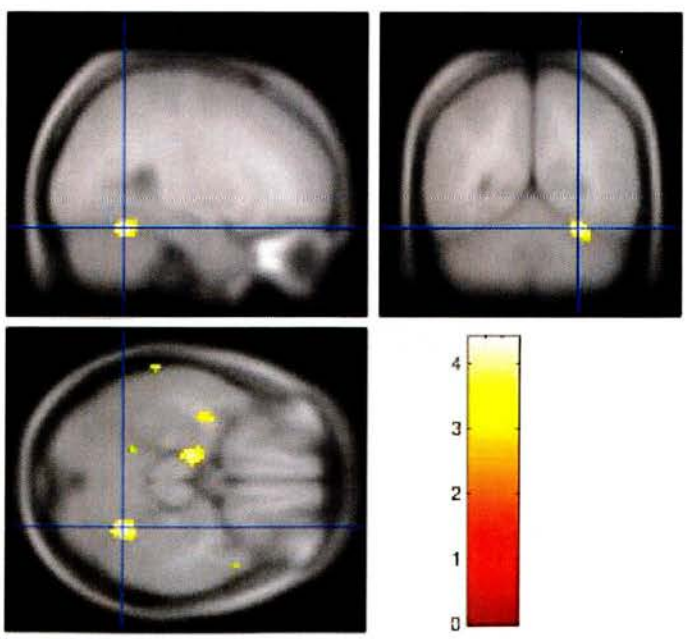
C showed no significant areas of greater activation compared to the HR group during recognition relative to rejection.

HR vs. C

The HR group as a whole showed a significantly greater response in the right cerebellum, before correction for multiple comparisons (Declive, posterior lobe; K_E = 160, Z= 4.2, p=0.26, p<0.05 *uncorrected*), as did the HR- (Declive, posterior lobe; K_E = 130, Z= 4.2, p=0.37, p<0.05 *uncorrected*). There were no other significant between group differences for this contrast (see figure 8.12).

Figure 8.12: Between group maps showing areas of increased BOLD fMRI response in HR relative to C during recognition relative to rejection (maxima coordinates are MNI (28 –56 –20) and indicate the right cerebellar cluster, voxel extent = 0). Sections show peak maxima of cluster overlaid on average T1 brain.





HR- vs. HR+

HR- showed a significantly greater BOLD fMRI response compared to HR+ in the right cerebellum, before correction for multiple comparisons (Tonsil, posterior lobe; $K_E = 176$, $Z = 3.8$, $p=0.21$, $p<0.05$ *uncorrected*).

8.4.6 Summary of recognition versus rejection results

During recognition (the classification of words, both correctly and incorrectly, as having been seen before), relative to rejection (the classification of words, both correctly and incorrectly, as not having been seen before), groups showed few significant differential areas of greater activation in the former relative to the latter, although HR- did show a significant increase in a sub-lobar cluster, extending to the medial dorsal thalamic nuclei, after correction for multiple comparisons. During rejection relative to recognition of words, both C and HR- showed greater activation in posterior visual brain areas such as the cuneus, fusiform gyrus, and precuneus, while both HR groups showed greater activity in the middle temporal gyrus. Notably, the HR+ showed the least difference between conditions, relative to the other two groups. In the HR- relative to both C and HR+, between group contrasts showed greater activation in the right posterior cerebellum. However, again, a large proportion of these results was not significant after correction for multiple comparisons, and so should be considered tentatively. Further, while combining both correct and incorrect responses (in order to compare recognition versus rejection decisions) increases the number of events included, the overlap in recruited brain areas for both response types may explain the lack of significant differences both within and between groups for this contrast.

8.4.7 Correct recognition relative to baseline: within group results

C increases:

During the correct recognition of words relative to a baseline activation (averaged fixation periods), C showed an increased BOLD fMRI response in the right frontal, precentral gyrus (BA6; $K_E = 281$, $Z= 4.8$, $p<0.005$), left IFG (BA47; $K_E = 347$, $Z= 4.6$, $p<0.001$), left middle frontal gyrus (BA9/44; $K_E = 137$, $Z= 3.6$, $p=0.059$), right superior parietal lobe (BA7; $K_E = 99$, $Z= 4.0$, $p=0.17$ and $p<0.05$ *uncorrected*), left temporal, fusiform gyrus (BA 19; $K_E = 1458$, $Z= 5.0$, $p<0.005$), and left caudate

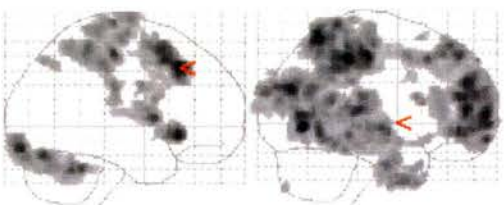
head extending to the left sub-lobar thalamus, ventral lateral and ventral anterior nucleus (K_E = 369, Z= 4.9, p<0.001). Significant areas of BOLD fMRI response increase were also evident in the right inferior occipital lobe (BA 18; K_E = 565, Z= 5.2, p<0.001) and the right cerebellum (anterior lobe, culmen; K_E = 623, Z= 4.8, p<0.001).

C decreases:

There was a significantly greater fMRI BOLD response during baseline activation relative to correct recognition in right medial frontal gyrus (BA10; K_E = 8648, Z= 5.5, p<0.001), the left middle temporal gyrus (BA38; K_E = 501, Z= 4.7, p<0.001) and the left inferior temporal gyrus (BA37; K_E = 141, Z= 4.6, p<0.05).

Figure 8.13: Within group maps (sagittal) of areas of (i) increased and (ii) decreased BOLD fMRI response during correct recognition relative to baseline, in C.

(i) (ii)



HR- Increases:

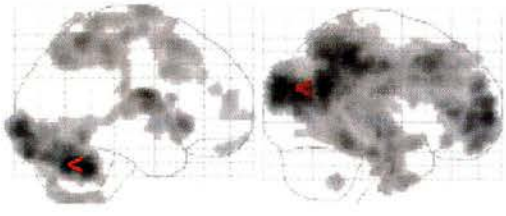
The HR- group showed increased BOLD fMRI responses during correct recognition relative to a baseline experiment activation in two clusters in the left middle frontal gyrus (BA9; K_E = 556, Z= 4.8, p<0.001 & BA10; K_E = 263, Z= 4.1, p<0.05), right middle frontal gyrus (BA11; K_E = 161, Z= 3.9, p=0.08 and p<0.005 *uncorrected*). An increased BOLD fMRI response was also evident in the left inferior parietal lobule (BA40; K_E = 263, Z= 5.6, p<0.001), as well as the right cerebellum (Tuber, posterior lobe; K_E = 14100, Z= 7.6, p<0.001).

HR- decreases:

The HR- showed decreased BOLD fMRI response during correct recognition relative to baseline experimental activation, in the right frontal lobe, sub callosal gyrus (BA25; K_E = 331, Z= 4.9, p<0.005) (see figure 8.14).

Figure 8.14: Within group maps (sagittal) of areas of (i) increased and (ii) decreased BOLD response during correct recognition relative to a baseline experimental activation in HR-.

(i) (ii)



HR+ increases:

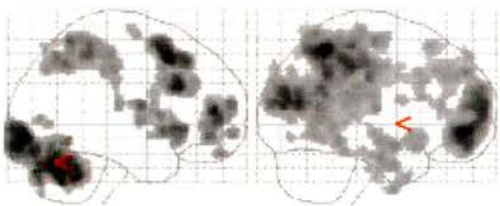
The HR+ showed an increased BOLD fMRI response during correct recognition relative to the baseline activation of the experiment in the left middle frontal gyrus (BA46; K_E = 776, Z= 5.3, p<0.001), and in the right middle frontal gyrus (BA9; K_E = 677, Z= 4.2, p<0.001). They also showed an increased BOLD fMRI response in the right inferior parietal lobule (BA40/7; K_E = 229, Z= 4.6, p=0.008), left superior temporal gyrus (BA22/38; K_E = 635, Z= 4.7, p<0.001), right inferior occipital lobe (BA18; K_E = 5492, Z= 5.8, p<0.001) and left cerebellum (Declive, posterior lobe; K_E = 3766, Z= 6, p<0.001).

HR+ decreases:

The HR+ showed a decreased BOLD fMRI response during correct recognition relative to the baseline activation of the experiment, in the right parietal lobe, precuneus (BA7; K_E = 26759, Z= 6.7, p<0.001), the left temporal fusiform gyrus (BA20; K_E = 375, Z= 4.4, p<0.001) and left parahippocampal gyrus (BA 35; K_E = 70, Z= 3.7, p=0.44, p<0.05 *uncorrected*) (see figure 8.15).

Figure 8.15: Within group maps (sagittal) of areas of (i) increased and (ii) decreased BOLD fMRI during correct recognition relative to baseline, in HR+.

(i) (ii)



8.4.8 Correct recognition relative to baseline: between group results

C vs. HR:

C showed no significant increased BOLD fMRI response relative to the HR group as a whole or the HR+ for this contrast, although they showed a significantly increased BOLD fMRI response relative to the HR- in the right frontal precentral gyrus (BA6; K_E = 131, Z= 4.2, p=0.16 and p<0.05 *uncorrected*). However, given that this statistic is uncorrected for multiple comparisons it should be considered cautiously.

HR vs. C

C showed a reduced BOLD fMRI response compared to the HR group as a whole during correct recognition relative to baseline activation in the right middle occipital gyrus (BA18; K_E = 124, Z= 4.1, p=0.19 and p<0.05 *uncorrected*). Surprisingly there were no left middle frontal lobe differences between these groups in spite of the apparent greater recruitment of these areas on the HR within group maps. HR- showed a greater BOLD fMRI response relative to controls in the right middle occipital gyrus (BA18; K_E = 119, Z= 4.2, p=0.21 and p<0.05 *uncorrected*). HR+ showed no significantly increased BOLD fMRI responses compared to controls. Once again, after correction for multiple comparisons there were no statistically significant values, therefore the uncorrected results are presented for interest, due to a lack of corrected clusters.

HR- vs. HR+

There were no significant supra-threshold clusters for this contrast.

8.4.9 Summary of correct recognition versus baseline results:

There were robust within group increases in the frontal, temporal and parietal lobes across groups for this contrast (although decreases across groups varied). The high-risk groups also showed more extensive increased bilateral frontal response and decreased middle temporal response than the controls. Nonetheless, the between group contrasts showed these apparent differences to be non-significant after correction for multiple comparisons. While before correction controls showed less activation compared to the HR group as a whole and HR- independently in the left occipital gyrus, and increased activation relative to HR- in the left frontal, precentral gyrus (BA 6), these differences may only be a feature of the larger participant numbers in the HR- and combined HR group relative to the controls.

8.4.10 Correct rejection relative to baseline: within group results

C increases:

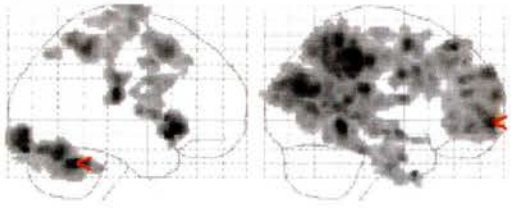
C showed a larger BOLD fMRI response during correct rejection responses relative to a baseline activation in the left IFG (BA47; $K_E = 632$, $Z = 5.4$, $p<0.001$), in the right frontal, precentral gyrus (BA6; $K_E = 249$, $Z = 4.2$, $p<0.001$) and the left medial frontal gyrus (BA6; $K_E = 752$, $Z = 4.6$, $p<0.001$). They also showed an increased fMRI response in the left temporal fusiform gyrus (BA37; $K_E = 1734$, $Z = 5.0$, $p<0.001$) and right cerebellum (Culmen, anterior lobe; $K_E = 1836$, $Z = 5.4$, $p<0.001$).

C decreases:

C showed a reduced BOLD fMRI response during correct rejection responses relative to baseline activation in the right inferior temporal gyrus (BA20; $K_E = 348$, $Z = 4.3$, $p<0.001$) and right occipital lobe, cuneus (BA19/18; $K_E = 309$, $Z = 4.2$, $p<0.001$) (see figure 8.16).

Figure 8.16: Within group maps (sagittal) of areas of (i) increased and (ii) decreased BOLD fMRI response during correct rejection relative to baseline experimental activation in C.

(i) (ii)



HR- increases:

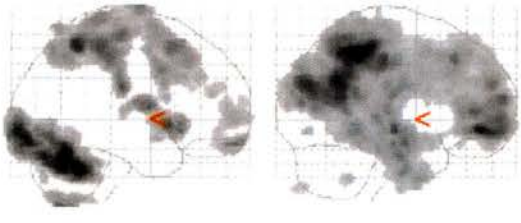
HR- showed a larger BOLD fMRI response during correct rejection responses relative to baseline activation in the right middle frontal gyrus (BA46; $K_E = 264$, $Z = 3.9$, $p<0.05$), the left IFG (BA10; $K_E = 324$, $Z = 4.1$, $p<0.005$), the left inferior parietal lobule (BA40; $K_E = 6362$, $Z = 6.3$, $p<0.001$), the left superior temporal gyrus (BA22; $K_E = 1451$, $Z = 5.9$, $p<0.001$), and the right cerebellum (Culmen, anterior lobe; $K_E = 11747$, $Z = 7.2$, $p<0.001$).

HR- decreases:

HR- showed a reduced BOLD fMRI response during correct rejection responses relative to baseline activation in the right cerebellum (Semi-lunar, posterior lobe; $K_E = 141$, $Z = 3.8$, $p=0.12$ and $p<0.005$ *uncorrected*) (see figure 8.17).

Figure 8.17: Within group maps (sagittal) of areas of (i) increased and (ii) decreased BOLD fMRI response during correct rejection relative to baseline experimental activation in HR-.

(i) (ii)



HR+ increases:

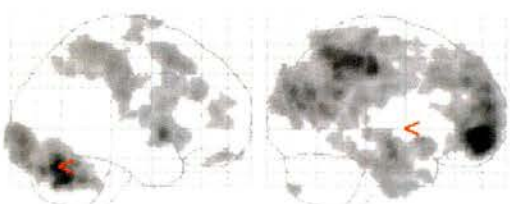
The HR+ showed a larger BOLD fMRI response during correct rejection responses relative to a baseline activation, in the right orbito-frontal gyrus (BA11; K_E = 213, Z= 4.2, p<0.01), the right middle frontal gyrus (BA46; K_E = 285, Z= 4.4, p<0.005), the right and left frontal precentral gyrus (LBA4; K_E = 171, Z= 4.3, p<0.05, RBA 4; K_E = 271, Z= 3.9, p<0.005), the left inferior parietal lobule (BA40; K_E = 2039, Z= 4.7, p<0.001), left superior temporal gyrus (BA22; K_E = 1050, Z= 4.3, p<0.001), and the right cerebellum (Culmen, posterior lobe; K_E = 4260, Z= 6.0, p<0.001) and left cerebellum (Declive, posterior lobe; K_E = 3965, Z= 6.8, p<0.001). HR+ showed additional enhanced bilateral fMRI response in the sub-lobar lentiform nucleus, putamen (right; K_E = 418, Z= 4.6, p<0.001, left; K_E = 497, Z= 5.4, p<0.001).

HR+ decreases:

The HR+ showed a smaller BOLD fMRI response during correct rejection responses relative to baseline activation in the left medial frontal gyrus (BA10; K_E = 31501, Z= 7.2, p<0.001) left limbic lobe, anterior cingulate gyrus (AC) (K_E = 371, Z= 4.9, p<0.001) and left parahippocampal gyrus (PHG) (BA35/36; K_E = 274, Z= 4.8, p<0.005) (see figure 8.18).

Figure 8.18: Within group maps (sagittal) of areas of (i) increased and (ii) decreased BOLD fMRI response during correct rejection relative to baseline experimental activation in HR+.

(i) (ii)



8.4.11 Correct rejection relative to baseline: between group results

C vs. HR

C showed no enhanced response relative to the HR group as a whole or compared to HR- or HR+ participants for this contrast.

HR vs. C

HR- showed a larger BOLD fMRI response relative to C in the left middle occipital gyrus (BA 18; K_E = 143, Z= 3.6, p=0.13 and p<0.01 *uncorrected*). There was an uncorrected trend for greater right middle occipital activation in HR relative to C (BA 18; K_E = 59, Z= 3.7, p=0.68 and p=0.076 *uncorrected*). However, there were no significant differences between C and HR+ for this contrast. There were no differences between HR- and HR+ for this contrast.

8.4.12 Summary of correct rejection versus baseline results:

During the correct rejection of words relative to baseline activation, there were no significant differences between groups after correction for multiple comparisons. Before correction, C differed from the HR- only in their smaller activation of the left middle occipital cortex (BA 18). However, some apparent differences between activations in the groups are evident in the within group contrast maps, with HR+ showing significant decreased activation in the limbic lobe (parahippocampal gyrus and anterior cingulate) during both correct old and correct new responses relative to baseline, an area not shown to have decreased activation in either the HR- or C groups. The nature of deactivations in contrasts was noted earlier, and it is interesting that this group might show an enhanced activation in this area during baseline experimental activation relative to correct new responses or alternatively, less activity during correct new relative to baseline. The parahippocampal gyrus has been associated with both recollection and familiarity processes during retrieval in healthy volunteers.

8.4.13 Correct recognition versus correct rejection: within group results

C increases:

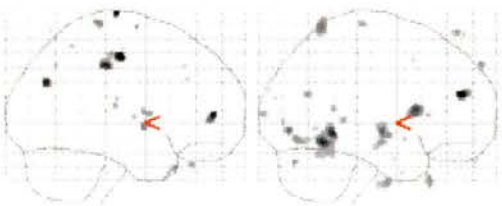
During correct old relative to correct new responding, and before correction for multiple comparisons, C had a greater fMRI response in the left parietal lobe, post-central gyrus (BA 2; K_E = 100, Z= 4.0, p=0.16 and p< 0.005 *uncorrected*).

C decreases:

C showed a greater response in the right lingual gyrus (BA19, K_E = 196, Z= 4.1, p<0.05) and left cerebellum, culmen (K_E = 132, Z= 4.1, p=0.057), during correct new relative to correct old (see figure 8.19).

Figure 8.19: Within group maps (sagittal) of areas of (i) increased and (ii) decreased BOLD fMRI response during correct recognition relative to correct rejection in C.

(i) (ii)



HR- increases:

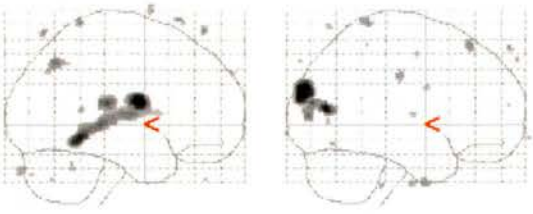
During correct old relative to correct new responses HR- showed an increased BOLD fMRI response in the left parahippocampal gyrus, extending into the left thalamus, pulvinar and left anterior lobe of the cerebellum, culmen (K_E = 959, Z= 5.1, p< 0.001) and before correction for multiple comparisons, a trend for significance in the right inferior parietal lobule (BA 7; K_E = 48, Z= 3.9, p=0.76, p=0.08 *uncorrected*).

HR- decreases:

During correct new relative to correct old events, the HR- showed greater responses in the left cuneus, occipital lobe (BA18, K_E = 282, Z= 4.8, p<0.005).

Figure 8.20: Within group maps (sagittal) of areas of (i) increased and (ii) decreased BOLD fMRI response during correct recognition relative to correct rejection in HR-.

(i) (ii)



HR+ increases:

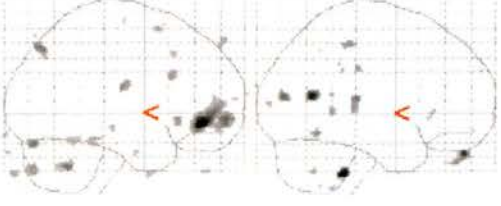
During correct old relative to correct new responses the HR+ demonstrated a greater response in the left middle frontal gyrus (BA 47; K_E = 343, Z= 5.2, p<0.001). Before correction for multiple comparisons, there were significant responses in the right and left cerebellum, (R anterior lobe; K_E = 66, Z= 4.0, p=0.52 and p<0.05 *uncorrected*; Pyramis, posterior lobe; K_E = 78, Z= 3.7, p=0.38 and p<0.05).

HR+ decreases:

HR+ showed larger activations in the left frontal orbital gyrus (BA11, K_E = 51, Z= 4.0, p=0.74 and p<0.05 *uncorrected*), left superior temporal gyrus (BA22, K_E = 54, Z= 4.6, p=0.69 and p<0.05 *uncorrected*) and left cerebellum (K_E = 564, Z= 4.2, p=0.66 and p<0.05 *uncorrected*) during correct new relative to correct old responses. However, none of these results survived correction for multiple comparisons and so should be considered tentatively.

Figure 8.21: Within group maps (sagittal) of areas of (i) increased and (ii) decreased BOLD fMRI response during correct recognition relative to correct rejection in HR+.

(i) (ii)



8.4.14 Correct recognition versus correct rejection: Between group results

C vs. HR

During correct old relative to correct new responding, C showed no significant areas of greater response relative to HR participants as a whole or HR with or without symptoms.

HR vs. C

During correct recognition relative to correct rejection, the HR group as a whole showed a significantly greater fMRI response in the right cerebellum (Tuber extending into declive, posterior lobe; $K_E = 388$, $Z = 4.4$, $p<0.001$), relative to C. Before correction for multiple comparisons, HR showed greater responses in the right middle temporal gyrus (BA 20/21; $K_E = 77$, $Z = 4.0$, $p=0.5$ and $p<0.05$ *uncorrected*), and in two clusters in the left cerebellum (Pyramis, posterior lobe; $K_E = 58$, $Z = 3.9$, $p=0.74$ and $p=0.06$ *uncorrected;* Culmen, anterior lobe:; $K_E = 61$, $Z = 3.5$, $p=0.71$ and $p=0.055$ *uncorrected*) relative to C. Moreover, the latter cerebellar response achieved significance after correction for multiple comparisons, when the threshold was raised to $p<0.005$. This also showed an increased response in the HR relative to C in a thalamic cluster before correction for multiple comparisons (11 –26 8; pulvinar; $K_E = 115$, $Z = 3.5$, $p=0.96$ and $p<0.05$ *uncorrected*) (see figure 8.22).

HR- showed increased BOLD fMRI response relative to C bilaterally in the cerebellum (Left culmen, anterior lobe; $K_E = 183$, $Z = 3.9$, $p<0.05$, and right culmen, extending into tuber, posterior lobe; $K_E = 202$, $Z = 3.9$, $p<0.05$). Raising the threshold to $p<0.005$ also showed the same increased thalamic response, significant before correction for multiple comparison (-9 -26 8; pulvinar; $K_E = 178$, $Z = 3.8$, $p=0.70$ and $p=0.02$ *uncorrected*) (see figure 8.23)

Figure 8.22: Between group maps of areas of greater BOLD fMRI response in HR relative to C during correct recognition relative to correct rejection (maxima coordinates are MNI (28 – 54 -20) and indicate right cerebellar cluster, voxel extent = 0). Sections show peak maxima of cluster overlaid on average T1 brain.

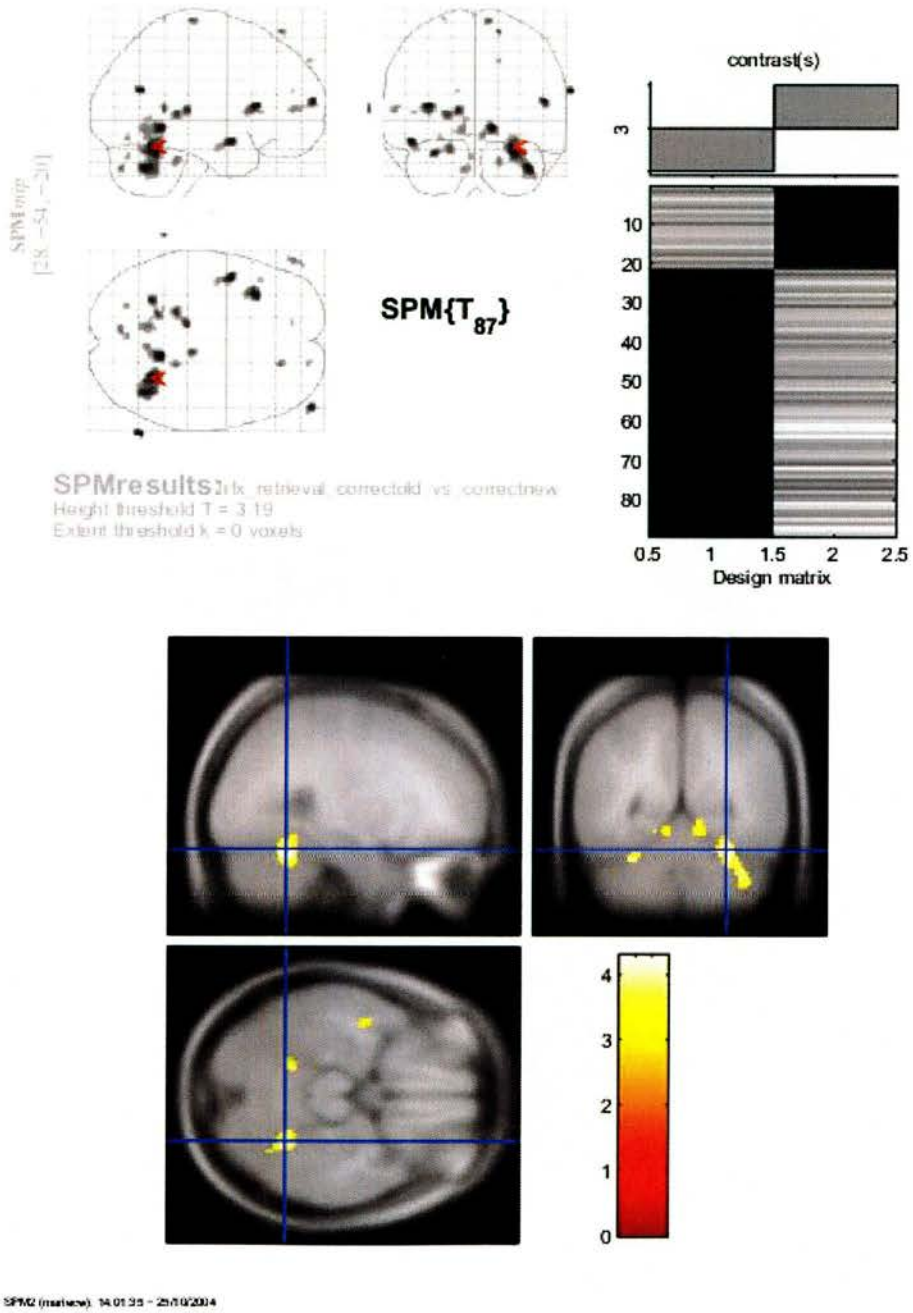
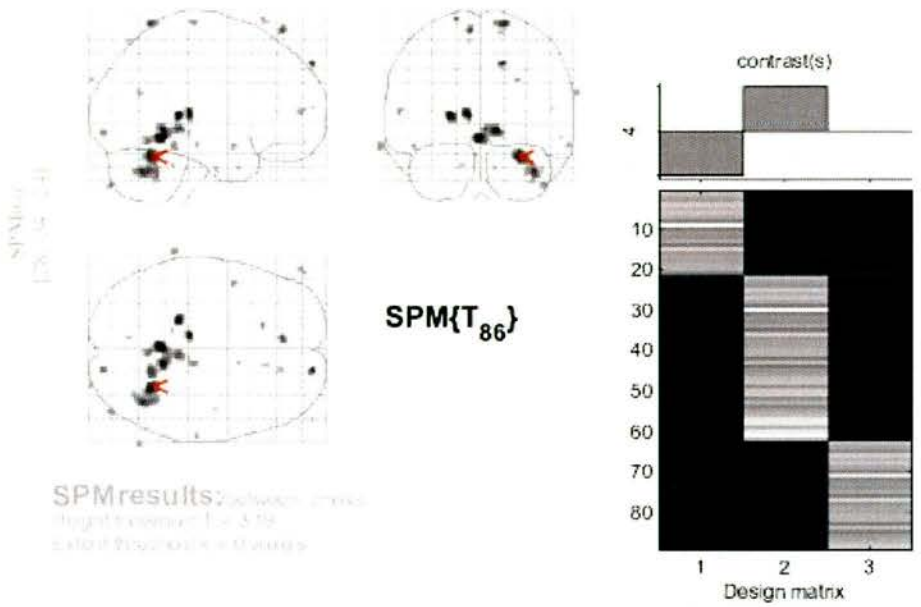
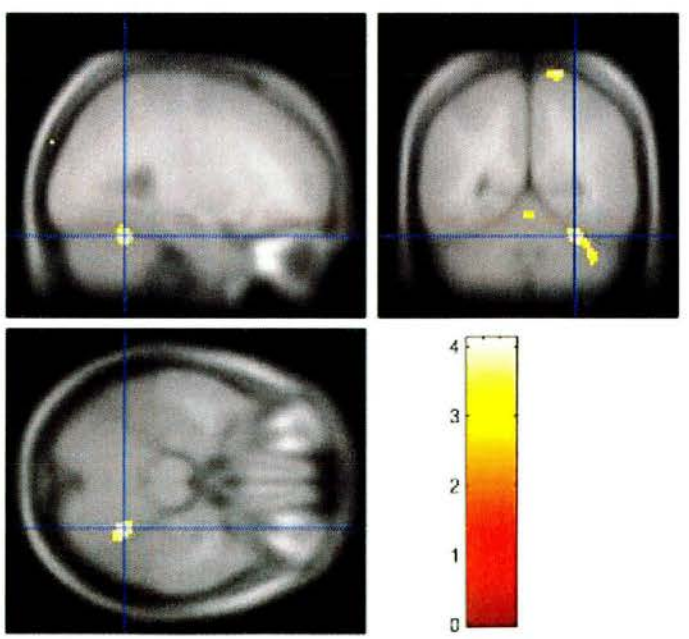


Figure 8.23: Between group maps of areas of greater BOLD fMRI response in HR- relative to C during correct recognition relative to correct rejection (maxima coordinates are MNI (28 –54 –24) and indicate right cerebellar cluster, voxel extent = 0). Sections show peak maxima of cluster overlaid on average T1 brain.





HR+ also showed a greater fMRI response relative to C in the right cerebellum (Tuber, posterior lobe; K_E = 300, Z= 4.4, p<0.005) and left cerebellum (Culmen, anterior lobe extending into limbic lobe, sub-gyral; K_E = 162, Z= 3.9, p=0.08). Before correction for multiple comparisons, there were increases in the right middle temporal gyrus (BA 20/21; K_E = 106, Z= 4.6, p=0.29 and p<0.05 *uncorrected*) and left cerebellum (Pyramis, posterior lobe; K_E = 58, Z= 3.9, p=0.75 and p=0.06 *uncorrected*)(see figure 8.24).

HR- vs. HR+:

During correct old relative to correct new responding, HR- showed a greater BOLD fMRI response in the right ventral anterior nucleus of the thalamus relative to HR+ (K_E = 190, Z= 3.9, p<0.05), while HR+ showed a greater response relative to HR- in the left middle frontal gyrus, before correction for multiple comparisons (BA11/47; K_E = 96, Z= 3.6, p=0.36 and p<0.05 *uncorrected*) (see figure 8.25).

Figure 8.24: Between group maps of areas of greater BOLD fMRI response in HR+ relative to C during correct recognition relative to correct rejection (maxima coordinates are MNI (40 –60 –38) and indicate right cerebellar cluster, voxel extent = 0). Sections show peak maxima of cluster overlaid on average T1 brain.

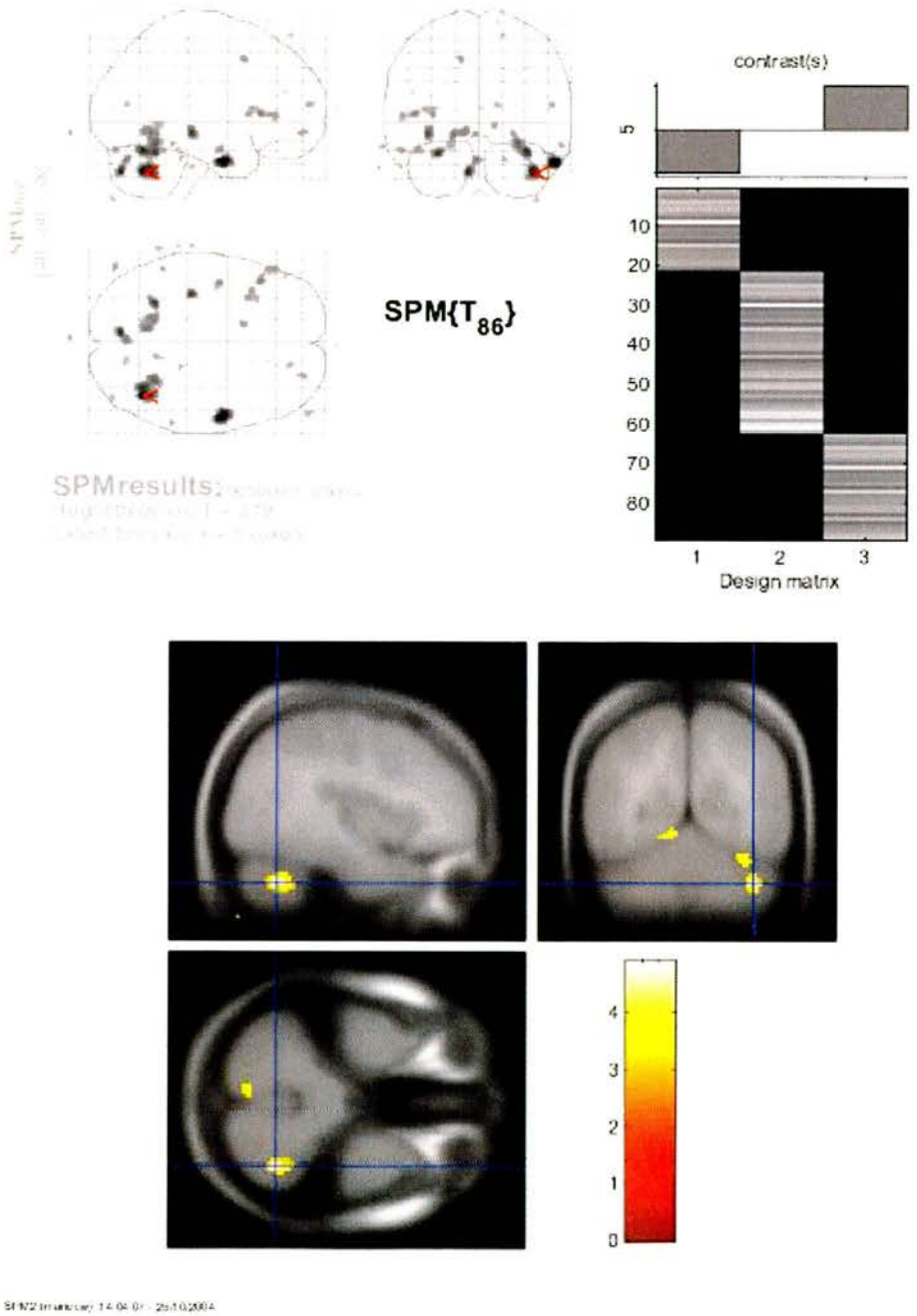
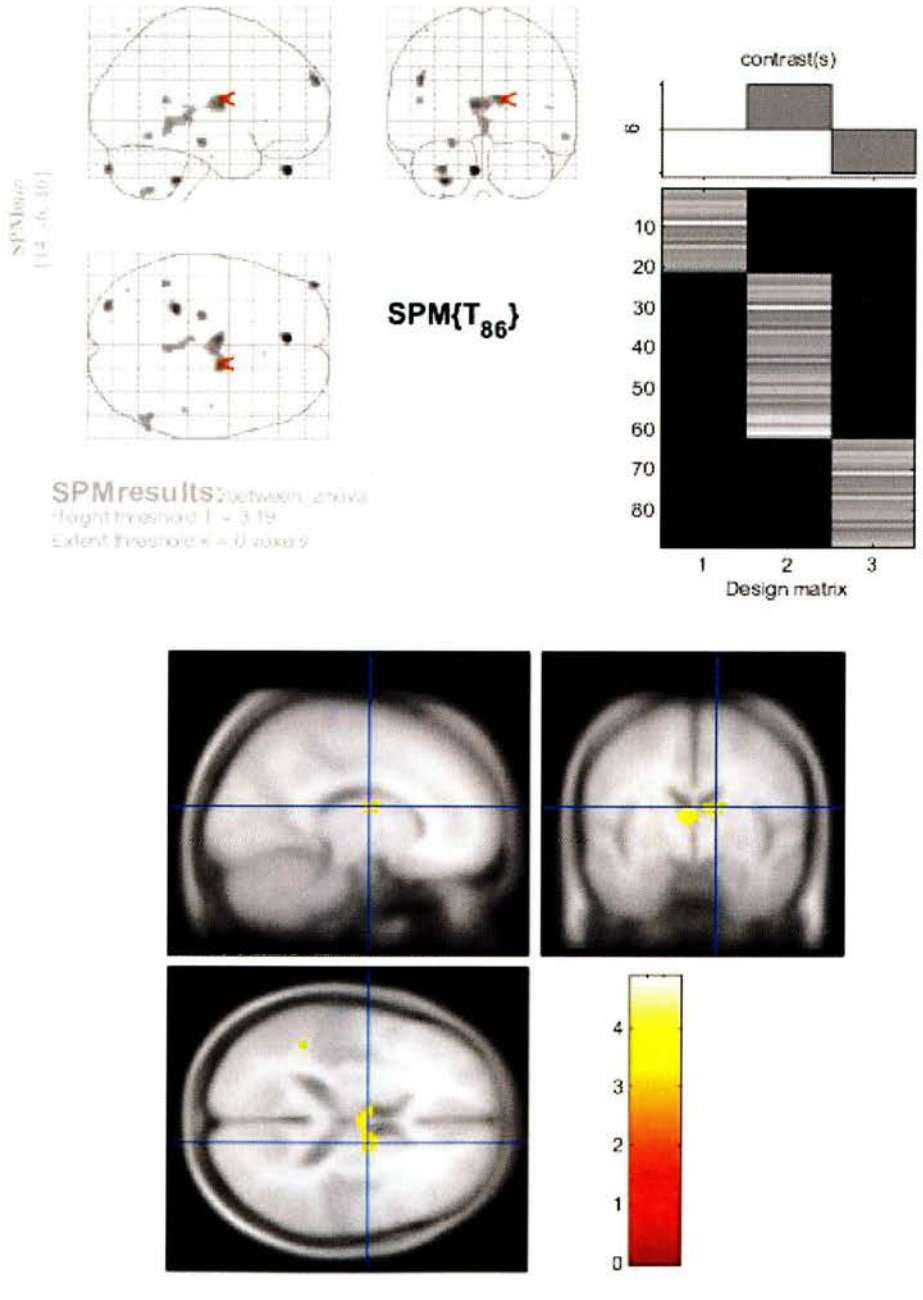


Figure 8.25: Between group maps of areas of greater BOLD fMRI response in HR- relative to HR+ during correct recognition relative to correct rejection (maxima coordinates are MNI (14 –6 16) and indicate right thalamic cluster, voxel extent = 0). Sections show peak maxima of cluster overlaid on average T1 brain.



8.4.15 Summary of correct recognition versus correct rejection results:

The statistical parametric maps for the within group contrasts, suggest that the increased BOLD fMRI response during correct old relative to correct new responding is very different in all three groups; with mainly parietal, precentral gyral activation in C; limbic, parahippocampal gyral activation in the HR- group; and mainly inferior and superior frontal activation in the HR+ group. In the results of the random effects between group contrasts, controls showed a reduced BOLD fMRI response relative to the HR group as a whole, and relative to HR- and HR+ independently, in the bilateral cerebellum. This represents an important and un-hypothesised trait deficit in the high-risk group, during successful recognition, when compared to the controls. Enhanced activation was also apparent in the right middle temporal gyrus in the HR group as a whole and in the HR+ relative to C, although this may be due to reduced within group activation of this area in the HR+ during correct recognition. HR- also showed an increased fMRI response relative to HR+ in the ventral anterior thalamus. Thalamic increase in the HR group as a whole and in HR- was apparent before correction for multiple comparisons, after raising the threshold to $p<0.005$. However, the HR group effect may be mainly due to the HR- response, given that there was no indication of thalamic increased response on the HR+ within group map.

The frontal response we did hypothesise was not apparent, although the fixed effects between group analysis did show an increased activation in right middle frontal gyrus (BA10) in the HR group relative to controls during the correct old relative to correct new contrast, and which could be considered a trait effect (see table 8.7). The absence of a similar result following the random effects analysis suggests that the participant-to-participant variance across scans, which is introduced as a random factor to the analysis, must be large enough to have removed this previous response difference. In order to further explore the loss of this result in the between group random effects analysis, we plotted individual responses at the coordinates of the significant fixed effects cluster (24 54 –8), during the correct recognition relative to correct rejection contrast (see figure 8.26).

Table 8.8: Correct old versus correct new fixed effects between group analysis: maxima of significant differences in brain fMRI response between HR+, HR- and C

Group Comparisons	Anatomy	Talairach Coords	MNI Coords	Z	Cluster P corrected value
HR > C	Right superior frontal gyrus (BA10)	24 52 –6	24 54 -4	4.79	0.06
HR- > C	Right medial frontal gyrus (BA10)	12 60 14	11 58 9	4.20	0.09
HR+ > C	Right middle frontal gyrus (BA10)	24 54 –8	24 56 –6	5.31	0.04

Height threshold p<0.001, Cluster size > 100

Figure 8.26: Plot of responses for the peak maxima of the right middle frontal gyrus cluster (24 54 -8) across participants during correct recognition versus correct rejection (coordinates noted are talairach).

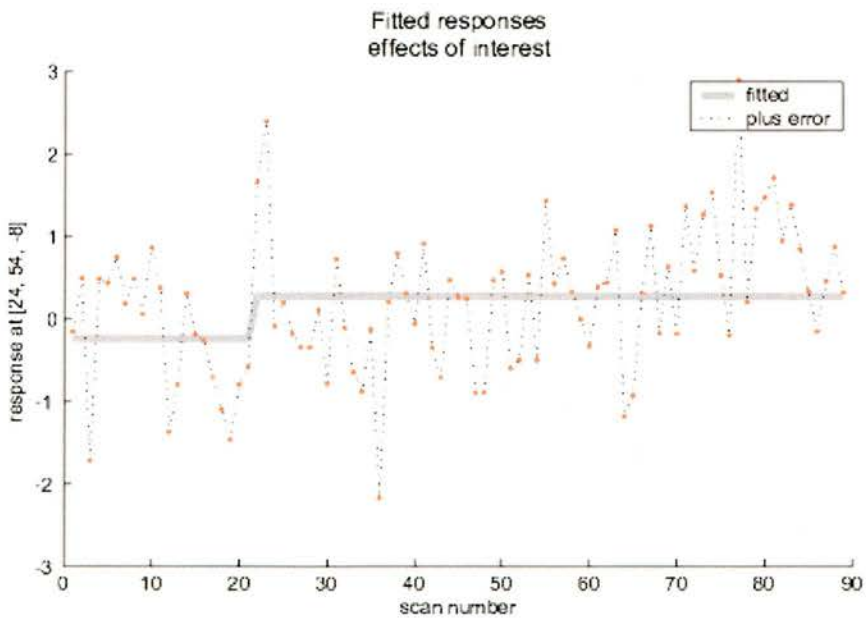


Figure 8.26 demonstrates that although not significantly different between groups, the fitted BOLD response at the specified coordinates in the right middle frontal gyrus, appears slightly greater across those in the HR group (both with and without symptoms) compared to C (first 21 scan numbers). However, individual heterogeneity across scans in the HR group is also apparent from the plot of fitted responses, and may therefore have reduced the power to detect significant between group

differences at this location following a random effects analysis. Alternatively, only a select number of HR participants may be characterised by this hyperfrontal response relative to C. It would therefore be interesting to further explore this area of response in an investigation of participants who have subsequently developed schizophrenia, in order to ascertain whether this is reflective of the development of schizophrenia in this group.

Chapter 9: Investigation 5- Discussion

We predicted that there would be no significant performance differences between the high-risk participants and controls during word classification and subsequent word recognition. Our behavioural results suggest this to be the case, although a very subtle difference in response predilection was apparent between the groups. Given roughly equated behavioural performance, we hypothesised that the high-risk participant group as a whole would show a significantly increased brain response in areas known to support verbal episodic encoding and retrieval, and which have also been demonstrated as functionally aberrant in schizophrenics and to a lesser extent in their biological relatives (i.e. frontal, temporal, parietal and cerebellar areas). We also considered several possible interpretations of the anticipated increased activations in the high-risk group as a whole, and in the sub-group with psychotic symptoms. Firstly, that it may be a reflection of different physiological brain responses in individuals with a genetic vulnerability for schizophrenia, hence a trait deficit. Secondly, where this response is more exaggerated in similar areas in high-risk participants with psychotic symptoms relative to controls and those without symptoms, it might represent a state related deficit, and therefore further along a continuum of cerebral dysfunction in individuals with a putative intermediate phenotype for the disorder. Thirdly, that increased response may be compensatory to deficient activation in aspects of the required brain networks (i.e. in fronto-temporal and fronto-parietal networks). Finally, that increased response might also be indicative of different processing strategies employed by the high-risk and control groups in order to successfully perform the task (e.g. recollection versus familiarity). Unfortunately, without a modified paradigm, we can make no inferences regarding the latter point.

9.1 Word classification

9.1.1 Within group contrasts

First level within group analyses showed that during the processing of words in the word classification task relative to baseline experimental activation, all groups showed enhanced frontal, temporal, parietal and cerebellar responses, mainly left lateralised in the controls, and in both hemispheres in the high-risk groups. These within group responses differ from the typical activations described in a number of other living versus non- living classification tasks, due to the absence of left IFG

(BA45/47) activation, and the presence of STG and parietal pre and post central gyrus activation across groups. However, Jennings et al (1997) and Kapur et al (1994), for example, contrasted semantic word classification (living versus non-living) with a perceptual, non-semantic judgment task, so that responses in the healthy volunteers were reflective of processing specific to semantic but not perceptual word processing. Conversely, Price et al (1997) showed no frontal response, but inferior parietal and middle temporal gyrus response during a living versus non-living relative to a phonological decision task in healthy volunteers. In our task, word processing across the entire word classification task was compared to the baseline experimental activation, so that any response differences may be due to both semantic and phonological word processing. Indeed, the parietal pre and post central gyri are somatosensory areas, and may indicate low level sensory processing. In addition to this, participants were aware that the classification task also preceded the explicit episodic recall of the words presented for classification, so that additional processing may have included an attempt to 'remember' these words for later recall.

The slightly reduced laterality in the high-risk group during word classification is consistent with a number of fMRI word generation tasks in schizophrenic patients (Artiges et al 2000; Sommer et al 2003a), and has been described as a compensatory recruitment of right hemispheric areas to support taxed left cerebral function, a diminished laterality in left hemisphere language areas, or a convergence of both verbal and visuo-spatial processing during task performance.

9.1.2 Between group contrasts

Right inferior frontal gyrus (BA45)

The second level between group analysis for this contrast showed a greater response in the right IFG (BA45) in the high-risk group as a whole (before correction) and in the high-risk participants with psychotic symptoms (at corrected trend level) relative to controls. While this did not achieve significance after correction for multiple comparisons, and therefore should be considered cautiously, it remains to be of interest given that it is line with our hypotheses. However, it is also an interesting result given the absence of greater activation in this area on the within group maps for this contrast, and high-risk participants with psychotic symptoms showed a greater right IFG activation (BA45)

during the baseline activation of the experiment relative to the word classification task. The more significant response difference between the controls and the high-risk participants with psychotic symptoms may therefore be attributable to the latter group's reduced activation in BA45 during the task relative to the experimental baseline response. This raises the issue of the value of 'deactivations' when interpreting brain response during cognitive performance. Several authors have postulated a default mode of functionality during baseline states, with the posterior medial cortices, the parietal lobes, cingulate cortices and precuneus hypothesised as involved in the continuous gathering of perceptual information, the posterior lateral cortices (e.g. superior temporal gyrus) involved in the directing of attention to salient environmental stimuli, and the ventral medial prefrontal and dorsal medial prefrontal cortices involved in spontaneous and task related performance, hence continuous and dynamic in their activity. During goal engagement, attention will be focused on task related performance, and so activation in some of these areas will be attenuated (Gusnard and Raichle 2001; Raichle et al 2001). Indeed, Daselaar et al (2004) suggested that deactivations in temporo-parietal areas including the precuneus, during encoding, were predictive of subsequent memory for successfully encoded events. In line with Gusnard and Raichle's hypothesis, this could be due to the reallocation of resources elsewhere (Daselaar et al 2004a).

Reduced IFG (BA45) response has been demonstrated in schizophrenic patients during semantic processing (Kubicki et al 2003; Nohara et al 2000; Ragland et al 2004) and has been interpreted as reflecting ineffective use of executive control to guide semantic processing. The IFG or ventrolateral prefrontal cortex (VLPFC) has been activated in verbal encoding tasks in healthy volunteers, and may be integral to semantic word processing, the generation of the semantic attributes of an item, and in the usage of cues to facilitate semantic information retrieval (Demb et al 1995; Fletcher and Henson 2001; Gabrieli 1998; Pilgrim et al 2002). This would suggest that the high-risk participants with psychotic symptoms are deactivating an area important in guiding the generation of semantic material, and therefore may not be effectively facilitating performance of the task. However, the absence of this response in the other two groups suggests that the task is usually performed without or with less recruitment of this area.

This response may be trait related, but appears to be more pronounced in those who are experiencing transient psychotic symptoms, suggesting a continuum of hypofrontal activation in the high-risk group. Hypofrontality has been reported in unaffected relatives of schizophrenics beyond the age of maximum risk for the development of the disorder (Callicott 2003). However, the latter study reported a parametric response in the DLPFC (BA9/46), associated with an increase in working memory load. It is yet unclear whether other functionally distinct areas of the frontal lobe exhibit the same capacity limited response as the DLPFC, or whether this IFC activation may be a more general reflection of aberrant frontal connectivity, as in schizophrenia.

Left inferior parietal lobe (BA40)

The second level between group analysis for this contrast also showed a significantly greater BOLD fMRI response, in the left IPL (BA40) in high-risk participants with psychotic symptoms relative to both those without symptoms (at corrected trend level) and controls (significant before correction for multiple comparisons), during word classification relative to the baseline experimental activation. The within group maps for high-risk participants with symptoms showed a greater bilateral IPL (BA40) response during word classification relative to baseline activation, a response not apparent in the other two groups. This is partially consistent with our hypothesis, that parietal areas implicated in verbal encoding may show an enhanced response in high-risk participants relative to controls, and where the deficit was related to state, enhanced response relative to high-risk participants without psychotic symptoms. However, there is no evidence from the within group maps of increased inferior parietal activation in the latter group, implying that this may not be a genetically mediated deficit. Moreover, despite a previously hypothesised effect, it remains significant relative to controls only before correction, and therefore should be viewed with this in mind.

This area of the left IPL was also shown to be hyperactive in the same high-risk participant group relative to high-risk participants without symptoms and controls, during a covert word generation task (Whalley et al 2004). This suggests that hyper-activation of the IPL in high-risk participants experiencing transient psychotic symptoms is indeed a state related deficit, broadly associated with for example, language or attention tasks. However, activity in this region was also noted in high-risk

participants without symptoms during the word generation task, and while not significantly greater than in the controls, suggests a genetic component of the functional over activation of this region. Of course, the genetic component may actually be for an alternative primary disturbance for which a secondary 'hyper-parietality' is compensatory.

Impaired IPL function has been demonstrated in neuroimaging studies of verbal memory in schizophrenics. However, this has been mainly during verbal retrieval (Fletcher et al 1998) or correct verbal recognition (Ragland et al 2004). There is less evidence for dysfunctional parietal response during encoding in schizophrenia. Kubicki et al (2003) showed hyper-activation in a cluster extending from the left STG to the left IPL in patients relative to controls during the semantic encoding relative to baseline condition. This region was active in patients during both the non-semantic and semantic encoding condition, suggesting it was not specifically related to the accessing of semantic information (Kubick et al 2003). Kubicki et al (2003) asserted that the fronto-temporo-parietal network supported the accessing and storage of semantic and non-semantic information, in which hyper-activation may well reflect a disturbance of semantic memory (Kubicki et al 2003). While Ragland et al (2004) showed no differential activation in this area in patients relative to controls during encoding, patients did show left IPL activation in within group maps for the encoding of correctly recognised words, a region not activated for the same contrast in controls (Ragland et al 2004).

In neuroimaging studies of verbal working memory in schizophrenia, hyper and hypofrontality is often concomitant with increases in the IPL (Quintana et al 2003). This would appear to be somewhat consistent with our finding of reduced right IFG along with increasee left IPL activation during word classification, with the latter possibly a compensatory increase due to ineffective frontal response. Evidence for structural deficits in the parietal lobes in schizophrenic patients is less robust than for other areas of cortex, and it is often suggested that the IPL retains a normal, albeit enhanced response in schizophrenia, in order to compensate for deficient frontal activation during tasks of greater cognitive demand. IPL activation has been shown during tasks of verbal working memory and in memory for spatial locations in healthy volunteers, and has been hypothesised as an area of transient

phonological (left IPL) and visuo-spatial material (right IPL) storage (Jonides et al 1998a; Jonides et al 1998b). However, Jonides et al (1998) have also suggested this region may be related to the shifting of attention from one internal representation to another (Jonides et al 1998a; Jonides et al 1998b). Indeed, Coull and Nobre reported bilateral activation of the IPL, in the right during tests of spatial orienting, and in the left during tests of temporal attention in PET and fMRI studies in healthy volunteers (Coull and Nobre 1998). This is supported by evidence from human and animal studies which implicate the IPL as an area involved in the top down allocation of attentional resources (Corbetta et al 2000; Hopfinger et al 2000; Wardak et al 2004) and which may play a role in tests of selective attention, during the monitoring and inhibition of responses.

More specifically, Drager et al (2004) showed increased right IPL activation (BA40) and superior parietal lobe (BA7) activation in healthy volunteers during a difficult relative to easy cue word generation task (i.e. word beginnings to be completed with as many different words as possible). This could be construed as requiring an increased maintenance in the phonological store of more difficult word stem representations, suggestive of the right IPL's supportive role in verbal representation maintenance. However, the authors assert it may be a compensatory recruitment in non-language lateralised areas, during difficult language tasks. The right IPL may therefore provide a more general executive and attentional role during a language task of increasing difficulty (but not complexity) (Drager et al 2004).

For the high-risk group experiencing transient psychotic symptoms, there were no significant differences in reaction time or accuracy between groups for the word classification task, suggesting that increased activation does not have a detrimental effect on the word classification task performance. Indeed, in the word generation task, IPL activation was not linearly related to task difficulty (Whalley et al 2004). Alternatively, this response may reflect explicit attempts to maintain words in memory for the future recall task. However, the enhanced activation in the same group during both a word generation and word classification task suggests that the latter explanation is insufficient. Both tasks require the accessing of semantic memory for the generation of a meaningful word or semantic information relevant to the sentence and word representations respectively. It is

therefore plausible that the right IPL is integral to the maintenance of representations in memory or that enhanced response may be an indication of increased attention during the accessing and retrieving of semantic information.

Taylor et al (2001) have suggested the IPL may be the locus of 'central representation', latterly described as a multimodal area, which combines sensory activity, spatial awareness and intentionality for future planning, into a central self-consciousness. Of interest is the implication of this area in everyday imagining and awareness of the body's movement and orientation in space. Lesions of the right IPL and right parietal lobe dysfunction have been associated with phantom limb phenomena and contralateral spatial neglect (Sirigu et al 2003; Taylor 2001).

Spence et al (1997) investigated motor control in a PET study of voluntary joystick movement in 7 schizophrenic patients experiencing delusions of alien control (passivity phenomena), 6 schizophrenic patients with delusions, but never of alien control, and 6 controls. The authors showed a hyper-activation of the right IPL (BA40) in patients experiencing passivity phenomena during free and specified joystick movement, relative to the other patients and control group. However, hyper-activation was shown to be reversible in patients with a decrease in levels of delusions of alien control over time, suggesting that spatial awareness may be only temporarily disturbed because of abnormal inferior parietal activation. These changes were described as independent of diagnosis and neuroleptic medication, given that they were specific to those experiencing passivity phenomena whose medication remained the same over time, while medication was introduced as a covariate in the analysis. Spence et al (1997) assert that the evidence for motor control difficulties, and failure to correct motor errors without feedback in patients with delusions of alien control, are consistent with the hypothesis of defective self-monitoring in schizophrenia (Frith 1992).

Cingulate gyrus

High-risk participants without psychotic symptoms showed an increased response in the right cingulate gyrus relative to high-risk participants with psychotic symptoms. Although not surviving correction for multiple comparisons, this is also an interesting result given the evidence for impaired

AC activity in schizophrenics during verbal memory tasks (Fletcher et al 1996). Fu et al (2002) showed AC activity to be associated with word generation following difficult relative to easy letter cues in healthy volunteers, and suggests this may be related to selective attention during tasks of increasing demand. The AC may also be important in the modulation of response interaction between the prefrontal cortex and temporal lobes, a suggestion supported by evidence for the strong reciprocal connections between the three regions (Fu et al 2002).

9.2 Word Recognition

9.2.1 Within group contrasts

Old versus new

The recognition versus rejection contrast is a comparison of brain regions recruited during the recall of words perceived as studied versus the rejection of words perceived to have been unstudied. This contrast showed very few areas of significant differential activation within or between groups after correction for multiple comparisons. This is probably due to the combination of both correct and incorrect responses, which despite increasing the number of events, will have resulted in multiple overlapping areas of activation. However, HR+ showed (uncorrected) increases in the frontal lobes (BA47), while HR- showed (uncorrected significant) increased response in the left thalamus and right posterior cerebellum, the latter area only apparent in the reverse contrast for controls.

Correct old versus correct new

This contrast enabled a characterisation of brain responses associated with successful recall of studied versus successful rejection of unstudied words. Although both require retrieval effort and monitoring, it can be assumed that only the former involve retrieval success. Recognition of the former normally entails the accessing of an explicit memory related to details of the learning event associated with that item (i.e. recency), whereas rejection of the latter may involve an items's failure to meet the basic criterion of familiarity and/or recency. While the extent of overlap between recollection and familiarity during forced choice recognition is unclear, it is assumed that the difference between correct old and new may be a indicative of brain regions specifically associated with accessing of

memories associated with the previously encoded word (i.e. the word is already stored, so the event has been tagged as having occurred at some point in time) (Henson et al 2000).

First level within group analyses of correct old events and correct new events, separately relative to the baseline experimental activation in the control group, revealed common areas for both types of event. These were apparent in the right precentral gyrus (BA6), left IFG (BA47), left fusiform gyrus (BA37) and right cerebellum (anterior lobe, culmen). During correct recognition versus correct rejection, the processes associated with the accurate identification of studied versus unstudied words in the control group were not separable, and were differentiated only by activation of an area of sensory processing. The reverse contrast however, revealed increased response in the right lingual gyrus and the left cerebellum.

First level analyses for correct old and correct new events independently, relative to the baseline experimental activation, in the high-risk participants without symptoms showed common responses in the left inferior parietal lobe (BA40), left frontal gyrus (BA10) and right cerebellum. Right cerebellar activation may reflect the contralateral connection between the tuber in the posterior lobe to the left inferior parietal lobe, while the activation of the right culmen in the anterior lobe, likely reflects links to the left prefrontal cortex during correct rejection. Additional enhanced activations in the right frontal gyrus (BA46) and left superior temporal gyrus (BA22) were apparent during correct rejections, but not recognition, which may reflect retrieval effort. However, for the correct old versus correct new contrast, the high-risk participants without symptoms only showed significant enhanced activation in the left parahippocampal gyrus (BA34) and right inferior parietal lobe (BA40). These activations may be consistent with successful retrieval. For the reverse contrast, increased responses were apparent in the visual processing areas and the right middle temporal lobe.

For high-risk participants with psychotic symptoms, first level analyses showed common responses for correct old and correct new items relative to baseline activation in the bilateral frontal gyrus (BA9/46 and 11) and left superior temporal lobe (BA22). However, during correct old relative to baseline experimental activation, there was a significant *right* inferior parietal (BA40) activation

concomitant with a left posterior cerebellum response (declive), while during correct new there appeared a significant *left* BA40 and bilateral precentral gyrus (BA4) response along with a right anterior lobe activation (culmen). During the correct old versus correct new contrast this group showed greater activation in the left middle frontal gyrus (BA47) and bilateral cerebellar areas (right anterior and left posterior), again an indication of activation associated with successful retrieval. For the reverse contrast, increases were shown in the superior temporal gyrus and left cerebellum.

The within group retrieval analyses demonstrated an apparently more extensive recruitment of the brain network which supports episodic retrieval in the high-risk participants than in the controls. Activation differences between the correct identification of studied and unstudied events are also more prevalent in the high-risk participant group, suggesting a quantitative and qualitative difference in brain regions recruited during these events. This further implies that the control group are recruiting similar brain regions to the same extent during the recall of both studied and novel information, and due to the ease of the memory task, may be using similar strategies for both types of event. The high-risk participants however, appear to recruit additional brain regions for the accurate recall of studied relative to novel words. It could be speculated therefore that these distinct increased activations during successful recognition of words seen before may be effort based. Alternatively, they could reflect differences in retrieval strategy e.g recollection versus familiarity.

9.2.2 Between group contrasts

Old versus new

During recognition relative to rejection, there was significantly enhanced right cerebellar activation in the high-risk participants relative to controls before correction for multiple comparisons, possibly due to the response in the HR- group. The high-risk participants without symptoms showed an additional increased response in the posterior cerebellum relative to the high-risk participants with symptoms. Based on our hypotheses the expected direction of the effect would have been the opposite. However, this contrast is a comparison of both failed and successful recognition, likely contaminated by the activations and 'de-activations' associated with false positives and false negatives.

Correct old versus correct new

Between group contrasts for correct old versus correct new events showed increased bilateral cerebellar activation (left and right anterior lobe, *culmen* and right posterior lobe, *tuber*) in the high-risk group relative to controls (both high-risk participants with and without psychotic symptoms). This was the most robust activation difference for this contrast, and is convincing evidence of a trait deficit in the bilateral cerebellum during verbal recognition memory.

Bilateral cerebellum

There has been an accumulation of evidence to suggest the cerebellum has a supportive role in the brain networks recruited during verbal episodic retrieval. Indeed, there is some evidence for impaired cerebellar function in schizophrenia during tasks of verbal memory and language (Andreasen et al 1996; Crespo-Facorro et al 1999). These findings are consistent with evidence from neuroimaging studies in healthy volunteers implicating the cerebellum not only in tasks of verbal working memory (Awh et al 1995; Desmond et al 1998; Li 2004; Paulesu et al 1993), but also in tasks of attention (Allen et al 1997; Desmond and Fiez 1998; Desmond et al 1997) sensory processing (Gao et al 1996), memory retrieval (Andreasen et al 1996; Schacter et al 1996b) and language. Andreasen et al (1999) proposed that a basic deficit in schizophrenia is a failure in the process of monitoring and coordination of cognition or 'cognitive dysmetria' due to a dysfunctional fronto-thalamic-cerebellar network (Andreasen et al 1999).

Although the cerebellum constitutes only 10% of the total weight of the brain, it contains more than 50% of the total neurons (Rapoport 2001). Dentate nuclei (superior) cerebellum efferents via the thalamus and inferior cerebellum afferents via the pons project contralaterally to the frontal lobes and temporo-parietal lobes respectively (Middleton and Strick 1997; Rapoport et al 2000). Desmond (2001) has hypothesised that the right superior cerebellum activations, apparent during tests of verbal working memory, may reflect connections with the left frontal lobes in support of articulatory control, whereas responses in the left inferior cerebellum may be supporting right temporo-parietal activations in the hypothetical phonological store (Desmond 2001). Although it is unclear by what mechanisms this support is contrived, Desmond (2001) suggests the cerebellum is integral in providing feed-

forward input to the frontal and temporo-parietal lobes, through comparison of the output relayed from these areas (Desmond 2001).

Maclullich et al (2004) recently demonstrated significant positive correlations between the cross sectional area of the posterior cerebellum (i.e. declive, tuber, folium) of healthy males, and tests of story recall (WMS Logical memory), visual recall (WMS Visual reproductions), Raven's Matrices and digit symbol substitution (WAIS). The area of the culmen (anterior cerebellum) showed a positive correlation with visual recall, and a trend for a significant association with NART, while total cerebellar volume correlated with Raven's Matrices, a test of intellectual reasoning (MacLullich et al 2004). This is of particular interest given that greater activation in the high-risk group relative to controls was shown during correct verbal recognition memory in both the right tuber and bilateral culmen.

Structural deficits in the cerebellum have also been demonstrated in schizophrenia (Levitt et al 1999; Nopoulos et al 1999), and may be linked to the dysfunctions in motor control and coordination shown in first episode and chronic schizophrenics, and the motor developmental abnormalities and neurological soft signs identified in biological relatives at high-risk for development of the disorder (Andreasen et al 1999; Niemi et al 2003). Other features of the disorder such as abnormal eye movement and vestibular function, present in patients and biological relatives, may also be associated with cerebellar dysfunction (Taylor 2001). This would suggest both a genetic and a neurodevelopmental aetiology to putative cerebellar linked abnormalities. The late development of the cerebellum may leave it vulnerable to insult at e.g. birth and the cerebellum's eventual maturation between 15 and 20 years of age coincides with the beginning of the peak period for development of psychosis in adults (Taylor 2001). Jurjus et al (1994) described a schizophrenia-like psychosis, predated by cognitive degeneration and cerebellar neurological signs up to two years before, in the case study of a 49-year-old man (i.e. ataxia, slurred speech and poor memory) (Jurjus et al 1994). Mental retardation, poorly systematized delusions, and catalepsy have also been reported in patients with abnormalities of cerebellar structure and function, with psychotic episodes reported (albeit

Correct old versus correct new

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anecdotally) late in the clinical course, some time after the emergence of neurological signs (Taylor 2001).

Right middle temporal gyrus

The high risk group as whole, and high risk participants with psychotic symptoms in particular, showed an increased response relative to controls in the right middle temporal gyrus (extending into right fusiform gyrus, BA20/21) during correct recognition versus correct rejection. However, given that those without symptoms did not show an area of similar increased response compared to controls, it may be that the response is driven those experiencing psychotic symptoms. Within group maps showed a deactivation in the right middle temporal gyrus in both HR- and HR+ during correct recognition (for HR+) and during correct rejection (for HR-). This increased response in the HR+ group relative to the controls may therefore be attributable to the reduced response in this area during recognition compared to rejection. This region of the temporal lobes has been linked to semantic processing, given that Wernicke's area (Right BA21/22) is reportedly the loci of stored information relating to the meanings and semantic properties of words (Ganguli et al 1997; Hofer et al 2003a; Hofer et al 2003b). This may therefore be indicative of ineffective retrieval of semantic information related to words presented in this group. Of interest is the presumed involvement of the right middle temporal lobe in auditory visual hallucinations in schizophrenia (Bentaleb et al 2002). Further, the right temporal lobe has been implicated in verbal self-monitoring in schizophrenia, and its disruption is potentially fundamental to the development of auditory hallucinations (McGuire et al 1996; Sherghill et al 2003).

Right Thalamus

Finally, the high-risk participants without symptoms showed a significantly greater response relative to those with psychotic symptoms in the ventral anterior nucleus of the thalamus. Moreover, when the threshold was raised, this area showed increased activation in the high-risk group as a whole relative to controls, before correction for multiple comparisons. HR- showed increased thalamus activation during correct recognition versus correct rejection and during old versus new contrasts. Similarly, the within group maps showed increased thalamus activation during ocrrect recognition versus baseline

and during old versus new contrasts, while HR+ showed only a decreased thalamic response during encoding. Reduced thalamic activation has been shown in schizophrenics relative to controls during working memory, verbal recognition and verbal recall tasks (Andreasen et al 1999; Barch and al 2002; Ganguli et al 1997). Further, Thermenos et al (2004) showed increased left dorsomedial thalamic activation in non-psychotic first-degree relatives of schizophrenics compared to controls during an auditory working memory task (relative to a baseline vigilance task). This is of interest given the connections via the thalamus from the prefrontal cortex to the cerebellum, and may be indicative of the relaying of information between these areas to effectively perform the task. The increased thalamic and cerebellar response in this group may be additional evidence to support a genetically mediated impaired circuitry in the fronto-cerebellar-thalamic network.

9.3 Strengths and Limitations

The study reported here is one of a very small number of functional imaging studies in the relatives of people with schizophrenia and one of an even smaller number of studies in people still at elevated risk. The in scanner performance measure demonstrated that the verbal encoding and retrieval task was performed well by all participants. However, very subtle differences in retrieval responses may be a mild reflection of the more pervasive memory deficit in schizophrenia, i.e. a non-significantly greater predilection for new over old responding in the high-risk group, compared to controls. While this difference was not hypothesised, difficulties in discrimination between studied and unstudied words have been reported previously in schizophrenia, and attributed to an ineffective binding of event features during encoding (Danion et al 1999; Huron and Danion 2002; Huron and Danion 2000; Huron et al 1995). Indeed, Cirillo and Seidman (2003) concluded that schizophrenics are impaired in the learning of new verbal information, possibly due to an inability to spontaneously semantically organise information (Cirillo and Seidman 2003).

By modifying this paradigm, for example, through the inclusion of a confidence judgement task, the basis of participants' memory judgements would have been established (i.e. high confidence, through explicit recollection of the word and its learning event, or low confidence, through only a feeling of familiarity about that word). Similarly, given that word classification performance was unimpaired in

all groups, it is possible that the increased inferior parietal response was compensatory for a reduced frontal response in the high-risk participants with psychotic symptoms specifically. However, any inferences about the nature of the encoding processes during this task (i.e. likely a mixture of both semantic and phonological coding) are also limited without an additional task controlling for phonological or perceptual judgement (e.g. counting number of T junctions in word). Future work may benefit from the introduction of a modified paradigm to allow for measurement of these factors in this group.

An additional limitation to this analysis is the moderate number of events included (i.e. 36 targets and 36 lures). This number was chosen to limit the amount of time participants were required to spend in the scanner (i.e. two paradigms were presented during the scanning period, this task preceded by the 13 minute word generation task). In total therefore, there were on average approximately 50 correct events across participants. For our correct old versus correct new comparison in particular, this most likely reduced statistical power to detect significant responses both within and between groups. Moreover, a comparison of incorrect old and incorrect new events was precluded due to too few incorrect response events.

The number of participants in our control and high-risk groups would however have at least partially offset this low statistical power in the analysis. 21 controls participated in the scanning paradigm, along with 27 high-risk participants with psychotic symptoms and 41 without. There were however more robust activations in the latter group, suggesting that equal groups of about 40 may have been more successful in detecting other between group effects, although it has recently been suggested that for SPM2 random effects analysis uneven group numbers should not affect the results (See SPM@JISCMAIL.AC.UK). Gender is also an important consideration in the interpretation of findings. However, there were no significant differences in gender ratios between our groups, nor has there been evidence of gender differences in the neuropsychology (Byrne 2003) or in the word generation task at second level in the EHRS groups (Whalley et al 2004). For this reason we chose not to introduce gender as an additional regressor to the analysis. Finally, there were significant differences in IQ between the high-risk and control group sample overall. However, this was not a

significant effect in the current group. Moreover, although IQ contributed to a proportion of the variance on our measures of memory described in investigations 1 to 3, memory deficits remained after introducing IQ as a covariate.

The reanalysis of the fMRI data in SPM2 following the same analysis in SPM'99 raises the issue of the need for correction for multiple comparisons?. We thought it necessary to conduct three between group comparisons. This was mainly due to the experience of psychotic symptoms among some of the high-risk participants, which could be considered an intermediate phenotype for the disorder. Few studies have addressed the effects of transient, isolated psychotic symptoms on performance or functional brain activations in unaffected biological relatives of schizophrenics. Despite our prior hypothesis that differences in BOLD fMRI between groups would be characterised by relative hyperactivity, two-tailed t -tests were computed in the event that alternative response differences emerged between the three groups (as is standard). This approach to the between group effects analysis may be considered a limitation, but, to counteract this, only the results of the random effects analysis have been reported and maps were thresholded at a conservative $p<0.001$. Again, we consider that this balances the chances of a type I and a type II error over the study as a whole. However, p values uncorrected for multiple comparisons for regions of interest were also reported when of particular interest. The extent of uncorrected p values reported may be considered a limitation. It was decided not to raise the threshold due to a lcak of specific apriori hypotheses. However, in instances where the threshold was periodically raised to $p<0.05$, some areas became significant. It is unclear why so many of the p values were only significant before correction. However, it is thought that the reduced number of events due to the types of contrasts used may have also reduced power. The similarity between event types being contrasted may also have resulted in fewer differential areas of response (e.g. ineffective cognitive subtraction), while the event related design may have resulted in a less robust averaged signal than achieved with a blocked design task of the same event types.

9.4 Conclusions

9.4.1 State effects

High-risk participants with transient psychotic symptoms showed an increased response in the left inferior parietal lobe relative to both controls and those high-risk participants without psychotic symptoms, during the word classification task. During correct recognition relative to correct rejection, the same group also showed a larger response in the right middle temporal gyrus (BA20/21), relative to controls, but not relative to high-risk participants without symptoms. It is conceivable that these responses may be fundamentally genetically mediated aberrations (i.e. there was a non-significantly enhanced response in the IPL in a previous study of the same group, and there were no significant differences between those with and without symptoms in the middle temporal gyrus). However, the more robust response in those participants with psychotic symptoms suggests that the enhanced functional activations in these regions are at least partly responsible for or exacerbated by the partially psychotic state of the participants. Furthermore, these areas, although integral to language and memory, may be directly linked to deficits in meta-cognition and the more florid symptoms of psychosis in schizophrenia. 21 of the 27 high-risk participants with transient psychotic symptoms underwent a clinical examination on the same day as the scan, while the other 4 were examined within 2 weeks, and the other 2 within 4 months of the scan. Although the PSE covers 1 month prior to examination, it is likely that the latter two participants may have been experiencing transient psychotic symptoms at the time of scanning. However, the nature of the interaction between psychotic symptom experience, task performance, and activation in these areas remains unclear.

9.4.2 Trait effects

The high-risk group as a whole showed a greater response relative to controls in the right inferior frontal gyrus during word classification. This response was significantly different between the high-risk participants with psychotic symptoms and controls, but non-significantly greater in those without symptoms relative to controls, and likely attributable to the reduced activation during word classification relative to baseline in the high risk group. The greater cluster size and response in those with symptoms suggests both a trait and state related continuum of activation, which is greatest in those with psychotic symptoms, then those without, and then controls. Activation of this area is

normally associated with the accessing of semantic networks and subsequent successful recall. It is possible that this is an indication of ineffective frontal response during the retrieval of semantic information from temporal regions, and could therefore be an indication of disrupted fronto-temporal connectivity.

During the correct verbal retrieval of studied versus unstudied words, the high-risk group (including both those with and without psychotic symptoms) showed an increased response relative to controls bilaterally in the cerebellum. Although less attention has been focused on this area in schizophrenia, it is a crucial component in the network of regions supporting verbal encoding and retrieval. The bilaterally increased activation may reflect the contralateral links to the temporo-parietal and frontal lobes, with projections from the superior cerebellum to the frontal cortex via the thalamus, and from the inferior cerebellum to the temporo-parietal cortex via the pons. This is a robust indication of an aberrant fronto-thalamic-cerebellar network in unaffected biological relatives, which may underlie the mild verbal memory deficits reported in this group.

Chapter 10: Final summary and conclusions

Evidence from neuropsychological studies in schizophrenia supports the notion of a core verbal memory deficit in schizophrenia, in both acquisition and retrieval processes. The point of deterioration is unclear, but the literature generally supports stability of cognitive function throughout the course of the illness. Furthermore, structural and functional imaging studies in schizophrenia have highlighted deficits in areas integral to memory processing, including the frontal and temporal lobes and cerebellum. Indeed, evidence from investigations of functional and effective connectivity in schizophrenia, suggest both fronto-temporal and fronto-thalamic-cerebellar dysconnectivity as fundamental to the cognitive deficits apparent in the disorder. Given the possibility that declarative memory is a differential deficit in schizophrenia, independent of executive and intellectual function, we chose to investigate this aspect of function in participants at enhanced risk of developing schizophrenia by virtue of their age and close blood relationship to individuals affected by the disorder (EHRS).

10.1 Quantification of verbal memory deficit in biological relatives of schizophrenics

A previous meta-analysis of neuropsychological function in schizophrenic relatives revealed the largest effect sizes to be for global memory and set-alternation. The systematic meta-analytic review presented in this thesis sought to quantify the nature of the declarative memory deficit in unaffected biological relatives of schizophrenics. We revealed small to moderate effect sizes, with overlapping 95% confidence intervals, across tests of verbal and non-verbal memory, and intellectual function. However, the largest effect sizes were apparent in immediate verbal recall and immediate and delayed prose recall. We concluded that this might be indicative of genetically mediated and possibly more left lateralised encoding and retrieval deficits, which are milder than those experienced in individuals with schizophrenia.

10.2 Verbal memory as a putative indicator of psychosis in the high-risk group

The Edinburgh High Risk Study is of especial interest given that participants with first and second degree relatives affected by schizophrenia were recruited while they were still in the age period of maximum risk for development of the disorder. It was expected that the study would follow these

participants through 60% of their period of maximum risk and that between 15 and 20% of the sample would eventually develop schizophrenia. Around the latter number have since developed the disorder and a greater proportion still have shown a predisposition to the experience of transient, isolated and partial psychotic symptoms. Analysis of the baseline performance of those who did and did not develop schizophrenia on average three years later, showed only one potential neuropsychological predictor of psychosis in this high-risk group. Total verbal learning over five trials, was significantly lower in the 13 individuals who are now schizophrenic relative to those in the high-risk group who remain unaffected. This putative indicator of psychosis may reflect pathological brain changes a considerable period before the onset of schizophrenia, and therefore implicates regions integral to verbal learning and memory including the frontal and medial temporal lobes.

10.3 Verbal memory performance over time and the influence of genetic liability in the high-risk group

Our investigation of neuropsychological performance between the first and latest assessments of those in the high-risk and control groups with at least two assessments, showed stable impairments in the former relative to the latter group on tests of verbal memory, executive and intellectual function. Only tests of verbal memory survived controlling for verbal IQ, suggesting a deficit independent of intellectual performance (as measured by NART). While those who are now ill showed the poorest performance of all groups, there were no significant groups by time interactions, suggesting that (on an average of three assessments prior to the development of schizophrenia) there were no neuropsychological performance decrements relative to the other groups. However, this analysis was limited in particular by the small group numbers, and by the varying periods between the first and last assessments between groups, which may have precluded the detection of a significant group by time interaction. Indeed, the mean verbal fluency scores of those who are now ill showed a decrease relative to an increase in the scores of all others, over time. Both tests have been shown to recruit both frontal and temporal regions during the access and retrieval of information based on phonological and semantic cues. This may implicate pathological brain changes in these areas associated with the development of psychosis.

There is no evidence to suggest that a predisposition to the experience of partial, isolated, and intermittent psychotic symptoms has any effect on performance over time. While patterns suggest a slightly poorer performance overall in this group relative to those who have never experienced psychotic symptoms, this has several potential explanations. It may be due to the transient interference of these symptoms at the time of assessments (i.e. where symptoms may have been present), as we now invoke to explain the apparent deterioration reported in this sample by Cosway et al (Cosway et al 2000). It could reflect an unidentified sub-group who is yet to develop schizophrenia, and may yet therefore exhibit worse neuropsychological performance over time. Alternatively, it could reflect that there are stable trait deficits in verbal memory that are possibly genetically mediated, as part of an extended or intermediate phenotype.

Similarly, genetic loading did not influence performance change over time. In fact, although increased genetic loading showed a negative linear association with performance on some tests e.g. prose recall and verbal fluency, this was not the case across all tests e.g. block design. This implies that some neuropsychological deficits are sensitive to genetic loading, while others have a more complex relationship.

10.4 Verbal and non-verbal learning and memory in the high-risk group

For the first one hundred participants to undergo a scan we investigated further any differences between the high-risk and controls in verbal and non-verbal learning and memory. The CVLT enables a more comprehensive analysis of aspects of learning e.g. clustering, which may impact on subsequent recall. While significant differences were apparent on aspects of delayed and immediate recall, semantic and serial clustering scores showed only non-significant patterns of differences between groups. This suggests that recall performance may be attributed to both encoding and retrieval deficits, and that these deficits worsen in individuals with the disorder. Performance on the test of visual recall and recognition surprisingly showed only a recognition deficit. The high-risk participants made significantly less correct old responses, but an equivalent number of correct new, compared to controls. This may be an indication of difficulties in discriminating studied items from novel items, which may share similar feature level properties. Conversely, novel items may be

rejected more confidently due to their lack of familiarity (i.e. recency judgement). This further shows that declarative memory impairments are not domain specific, but are apparent for the acquisition and retrieval of both verbal and visual information. However, without the neuroimaging of the brain during engagement in these tasks, it is difficult to be sure that participants are recruiting areas, which support visual processing alone. Indeed, it is possible that some visual tasks will recruit both verbal and non-verbal strategies to perform the task.

10.5 Functional MRI of word classification and old versus new recognition

Functional MRI enables the in vivo imaging of the brain BOLD functional response, while engaged in specific cognitive operations. Based on the preceding evidence for verbal declarative memory impairment, we attempted to characterise any differences in physiological brain responses during a low level word classification/explicit encoding and old versus new forced choice recognition paradigm. All groups performed both tasks well, and there were no significant differences in accuracy or reaction time. However, there were subtle differences in the nature of responses between groups, with the high-risk participants showing a non-significantly greater predilection for new over old responses relative to the controls. Similarly, the difference in reaction time in the high-risk participants with symptoms during correct old relative to correct new responding was non significantly greater in magnitude than the difference in the control group. This result was consistent with the previous visual recall test (investigation 4), and also suggests that the high-risk group may have a subtle difficulty in identifying old items, but not in identifying those that are new (and therefore less familiar). While these results suggest that the basis for recognition (e.g. explicit recollection or familiarity) may be different between the high-risk and control groups, these results are not significant. Further, without a modified paradigm or subjective report as to the confidence and nature of judgements made, we can make no conclusive inferences regarding this pattern. However, it can be said that this pattern of responding is milder but consistent with that apparent in people with schizophrenia.

Our paradigm did however enable the characterisation of differences between groups in functional brain response during the accessing of semantic information and the recognition of studied

(semantically) versus unstudied words. An uncorrected state related hyper-activation in the left inferior parietal lobe is consistent with a similar result in the same group during a covert word generation task. This regional activation was therefore not task specific, although considered integral to both language and memory. Moreover, this activation was not associated with a linear increase in task difficulty in a similar paradigm in the same group. It is suggested therefore that the left inferior parietal lobe, previously demonstrated as associated with meta-cognition in schizophrenia (Spence et al 1997), may be reflective of the development of some (possibly early) features of psychosis in biological relatives of schizophrenics. While this difference in activation was not detrimental to performance, it does highlight the increased sensitivity of fMRI to detect state related differences between groups, which are not revealed using neuropsychological tests. In the word generation task with the same group, this regional activation was less in those without symptoms than those with, but greater in those without than controls. This suggests a fundamental trait deficit, but a manifest dysfunction only in those experiencing psychotic symptoms.

The possible trait deficit apparent in the hypoactivity of the right inferior frontal gyrus during the word classification task also implies a genetic basis to functional deficits, which are heightened in those who have developed some psychotic symptoms. There may therefore be an interaction between genetic vulnerability and psychotic symptom experience, which is only very tentatively indicated in patterns of neuropsychological performance. Future research in this group would benefit from an analysis of this middle frontal gyrus activation in those participants scanned, who have since developed schizophrenia (of which there are now six). Otherwise, an apparent lack of frontal abnormalities suggests that these may be a feature of task difficulty or effort.

An unexpected and significant increased bilateral cerebellar response during the successful recognition of old versus successful rejection of new words in the high-risk group relative to controls is a robust indication of a trait deficit in physiological brain response in this area. The cerebellum is a crucial component in the brain network supporting verbal episodic retrieval. It is plausible therefore that this represents an additional genetically mediated dysfunction in the fronto-thalamic-cerebellar network. Performance was not significantly worse in the high-risk group than in the controls, making

it likely that this hyper-activation is a compensatory one to assist in the recognition of previous semantically processed information. Anterior and posterior cerebellar areas were demonstrated as significantly correlated with aspects of cognitive function, including story recall, visual recall (WMS visual reproductions), and digit symbol substitution. The strong contralateral anatomical connections between the cerebellum and temporo-parietal cortex, suggests impaired fronto-thalamic-cerebellar integrity in this group may underlie our previously identified stable trait deficits in areas of function including both story recall and digit symbol substitution. However, further work on the functional nature of the connections in this network may shed light on the cerebellum's role and therefore it's influence on cognition in schizophrenia.

10.6 Final conclusions

Stable verbal declarative memory impairments along with intellectual and executive function deficits are apparent in biological relatives of schizophrenics compared to controls. We could demonstrate only mild patterns of encoding dysfunction in neuropsychological tests. However, the pattern of results does suggest the contribution of both encoding and retrieval difficulties to declarative memory deficits of a similar nature to those seen in patients. Moreover, while these are to some extent associated with the presence of or predisposition to psychotic symptoms, they were a putative predictor of later schizophrenia development in relatives who developed the disorder an average of three years later. This suggests that some pathological brain changes linked to the development of schizophrenia may have occurred before or during adolescence in this group. Furthermore, the verbal memory performance deficits appear to remain stable over time in the high-risk group, suggesting only at most a slight worsening of performance in those who eventually develop the disorder. It would appear therefore that verbal memory deficits are a genetically mediated intermdiate phenotype, apparent in many more people than will develop schizophrenia, while those most impaired are most likely to develop the disorder.

Functional imaging has allowed us to investigate further differential brain activations between the high-risk and control groups during verbal encoding and retrieval processing. Our results revealed possible state deficits in the *left inferior parietal lobe* during word classification, and in the *right*

middle temporal lobe during successful verbal recognition. However, it is important to note that these were not significant after correction for multiple comparisons. Further, both regions may be fundamentally regions of genetic aberration, dysfunction being evident only on sensitive interrogation (with fMRI) and only in those experiencing psychotic symptoms. These regions have been linked to deficits in meta-cognition in schizophrenia, and therefore are likely to be involved in the development of psychotic symptoms. The interaction with cognition in these areas is yet unclear. Given the successful task performance, hyper-activations do not appear to be detrimental and could therefore be compensatory to dysfunctions within brain networks; although without functional and effective connectivity analyses this can only be inferred. However, it is conceivable that additional stress on such brain networks may lead to disrupted function, which then fails to effectively compensate for reduced functional integrity in other areas, leading to increased cognitive deficit.

A possible, but again uncorrected trait deficit was apparent in the *right inferior frontal* gyrus during word classification, but not during recognition, and attributable to the reduced activation apparent on the withing group map for the high risk participants with symptoms during word classification relative to baseline. This may be related to the ineffective activation of semantic networks during the former task, and previous studies in schizophrenia have indicated hyperactive semantic memory networks as fundamental to language difficulties in the disorder (Kubicki et al 2003). However, the most robust indication of a genetically based hyper-activation was shown bilaterally in the *anterior and posterior cerebellum* during successful verbal recognition. This could suggest increased relaying of information between the frontal and cerebellar lobes, in order to compare sensory output and feedback for effective response. This is also a convincing indication of genetically mediated dysfunction in the fronto-thalamic-cerebellar network in biological relatives both with and without psychotic symptomatology. Further, this provides an important insight into the possible functional basis of mild verbal declarative memory impairments in biological relatives of schizophrenics. It also holds promise as a task, which could reveal deficits linked to the early development of psychopathology and schizophrenia in this group.

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APPENDIX 1: Tables and figures to accompany chapter 1

Table 1A: Studies of general cognitive and mnemonic function in schizophrenia

(For abbreviations and acronyms see 'Abbreviations and acronyms table')

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
Abbruzzese 1993	61 SCZ 40 C	49M: 12F: age 27.1 years 15M: 25F: age 29.8 years	Story recall (Auditory Comprehension Test)	C recalled more than SCZ based on length & story complexity		
Aloia 1998	20 chronic SCZ 21 C	15M: 5F 12M: 9F Matched on age but not IQ SCZ high TD (N=9) vs. low TD (N=11)	Semantic word pairs priming paradigm WRAT- Reading Word fluency Category fluency Letter-number span test Peabody Picture Vocabulary WCST	No correlations between WRAT or executive function and priming (priming is increased recognition speed in presence of 2nd word related to 1st in a pair, rather than unrelated-linked to theory of spreading activation-words/nodes excite or inhibit each other within a network). Priming in C for high-association word pairs, less with medium, but not always with low-association pairs (these are not environmentally useful or relevant for C) Low level thought disorder SCZ showed same pattern as in C, but at enhanced levels. However, less differentiation between medium and low associates is evidence of hyper-priming. Suggests incomplete network/disorganised network (See Chen 1994 and Gurd 1997). High thought disorder SCZ		Thought disorder may be on a continuum of severity and authors divided groups accordingly. First study associated though disorder not with executive function, but with speech and language

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
				showed no and negative priming at any level of association-difficulty activating automatically the semantically related elements in speech-may go for less relevant word instead i.e. loosely associated words.		
Bacon 2001	19 SCZ 19 C	Mean 39.5 years No difference in WAIS-R IQ.	Semantic recognition (general knowledge) memory test (remember/know) WMS-R WAIS-R	SCZ impaired semantic memory relative to C Confidence judgements (CJ) and Feeling of Knowing (FOK) not significantly different between groups. Correct recall and low FOK more frequent in SCZ than C		
Babcock 2004	149 C 109 SCZ	Split into IQ score categories NP on different IQ groups Preserved IQ <10 pt difference pre-current (N=45); Deteriorated IQ >10 pt drop pre-current (N=47); Compromised IQ Pre & current <90, no decline (N=17)	Shipley Institute of Living Scale (SILS-WAIS-R IQ current estimate derived) NART Neuropsychological battery (inc. inspection time/speed of processing; memory; executive function)	1/ hypothesis: that speed of info processing is directly correlated with intelligence, so preserved intellects would process faster than compromised and deteriorated. 2/ hypothesis: is that slow processing is a feature of SCZ compatible with preserved intellect. Results in favour of 2. Those with preserved intellect show deficits in speed of processing, equivalent to those with deteriorated or compromised and less than controls (no correlation between inspection time and medication dosage).		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
				Executive dysfunction better in preserved SCZ but still reduced relative to C-so dysfunction exists despite preserved intellect.		
Barch 1996	75 medicated SCZ 25 unmed SCZ 10 Ds 28 C		Semantic Priming in word pronunciation	At stimulus onset < 950 msecs, SCZ equivalent to other groups in priming. At > 950 msecs, SCZ less priming than C. Automatic priming is normal in SCZ at less than 950msecs, but above that higher level processing may be affected.	Medication dosage associated positively with priming <950 msecs.	
Basso 1998	62 SCZ	45M: 17F: mean 32.2 years	Word fluency Category fluency WMS WCST Halstead-Reitan Battery WAIS-R			Negative and disorganised symptoms related to general poor performance, executive function and also related to memory & attention. Psychotic symptoms not associated with NP- increases in severity often showed enhanced performance
Bazin 1996 (abstract)	SCZ, C		(Implicit &explicit) Paired Associates task	SCZ =C implicit task and used contextual info to same extent. SCZ impaired explicit task. Context improved performance in both tests. Deficit in 'interactive context' (Baddeley 1992?)		
Bazin 2000	30 SCZ 30 C	22M: 8F: mean 32.4 years 15M: 15F: mean 28.5 years	Sentence Completion and Semantic Priming Task Incomplete sentences and to fill in last word-based on presumed meaning of ambiguous word in sentence. Target sentences followed with other	SCZ used most common meaning of ambiguous word irrespective of whether relation of context and target sentence was implicit or explicit.		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
			sentence which explicitly primed (or not or implicitly) the less frequent meaning of previous sentence's ambiguous word-could use context to inform your interpretation of target sentence..	Suggests SCZ don't use context appropriately.		
Beatty 1993	26 SCZ 20 SCZaff 20 C	10M: 3F :mean 33.2 years 6M:7F: mean 32.5 years 9M: 11F: mean 34.7 years No significant differences in education	Word fluency Category fluency Design fluency Immediate and delayed verbal list recall WCST Digit span FW and BW	Memory: SCZ and SCZ aff produced less letters and recalled less words immediately and after delay than C on word list learning. Worse visual memory than C Increased rates of forgetting in SCZ relative to. SCZaff and C, but recognition preserved. Possibly reflects retrieval problems Executive function: SCZ and SCZaff less well than C on all measures		
Berthet (abstract) 1997	35 SCZ 35 C	Mean 31.9 years Mean 31 years Age, sex & education matched	(1) Explicit vs. implicit memory	Difference between groups in conscious but not automatic memory. Suggests automatic (implicit) processes are unaffected in SCZ.		Negative correlation between positive symptoms and consciously controlled memory. Independent of psychotic symptoms or related to temporal lobes.
Bilder 2000	94 FE SCZ (<12 wks medication) 36 C	Mean 25.7 years Mean 25.3 years Significant differences in education, but not gender.	Word fluency Category fluency WMS Logical Memory test WMS Paired Associates CVLT WMS-R visual reproductions RCFT WCST	Generalised deficit of 1.5 points below C. Language preserved but memory worst (but not amnesia) and executive deficits also apparent. Both memory, executive and	Medication inversely correlated with memory and global performance-chlorpromazine and benztropine.	Symptoms not correlated with NP at entry but not at clinical stabilisation

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
			Trail-making A&B WAIS-R full test WRAT-Reading Motor tests	attention deficits in more severely cognitively impaired SCZ. SCZ with better general ability/non impaired just show memory deficits. Parallels deficits in chronic patients, though less severe-is this reflective of deterioration or sampling bias, i.e. some FEs don't become chronic. After controlling for memory deficits only motor problems differentiated SCZ from C.		
Binder 1998	20 (short prodrome) SCZ, 20 (long prodrome) SCZ, (All FE) 40 C	10M: 10F: age 30.9 years 10M: 10F: age 32.2 years 20M: 20F: age 31.7 years	WAIS-Information and similarities tests Category fluency (semantic supermarket test) WAIS Block Design and Picture Completion tests WMS-R Logical memory WMS-R Visual Reproductions CVLT Stroop WAIS Digit Symbol CPT SAT WCST	SCZ worse than C in all tests except visual memory, short-term memory and abstraction which were no different from C. No difference between patients groups. This suggests no effects of time of illness onset in SCZ.		No relationship between length of illness and psychopathology and cognitive impairment.
Binks and Gold 1998	30 SCZ	25M: 5F: mean 34.8 years (mean illness duration 13 years)	CVLT Verbal fluency WRAT WMS-R WAIS-R WJ-R WCST Trail-making Line orientation judgement Tasks matched for difficulty.	Differential deficits in processing speed, visual processing and delayed memory. SCZ Strengths in auditory processing and crystallised intelligence/language skills (as revealed by WJ-R)		
Blanchard & Neale 1994	28 SCZ	All males	WMS Logical Memory	SCZ impaired relative to C in		No significant correlations

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
	non-medicated for 2 weeks for research purposes 15 C	Mean 39 years Mean 37.9 years	WMS Visual Reproductions Verbal Fluency Facial Recognition WCST Motor tests (Purdue peg board) Standardised residual scores	verbal and non-verbal memory, executive function, motor and perceptual ability. Deficits are generalised and not differential in memory (although largest mean difference apparent in semantic memory and smallest in motor function). Used Saykin's method of standardised residual scores, but still not enough to meet Chapman & Chapman criteria, i.e. does not remove effects of a global deficit.		between medication and NP
Brebion 1997A	40 SCZ	Assessed on positive and negative symptoms and depression.	Immediate & delayed free recall of non- organisable & organisable (semantically) lists Immediate & delayed recognition Implicit memory (stem completion task)			Depressive symptoms associated with deep but not superficial encoding. No associations with negative symptoms. Erroneous memory associated with positive symptoms.
Brebion 1997B	38 SCZ 38 C	26M: 12F: mean 34.4 years 24M: 14F: mean 37.7 years Age, sex & education matched	Verbal encoding (shallow & deep) Immediate and delayed free and cued recall (X 6 lists 16 words (2 organised semantically). Recognition (implicit recall-stem completion Digit span FW & BW	Support for hypothesis of encoding deficit in SCZ (could also be retrieval problems too). SCZ didn't use semantic properties to encode as much as C, and despite cues, didn't recall as much-suggests poor encoding organisation. Fewer categories recalled. Serial recall used more often and is unimpaired.		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
				Smaller FW & BW Digit span. No problems in stem completion-implicit memory intact.		
Brebion 1999	33 SCZ 40 C	27M: 13F: mean 33.7 years 26M: 14F: mean 37.1 years Significant differences in age and education (covaried)	Free word list recall (see above) Intrusions and false alarms Recognition following intentional and incidental learning-False alarms	No differences between groups on memory error types.		Positive symptoms associated with more errors (intrusions & false alarms).
Brebion 2000	49 SCZ 40 C	31M: 18F: mean 33.1 years 26M: 14F: mean 37.1 years Age, sex and education equivalent	4 lists 16 words-Superficial encoding-recall of list items sequence Deep encoding-2 semantically organisable lists-number categories recalled Storage-difference immediate and delayed recall Stroop & digit symbol processing speed times Digit span FW and BW	Processing speed predicts number of words or digits recalled in a sequence. The faster the speed, the more often they can be rehearsed in the loop. Differences between numbers of items recalled were significant between groups until controlling for processing speed. Large inference though that faster processing speed = more rehearsal in phonological link.		
Bruder 2004	29 SCZ (23 SCZ and 6 SCZaff) 26 C	17M: 12 F: mean 32.7 years 14M: 12 F: mean 28 years Significant differences on education (covaried) Successful auditory tone discriminators –i.e. equivalent	Tone discrimination screening test=SATDs and NSATD groups Word serial position test WSPT Dichotic listening test WMS-R WAIS	SCZ SATD performed more poorly than C on WSPT and verbal memory test (but not visual), but equally on perceptual processing. WSPT performance not due to difficulty-managed tone discrimination well. Trouble with words in beginning and middle indicates verbal memory deficit.		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
		to C(SATD) (N=17) vs. non successful (NSATD) (N=12)		SCZ NSATD showed overall poor performance suggesting more general deficit. A disturbance common to working memory and long-term memory recall?		
Bryson 2001 (abstract)	33 deficit SCZ 57 non deficit SCZ		WMS-R HVLT WCST WAIS-R Factor analysis 3 factors: simple verbal memory , semantic verbal memory, executive function.	Deficit SCZ worse than non deficit on executive function but not verbal memory (semantic or simple). Verbal memory may be more general trait deficit?		
Buchanan 1994	18 deficit SCZ 21 non-deficit SCZ 30 C	15M: 3 F: mean 35.3 years 17M: 4 F: mean 32.3 years 20M: 10F: mean 34.2 years Difference in WAIS-R IQ (covaried)	WMS Word fluency WCST Stroop Trail-making B Line judgement Face recognition (Mooney) WAIS Block Design WAIS-R FSIQ	Intelligence perhaps should not be covaried for as a nuisance variable (as was here). The involvement of IQ and other areas of cognition cannot be disentangled by statistical measures alone. C better than deficit SCZ on all NP scores. No difference between non-deficit SCZ and C on Stroop interference, trail-making and face recognition. No differences between deficit & non-deficit on memory measures (temporal) Differences between deficit and non-deficit only on Stroop interference, trail-making (frontal) and face recognition (parietal) Seems to specify memory		Negative/deficit SCZ associated with general poor cognitive performance-fontal impairment

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
				tests as temporal and executive as frontal, but cannot be sure these are only areas implicated.		
Calev 1984A	10 chronic SCZ 10 C	6M: 4F: mean 19.7 years	Verbal (episodic) recall Verbal recognition Ammons/Ammons Quick IQ test Tasks matched for difficulty using Chapman & Chapman methods-based on mean no. of controls recall, so that differences cannot be attributed to task difficulty and discriminating power, but mnemonic difficulty due to ineffective encoding	SCZ performed significantly better on recognition than recall relative to C. SCZ performed significantly less well than C at recall, and marginally significantly less well than C at recognition. SCZ used significantly less categorical clustering (chunking during encoding-Koh 1978) than C.	No differences between anticholinergic patients and those patients not medicated on memory performance.	
Calev 1984B	10 (non chronic) on neuroleptics SCZ 10 (non chronic) on neuroleptics + anti-cholinergics SCZ 10 C	7M: 3F: mean 33.8 years 7M: 3F: mean 33.4 years 7M: 3F: mean 33.8 years	Verbal (episodic) recall Verbal recognition Ammons/Ammons Quick IQ test Tasks matched for difficulty as above	Non-chronic SCZ on neuroleptic medication don't perform better on recognition than recall-may have been finding previously due to unmatched tasks. SCZ on antcholinergics and neuroleptics do perform better on recognition than recall, & worse on recall than just neuroleptics SCZ-but lower IQ. However SCZ on both types of drugs were perhaps more severe in illness than the others		
Calev 1987	16 chronic SCZ 16 C	No differences on IQ, age or education.	Remote Memory questionnaire (famous events) Blocked word list recall in categories	SCZ worse on list recall than remote memory, and worse on list recall than C.		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
			(distractor task with digit-then recall, write down words) Ammons/Ammons Quick IQ test Ran matched difficulty task check with C	No evidence of amnesic gradient in remote task for SCZ.		
Chan 2000	20 chronic SCZ, 20 acute SCZ & 20 young C 20 old C No differences in age or education	11M: 9F: mean 33.5 years 11M: 9F: mean 24.1 years 11M: 9F: 26.5 years 11M: 9F: 34.3 years	Immediate word recall over 3 trials Delayed recall Recognition task after 30 mins Same task, but with guidance on semantic categories, order of presentation and word number.	SCZ recall less than C in both random and organised list conditions. Immediate recall problems show encoding deficit in SCZ. Controls also recalled more after a delay and retrieved more words than SCZ. Acute SCZ show deficit in spontaneous clustering relative to controls. Organisation aided retention in SCZ. Acute and chronic exhibit similar level of deficit so does not appear to progress with illness.		
Chenerey 2004	14 SCZ 12 C	11M: 3F: mean 33 years 9M: 3F: mean 33.4 years No significant differences on age, sex, education or NART-IQ	Semantic Priming and Context processing of word pairs NART	SCZ enhanced priming at short stimulus onset and low pair relatedness. Decrements at long stimulus onsets		Semantic processes not related to illness duration or thought disorder.
Clare 1993	12 SCZ 12 C	7M: 5 F: mean 42.7 years 7M: 5 F: mean 43.2 years Age, sex and NART IQ matched	RBMT Story recall Face and word recognition forced choice SCOLP Category judgement Pursuit rotor task Jigsaw completion Word stem completion Implicit lexical priming task NART	(a) SCZ worse than controls on episodic memory (inc face recog) tasks. (b) Slower and more errors in SCZ in semantic tasks. (c)Normal priming in implicit memory tasks.		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
				(d) Both recognition and recall affected in SCZ-reflects the amnesic syndrome?		
Colombo et al 1993	18 SCZ 18 C	12M: 6F: age 28.4 years 13M: 5F: age 33.4 years	WMS MRI scan	(a) No differences in temporo-limbic morphology between patients and controls. (b) Differences between groups on factor 1(immediate learning and recall) and factor 2 (attention and concentration) of the WMS (but not factor 3 info and orientation) (C)No apparent relationship between structure and function-disputes theory of functional localisation.		
Cuesta & Peralta 1995	40 SCZ	31M: 9F: mean 27.7 years	Story recall (immediate & delayed) Text comprehension WMS Visual memory RCFT Word fluency Category fluency Luria's executive function test Trail-making WAIS Digit Symbol WAIS Digit Span			Positive symptoms only positively correlated with visual-motor function. Negative symptoms negatively correlated with intelligence and visuo-motor control & attention. Disorganisation negatively correlated with verbal memory, language and visuo-motor control.
Danion 1999	25 SCZ 25 C	17M: 8F: mean 29.9 years 17M: 8F: mean 30.8 years No significant differences in age or education	Object pairing. Recognition memory for source and object. Remember/Know response RBMT picture and face recognition WMS-R WAIS-R IQ	(a) SCZ recognition based on noetic awareness (Know/Familiarity). (b) Source recognition most accurate when based on autonoetic (remember) memory.	Short WAIS-R IQ & medication did not correlate with performance	

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
				(c) Object but not soured recognition at chance level only. (d) Problem binding aspects of events into whole.		
Danion 2003	24 SCZ 24 C	15M: 9F: mean 32.4 years 15M: 9F: mean 32.4 years Same level of education	Episodic memory-autobiographical memory fluency. Semantic memory-autobiographical memory enquiry	Impaired episodic and semantic memory in SCZ.		
Danion 2003	24 SCZ 24 C	15M: 9F: mean 32.4 years 15M: 9F: mean 32.4 years Same level of education	2 lists of 30 words with mixture of negative, positive and neutral emotionality. Recognition after reading and making judgment on pleasantness. Remember/Know decision.	(a) SCZ gave fewer remember responses than C (b) SCZ consciously recollect/remember emotional over neutral words.		
Dickinson 2004	97 SCZ or SCZaff 87 C	74M: 23F: mean 40 years 61M: 26F: mean 37.6 years Age and education covariates.	WMS WAIS-R To investigate differential or general deficit using single common factor analysis	(a) SCZ accounted for 47% variance between SCZ & C on WAIS-R subtests & Single Common Factor Analysis suggests 65% variance is through single common factor. (b) Only selective independent factors of digit symbol & family pictures (visual episodic memory). (c) Processing speed separate from other cognitive factors- true also in normal populations (Keith 1997). (d) Vocab & info of WAIS were preserved in SCZ & block Design less affected than other matrix reasoning tests. (CRYSTALLISED INTELLIGENCE).		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
				(e) WAIS-R loaded higher on common factor (IQ) than WMS-R . Verbal memory variance accounted for by common factor. SCZ performance mediated by a single common underlying factor.		
Drakeford 2002 (abstract)	10 SCZ 10 Ds 10 C		Auditory recognition memory for previously heard and novel sentences. Remember /Know decision.	(a) No significant differences between groups on recognition (hits and false alarms) (b) SCZ had more know than remember responses than other 2 groups. (c) SCZ made fewer remember responses than C & depressives.		
Duffy & O'Carroll 1994	40 SCZ 18 Korsakoff patients	MMSE and age (Korsakoffs older) covaried for in second analysis-significant differences retained.	RBMT Digit span FW and BW WMS Paired Associates Silly sentences semantic memory test Verbal fluency	(a) Both groups showed normal STM on Digit span tasks. (b) SCZ worse on semantic memory than Korsakoffs (slower & more errors) (c) SCZ had poor episodic memory (5% severe as in Tamlyn 92 & McKenna '90), though superior to Korsakoffs (100% severe). of semantic memory? (d) Evidence of double dissociation. Calev says VF is semantic, but no differences on VF here-do silly sentences and VF measure diff aspects of semantic memory?		Positive symptoms neg correlated with RBMT screening score

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
Egeland 2003 (abstract)	53 SCZ 50 Ds 50 C	Significant differences between groups in IQ	Declarative and working memory tests.	(a) Memory deficit exceeds IQ deficit in SCZ (b) Depressives impaired in working memory only-suggests retrieval failure. (c)SCZ impaired in all memory tests-suggests acquisition failure.		No correlation with positive symptoms (i.e delusions) and semantic memory. Significant positive correlation between semantic memory & chronicity- cortical atrophy of storage?
Elliot et al 1998	32 chronic SCZ 24 C	Mean age 39.8 years Mean age 38.2 years No differences in IQ (NART)	Attentional Shift Test (CANTAB) Recognition Memory Test (CANTAB) MMSE	SCZ impaired on perseveration (stuck in set) but not on learned irrelevance (even those in preserved IQ group) Impaired on both pattern and spatial recognition	No correlation of attentional shifting with recognition or MMSE No differences between medication types groups (clozapine vs. traditional neuroleptics)	
Elvevag 2000	20 SCZ 28 C	16M: 4F: mean 36.9 years 15M: 13F: mean 32 years Significant differences on IQ	2 lists 15 words at different time periods-asked to reproduce list orders from random word array WRAT Cattel's Culture Fair Fluid Intelligence Test WAIS-R Short Form	(a) Recall and recognition of lists impaired. Temporal order placing of words impaired in SCZ relative to controls. When controlling for recall differences this temporal order impairment disappears. (b) Could be related to constructive memory/context memory impairment		
Elvevag 2002B	26 SCZ 33 C	Mean 33 years Mean 33 years Significant differences in IQ	Probed serial recall for letters task WRAT WAIS-R Short Form	(a) Okay in recall for more recent items, but SCZ impaired in recall of earlier list items- (b) Could be due to impaired item maintenance and not temporal order deficit.		
Elvevag 2004	22 SCZ 25 C	17M: 5F: mean 33.4 years 9M: 16F: mean 34.6 years	Word list recognition of studied words along with unstudied (some of which	(a) C more susceptible to lures at free recall than SCZ, and		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
			semantically related to studied). Free recall	made more false recognition errors than SCZ. (b) Despite poorer memory, SCZ are not susceptible to interference from previous tasks to extent of C!!! (c) Huron & Danion (2002) showed less false alarms in SCZ too.		
Evans et al 1997	31 SCZ 35 brain injured 26 C	Mean age 38.9 years Mean age 40.4 years Mean age 39.1 years	BADS RBMT	Both patient groups impaired relative to controls. SCZ showed dissociated impairment in executive function and memory. Even in SCZ with preserved IQ, showed executive deficit.		
Fossati 1999	14 SCZ 20 Ds 20 C	8M: 6F (18-45 years) 6M:14F 7M: 13F Age, sex & verbal IQ matched	Verbal memory task for list of 16 words presented with category cue. Category cued recall Free recall and interference Free recall Recognition memory Word fluency Cognitive estimate WCST Delis card sorting test Digit span FW and BW	SCZ but not depressives showed verbal memory impairment. Both show executive function deficit.		
Feinstein 1998	23 SCZ 10 Ds (8 unipolar, 2 bipolar) 11C	Mean 37.7 years Mean 38.7 years Mean 25.3 years	Category fluency (cued and uncued) Word fluency Temporal order memory Remote memory	(a) Category fluency worse than phonological in SCZ. (b) SCZ & C both benefited from cues, so disproportionate impairment on semantic fluency not just due to poor retrieval-affected storage? (c) Type of info to be retrieved (semantic over phonologic) & not act of retrieval itself is affected. (d) Memory for temporal order:		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
				C showed equivalent memory for stages of life memories. SCZ showed u shaped profile, unlike controls a dip in recall of memories in early adulthood-start of illness-acquisition of new info impaired –poor encoding or accelerated forgetting? Core deficit in organisation & not retrieval then? Memory deficits due to problems in temporo-parietal areas (like Alzheimers).		
Gilvarry 2000	91 SCZ 85 relatives of SCZ 66 affective psychosis 50 C		NART	SCZ have lower NART than relatives and affectives		
Gold 1992	36 SCZ 18 C	Mean 33 years Mean 33.5 years C > SCZ education No differences on IQ	Effortful vs. automatic retrieval (3 lists of 20 words varying in semantic organisation (random, unblocked, words from same categories mixed, blocked, words from same categories presented together). Free recall Recognition Frequency estimation of deck of cards with words on them.	(a) SCZ impaired in recall, recognition, semantic encoding & frequency estimation relative to C.. (b) Random & unblocked list recall differed for C but not SCZ-(who did not benefit from semantic cues). c) All in spite of varying attentional demands.		
Gold 1992	45 SCZ	33M: 12F: mean 32.5 years	WMS-R ((1)verbal (2) visual (3) attention (4) delay (5) general) Word fluency Boston naming test Trail-making A and B WRAT-Reading WAIS-R Compared full scale IQ (FSIQ) with general memory index (GMI) and delayed memory index (DMI) measures using matched t-tests, to	(a) GMI was lower than FSIQ for approx 71% SCZ (FSIQ > by 8.64 points). (b) DMI was lower than FSIQ for approx 62% SCZ (FSIQ > by 5.13 points). (c)Attention also lower than FSIQ-73% better IQ than attention. Attention and memory impairments were not	IQ-DMI and IQ-GMI compared to patients on neuroleptics + anti-cholinergics vs. patients on neuroleptics alone: Non significant. Deficits cannot be attributed to medication.	

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
			compare relationship between IQ and memory.	correlated & hence attention is not responsible for memory deficit. (d) No correlations between above memory difference scores and other measures of memory or trials B, though trails A correlated with FSIQ-GMI score. (e) Non memory variables account for little of variance in FSIQ and MI scores. (f) Measures across WMS-R similarly impaired (visual & verbal memory, attention, immediate & delayed recall).		
Gold 1995	70 SCZ 30 Left Focal Temporal Lobe Epilepsy (LTLE) 42 Right Focal Temporal Lobe Epilepsy (RTLE)	48M: 22F: mean 32.6 years 12M: 18F: mean 32.3 years 17M: 25F: mean 32.9 years	WMS-R (5 index scores as above) WAIS-R Re-ran analyses with ANCOVA to covary for attention index, due to SCZ difference on attention score relative to other two groups. Previous comparisons using CVLT did not distinguish groups, except that LTE were worse than others.	so…memory impairment in SCZ attributable to non-temporal areas too RTLE better on general and verbal memory than LTLE and SCZ, also better than LTLE on delayed memory and than SCZ on attention index. Both R&LTLE better on visual memory index than SCZ. IQ > GMI in 60% LTE, 43& RTLE, and 72% SCZ. Only SCZ had worse attention than IQ. SCZ higher DMI than GMI, but in R and LTLE the opposite pattern is apparent.		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
				After controlling for attention SCZ have significantly superior delayed memory to the LTLE group, but still sub-normal-		
Gras-Vincendon 1994	24 SCZ 24 C	13M: 11F: age 28.2 years 13M: 11F: age 26.7 years	Free recall and frequency monitoring (explicit) Word stem completion/ priming (implicit) Tower of Toronto puzzle (implicit)	SCZ impaired relative to C on explicit but not implicit tasks, except in tower puzzle 'problem solving' aspects.		
Green 2004	32 SCZ 15 C	26M: 6F: age 45 years 6M: 9F: age 27 years	Semantic Category Picture Sorting Task (overincluder-items from more than 1 category includd together, underincluder-one or more members of same category grouped separately, or normal-all 9 items of 5 categories grouped correctly) Category based inductive reasoning task with Likert scale NART Ammons/Ammons Quick IQ test	(1) 5 of 15 C were underincluders and 10 normal. (2) 11 of 32 SCZ were underincluders, 9 were overincluders and 12 normal. (3) Over and under includers remove items from categories due to low level of perceived semantic similarity, so should be less good at inductive reasoning whose judgements rely on semantic similarities. This in actual fact did not effect reasoning in SCZ !! (4) Given good context, meaning can be properly inferred, but given free reign, they are likely to over or under include, or let ideas 'run away' with themselves!		
Gurd 1997	19 medicated SCZ 21 C	Mean age 36.5 Mean age 41.3 Similar IQ	Simple word search Category word search Cattell's Fluid Intelligence test	SCZ slower and less accurate than Con semantic but not simple search. Reflects weakened connections between lexical semantic network nodes.		
Harris 1997 (Abstract)	32 SCZ 32 C	Similar age, sex and education	CVLT	SCZ worse than C on free recall, retention & semantic		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
				clustering. Equivalent on cued recall and recognition. Deficits reflect semantic organisation and/or executive control problems		
Harvey 1986	24 SCZ 20 MDs 10 C	20M: 4F: age 33.9 years 12M: 8F: age 34.3 years 4M: 6F: age 27 years	Encoding speech (listen to random passage, organised passage and self-generated passage of speech). Verbatim passage recall	(a) Encoding (level of organisation present in recalled speech) predicts memory in SCZ & C. (b) SCZ poorer overall than C, but manics and SCZ didn't differ except on manics increase in encoding on integrated story (c) C imposed organisation to random passage recall (as seen in more organisation at recall than given at encoding)-SCZ did not. (d) Asked to generate own structured passage-or using encoding criterion, the SCZ performance normalised		Thought disorder predicted memory in manic depressed because of disruption to recall.
Heinrichs 1994	SCZ Korsakoff Personality disorder		CVLT			
Hijman 1999 (abstract only)	50 SCZ 50 C	Age matched	Dutch CVLT WMS Logical memory	SCZ compared to C impaired on logical memories, CVLT short delay recall, total recall and recognition		
Hill 2003	62 FE SCZ unmedicated 67 C	37M: 30F: age 28 years 36M: 26F: age 26.3 years Intelligence matched Education covaried in re-run analyses-no changes.	CVLT Ammons/Ammons Quick IQ test	(a) SCZ worse on verbal learning, immediate and delayed recall and recall consistency. (b) No differences on organisational strategies, but semantic clustering is more strongly correlated with overall learning in SCZ than in C.	Effects independent of medication and chronicity and education.	

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
				(c) When semantic structure is given to SCZ, their performance improves, but are still significantly worse than C-suggests they do use cues, but not as efficiently as C.		
Holthausen 2002	23 cognitively normal SCZ 95 cognitively impaired SCZ 45 C	15M: 8F: age 24.8 years 72M: 23F: age 22.9 years 38M: 7F: age 24 years	Dutch CVLT RCFT Word fluency Category fluency Spatial Working Memory Task CPT Stroop Trail-making A, B and C Finger Tapping Test Dutch WAIS (estimate on 4 sub-tests) Additional variables of: OC's Drugs	(a) SCZ without cognitive impairment (CN) actually show sub-clinical impairment in perceptual & motor speed and verbal encoding (CVLT1-5) (medium effect sizes). (b) No diffs in OCs, social function etc, suggesting they are not an aetiologically distinct population. (C) CN group scores higher than CI (cognitive impaired) on education & intelligence-so can compensate for negative brain pathology. (d) This compensation not enough for CVLT1-5 & motor speed-differential deficits? Cognitive compensation could explain essence of cognitive normality in SCZ.	Cog deficits did not affect psychopathology in either CI or CN groups, so not a core deficit? No differences between patient groups on anti-cholinergic medication usage.	
Holthausen 2003	84 FE SCZ 19 SCZffm 15 SCZaff 45 C	66M: 18F: age 22.4 years 12M: 7F: age 26.6 years 9M: 6F: age 23.8 years 38M: 7F: age 24 years Covaried for education	CVLT (aspect of organisation) Category fluency RCFT Stroop (used as speed of processing measure and attention) Trail-making A and B (used as speed of processing measures and attention) CPT (attention)	(a) SCZ worse than C on verbal learning & retrieval, category fluency, semantic clustering. (b) Verbal also worse than visual deficits, but more probably caused by difference in task characteristics and not a differential verbal deficit or		Symptomatology had no effect on verbal memory performance

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
				modality specific processing deficit (See Tracy 2001). Executive and processing speed difference between C and SCZ, but with speed, organisation and education as additional predictors, group membership still explained more of the variance in verbal memory. Long term memory impaired in SCZ, in spite of control of additional factors which might impact i.e. attention and speed. Most likely due to encoding and perceptual process aberrations due to learning deficit.		
Huron 2002	30 SCZ 30 C	23M: 7F: age 31.5 years 23M: 7F: age 31.8 years No differences in education Significant difference on IQ	16 lists of 15 words studied (every 2 lists had words associated with each other and 1 lure which was not studied). 8 lists followed by free recall & 8 by arithmetic tests after each list & (8 lists not studied). Instructed to memorise all words for test later. 15 minute delay with oral and written instructions for Remember/Know/Guess task. Practice task with 10 words then actual Yes/No Recognition task with all 24 lists. If yes, they went on to say if R/K/G WAIS-R FSIQ	SCZ had fewer true and false memories than c. Familiarity and guessing did not differ between groups, only conscious recollection. Impairment in constructive conscious memory?	No correlation between IQ or drugs and performance in SCZ.	No correlation between symptoms and performance
Huron 2003	24 SCZ 24 C	16M: 8F: age 34.6 years 16M: 8F: age 34.6 years Education matched	Words and pictures 15 minute delay followed by yes/no recognition & if yes, then Remember/Know Guess	Poorer recognition in SCZ overall. SCZ lower picture superiority effect (only in remember responses) than C.		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
			task + Memory characteristics 8 item questionnaire	Unlike C no word superiority effect in relation to guesses (superiority effect: recognise one stimuli type over another due to more elaborative encoding processes)		
Huron 1995 (oral presentation abstract)	30 SCZ 30 C		Lists of words semantically related to non-presented lure Recognition yes/no task if yes then a remember/know/guess response.	SCZ impaired false recognition to same extent as true and only during remember responses.		
Hutton et al 1998	30 FE SCZ 30 C	23M: 7F: age 27.8 years 15M: 15F: age 26.1 years matched for IQ	CANTAB WMS-R Verbal fluency For category and letters	Planning and strategy rather than attentional set shifting affected in FE SCZ. Mnemonic deficits also apparent. Recognition less affected than recall-maybe executive?		
Iddon 1998	20 IQ preserved SCZ 20 C	16M: 4F: age 39.1 years 14M: 6F: age 40.7 years Age & IQ matched	Verbal Strategy Task: 16-word list with 4 possible categories (subject unaware of these categories). Told to memorise words. After 1 minute, list removed and asked to immediately recall as many words as possible. 2nd part gave them same list with possible categories and to put words into them (timed) 3rd task again given new 16 word list again with implicit possibility of 4 categories and asked to remember after 1 minute. Visuo-spatial task NART IQ	SCZ recalled fewer words. SCZ used serial strategy more than c. SCZ did not use semantic strategy to same extent as c, even after training SCZ showed no semantic strategy whereas controls showed an increase in strategy. SCZ were slower at word category sorting than C. Semantic categorisation accounted for 84% of variance on recall after training in c but only 55% in SCZ. SCZ more impaired on verbal relative to visuo-spatial strategy task. (Frith) &(Shallice)		
Jeste 1995 (abstract)	25 late onset SCZ 39 early onset SCZ		Neuropsychological tests	No diff in late and early onset SCZ.		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
	35 C					
Joyce et al 2002	136 FE SCZ 81 C	107M: 29F: age 25.7 years 49M: 32F: age 26.1 years	CANTAB NART	Memory and executive deficit independent of IQ. 75% FE passed attentional shift, and those who failed had longer DUP.		
Kareken 1996	29 SCZ 29 C	19M: 10F: age 29.4 years 19M: 10F: age 27.5 years Balanced on education	CVLT Proactive (PI) and Retroactive Interference (RI) CVLT semantic and serial clustering chance adjusted CVLT errors of recall and recognition	SCZ less build up of PI than C, suggesting less susceptibility due to less semantic clustering. SCZ showed less semantic but more serial clustering than controls. Semantic clustering NOT correlated though with PI. SCZ made greater no. of phonemic errors. 1/ there is a deficit in semantic network hence poor encoding=temporo-parietal problems OR 2/ Lack of executive controls over list organisation=frontal deficit.		
Kazes 1999	35 SCZ 35 C	25M: 10F: age 31.9 years 25M: 10F: age 31.9 years Age & education matched Significant difference IQ	48 word list for study/encoding. Inclusion task- Word stem completion task to complete stems with words studied earlier Exclusion task- Word stem completion task to complete stems with words NOT studied earlier (explicit-trying to recollect vs implicit- trying NOT to recollect) WCST WAIS-R FSIQ	Conscious but not automatic memory is impaired in SCZ.		Conscious memory neg correlated with positive SCZ symptoms. Positive symptoms = loss of controls/slef monitoring (Frith?). Impaired attentional system (Shallice?)
Keefe 2002	29 SCZ 19 C		Source monitoring recall task (self generated and other generated items, pictures and words)	Deficit in recognising self generated items but equivalent to c in knowing soured of other generated items. Autonoetic agnosia in SCZ?		This deficit was worse in SCZ with hallucinations & thought insertion than in other SCZ.
Kenny 1997	17 SCZ	12M: 5F: age 15.7 years	Verbal list learning immediate recall	General NP impairments.		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
	17 C	9M: 8F: age 15.1 years	Verbal list learning delayed recall Verbal list learning and semantic clustering WMS Logical memory test Category instance retrieval test Word fluency WCST Stroop Digit Span Paced auditory serial addition task WISCWIS-R Maze WISC-R IQ (based on 4 sub-tests)	No differences between groups on immediate recall or fluency. Significant differences on delayed list recall, logical memory test & category instance test. Strongest effect sizes for differences on the tests of focused and divided attention though!		
Kern 1997	18 SCZ 15 C	18M: age 36.7 years 15M: age 37.9 years Approx equal education	Procedural/implicit memory test-Pursuit Rotor Tracking Test Declarative/explicit memory-Nonsense Syllable List Learning	SCZ and C no differences on implicit learning. Differences in explicit memory. Shallower list learning slope in SCZ than C.		
Koh 1980	15 SCZ 15 non psychotic SCZ patients 15 C	9 M: 6F: age 24 years 9 M: 6F: age 26 years 9 M: 6F: age 22 years Comparable education & vocabulary	Free recall of sentences (5 sentences presented followed by 15 second subtraction task then recall –repeated for 3 sets then total & cued recall. 10 min break then asked to construct sentences from scrambled words No. words and no. sentences correctly recalled scored	SCZ recall less words and less sentences than non-SCZ and C. Cueing benefits SCZ less than C. Internal sentences representation intact in SCZ, but enhanced with semantic-syntactic encoding.		
Kravariti 2003	20 FE SCZ 21 C	Adolescents Significant differences in IQ (used as covariate in analyses)	WMS-R full test WAIS-R FSIQ (17-18 years) WISC FSIQ (13-16 years) Tower of London Task Executive Golf Task Trail-making Dual Task Performance	(a)Verbal IQ and sustained attention intact. (b) General IQ deficit encompassed/accounted for deficits in visual memory, perceptual-motor, speed, planning, delayed memory, spatial working memory. (c) Verbal memory and	Medication showed no correlations with NP (as in Cassens 1990 & King 1990)	

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
				general memory impaired even after controlling for IQ differences.		
Kremen 1994	11 paranoid SCZ 15 SCZ with systematised delusions (non paranoid) 15 SCZwithout delusions (non paranoid)	6M: 5F: age 33.3 years 12M: 3F: age 33. 8 years 11M: 4F: age 35.3 years	Neuropsychological tests-9 domains of function including Verbal (logical stories) Visual memory WRAT WAIS-R	Systematising delusions reflects attempts to consolidate and understand aberrant psychotic experiences-suggests that those who cannot do this are less bright, i.e. poorer executive and language function? Premorbid and general verbal ability, as well as immediate and delayed verbal recall best in those with systematised rather than non syst. delusions		With & without systematised (around 1 theme) delusions different from each other-Systematised better premorbid function (more intelligent?)with better on verbal memory than without No differences between paranoid and non paranoid
Kremen 1995	35 relatives of SCZ 71 C		WRAT-Reading, spelling Arithmetic WAIS-R IQ (Vocabulary & Block Design)	Matching fallacy-that matching C and SCZ on education or IQ may be matching on measures already attenuated in SCZ-so could underestimate the expected intellectual ability. Predicted that due to biological risk, rels at equivalent educational attainment to C would have higher reading and spelling scores, but lower arithmetic than C. Rels lower IQ (lower in verbal then performance), but equivalent reading and spelling to C. IQ more susceptible to illness than reading/spelling. Because of this should match on NART or WRAT-Reading scores.		
Kremen 2001	36 SCZ	Split into IQ score categories:	WAIS IQ estimate –(based on 4 sub-	At each IQ level SCZ		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
	36 C	high & low average IQ groups	tests-Vocabulary, Digit Span, Block Design, Digit Symbol WRAT-R Neuropsychological test battery	performed worse than C. SCZ > verbal but < performance IQ than C (when matched for IQ level). SCZ had higher pre-morbid than current IQ levels. Consistent with decline from premorbid levels. Verbal declarative memory impaired in average IQ & attention in low IQ grps & executive function impaired in both the IQ grps.		
Lecompte (Abstract)	SCZ C		Neutral, positive or negative picture presentation. Recognition task of old plus new pictures.	SCZ produced less remember responses and more know responses than C. SCZ provided less neg and more pos memories than C for pictures.		
Lussier 2001	16 med naïve SCZ 20 C	11M: 5F: age 28.8 years 10M: 10F: age 30.8 years Education matched	Explicit and implicit memory for related and unrelated associations tests	Overall c recalled more pairs than SCZ & SCZ recalled fewer related than unrelated than c (related =associative memory). No differences on implicit recall. SCZ made more errors than C.		
Manschrek 1997	19 SCZ 19 SCZaff 19 MD patients 19C	12M: 7F: age 37.2 years 6M: 13F: age 34.7 years 9M: 10F: age 36.2 years 12M: 7F: age 34.7 years Individually matched for age, sex & recall performance. Patients matched for illness duration.	Verbal context recall task: audio 20 word list presentation (x 4 lists) varying in contextual constraint. Then to write down recalled words.	SCZ groups gain less from context than C and MD. Same level of recall in SCZ and SCZaff. Deficit prominent in primary parts of list		
Marusarz & Koh 1980	16 SCZ 16 non-SCZ patients 16 C	Comparable age, education & vocabulary.	Sternberg item recognition with categorical cues (letters & digits) followed by context-recall task for FW and BW recall.	SCZ utilised categorical cues as well as C. Serial context recall equivalent to C. STM for categorical and sequential material intact in SCZ (as		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
				estimated from RTs)		
McCreadie 1997	19 (Never treated elderly) SCZ 25 (treated) SCZ 55 C	12M: 7F: age 62 years 13M: 12F: age 62 years 27M: 28F: age 62 years	WMS-R memory scale	C had higher memory quotient than SCZ. (McDaniels 2000 says neg symptoms =verbal memory deficit, but McDermid 2002 says positive symptoms=memory deficit)	No differences between never treated & medicated patients.	negative symptoms associated with poor memory in never treated group. Dyskenisia not associated with poor memory.
McKay 1996	46 SCZ (Core group=20 chronic non elderly Elderly group= 12 chronic elderly Mild group= 14 mild 22 DAT patients 40C	 10M: 10F: age 40.6 years 6M: 6 F: age 64-72 years 8M: 6F: age 20-64 years age 69.5 years age 51.2 years	Category fluency Naming (line drawings) Sorting (pictures into categories) Word-picture matching Definitions (generate defining features of items) NART WAIS-R NART-WAIS Discrepancy score (>15 pt difference from pre-current=decline)	All SCZ and DATs were significantly worse than C on tests. Performance of elderly SCZ comparable to DATs. SCZ impaired semantic memory despite preserved overall intellectual function		
McKenna 1990	60 SCZ 176 Brain Damaged patients (BDs) [=60 moderate-severe closed head injury 76 strokes 40 tumours/ carbon monoxide poisoning] 118 C	age 44.4 years age 44.4 years age 41.4 years	RBMT Estimates of IQ Mini Mental State Exam (MMSE) Middlesex Elderly Assessment of Mental State (MEAMS)	10 of 60 SCZ were in normal range of RBMT, were moderate to severely impaired. 49 SCZ normal on MMSE, 4 mildly demented only. 27 normal on MEAMS, 22 borderline & 10 severe. SCZ just as likely as BD patients to be memory impaired (4% C had < 7 screening score RBMT, but >50% SCZ & BD <7 score)		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
				From MMSE&MEAMS SCZ more comparable to depressed than demented patients. RBMT not correlated with medication or age, but with severity of illness & chronicity. SCZ generally better intellectual MEAMS & MMSE than elderly depressed patients. Spared STM, but impaired LTM. Distinctive group with preserved intelligence but poor memory.		
McKenna 1994	20 (non-elderly, chronic & severs) SCZ 26 C 22 ALZHEIMERS WAIS IQ MMSE	N/A	Category Fluency Naming Sorting (categories) Word to picture matching Definitions (facts/items)	SCZ < C on all tests, except word to picture naming (which was v poor in ALZ). SCZ approached level of ALZ in all other tests. Over-inclusive thinking notes as SCZ disorder by Cameron in 1947-blurred boundaries of semantic knowledge-specifically seen in acute/positive symptom patients.		
Mohamed 1999	94 FE medication naïve SCZ 305 C	53M: 41F: mean 26.1 years 162M: 143F: mean 25.5 years Differences on education	RAVLT WMS- Logical memory test Word fluency Savings scores RCFT CPT Stroop Trail-making WCST WAIS-R	SCZ worse than C on all memory scores. Not on story recall savings scores though (forgetting rate). Largest effect size for recognition trial 5, immediate recall then delayed recall of story.	No differences in performance with or without medication	

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
			Finger tapping WAIS sub-tests administered individually	Executive function and attention also equally impaired. Effect sizes show this to be generalised across several areas of function and not differential to any one domain.		
Morice and Delahunty 1996	17 SCZ 17C	10M:7F: age 32.4 years 5M: 12F: age 34 years	WCST Tower of London WAIS-R Digit span (FW and BW) Word, alphabet and sentence span Sentence verification WAIS-R FSIQ NART	Planning and flexibility impaired in SCZ relative to C- independent of premorbid IQ (NART). No differences between groups on STM, but on alphabet and sentence span (working memory)-worst in those with IQ decline. Tower London deficits emerged with task difficulty.		
Moritz 2001	25 SCZ 25 Depressed (unipolar) patients 25 C	Significant difference in age-covariate in analyses	RAVLT	SCZ and depressed patients worse than C on short and long recall and recognition but not interference.		Negative symptoms correlated with memory deficit. May be problem with verbal learning. No differences between SCZ and depressed
Moritz 2002	32 SCZ {12 thought disordered (TD) 20 non TD} 65 C	23M: 9F: mean 32.5 years 37M: 28F: mean 34.2 years	(1) Semantic Priming Task (semantic, unrelated in meaning and indirectly related conditions)	TD patients showed greater indirect semantic priming than non TD and C, relative to a neutral or unrelated baseline condition and could be associated with the loosening of associations in other disorders. Enhanced spreading of activation.	Medication and psychomotor slowing had no effect on priming.	
Nathaniel James 1996A	25 SCZ 25 C	Each matched (as closely as possible) on age, sex, education and pre-morbid	Recognition memory for words & faces (Warrington) CVLT	SCZ learned less material overall than C but learned at same rate as C.		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
		NART IQ	Verbal associative fluency HSCT WCST NART	Serial position recall & proactive interference normal. SCZ used serial in preference to semantic encoding unlike the C. No differences on recognition memory (could be familiarity). SCZ worse on verbal fluency than C. Also executive function deficits, which may overlap with memory problems. Frontal and less MTL		
Nathaniel-James 1996B (Confabulation)	12 SCZ 12C (3 Ds.)	age 37.2 age 35.3	Recognition memory for words & faces (Warrington) CVLT Verbal associative fluency HSCT Modified CST Confabulation test Ravens Progressive Matrices-IQ NART	C>SCZ on interference list, long delay free & cued recall, intrusion errors, Verbal fluency & HSCT-errors., story recall. No differences on recognition, story gist or verbal learning Each of 12 SCZ confabulated about story at least once (relative to just 1 C). After matching for recall performance, the high confabulation rate in SCZ relative to C was still evident, hence is shown not to be explained by poor memory recall, although SCZ with poor recall did confabulate the most. No relation to intelligence or understanding of story morals or gists. Diff between high and low confabs on the HSCT error scores (INHIBITION of RESPONSES-not same as intrusions!) and thought		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
				disorder measure and mildly assoc with intrusions in recall. ALZS & KORSAKOFFs produce meaningless & irrelevant confabulations based on intrusions in recall of stories, but SCZ are reorganising ideas to reconstruct story & coming up with different ideas i.e taken heard words from text and reused in a different CONTEXT (Points to frontal deficit?)		
Nestor 1998	18 SCZ 21 C	All M: age 44 years All M: age 39.9 years	Word list (32 words) recall. Associative strength and number of associates varied. High connectivity-small network, low connectivity-large network	SCZ recalled fewer words than C. Improved with highly connected words regardless of network size and declined on unconnected words. C showed best recall for high connectivity-small network followed by low small network then high-large, low large. C more influenced by network size.		
Oie 1999 (abstract)	19 adolescent SCZ 20 adolescent ADHD 30 C		Long-term episodic memory task, free recall & recognition.	SCZ worse than c on all memory tests. ADHD worse on working memory and didn't show visual impairment seen in SCZ.		
O'Carroll	20 RBMT memory impaired SCZ, 21 memory unimpaired SCZ) 20 C	11M: 9F: age 35.6 years 15M: 6F: age 36 years 12M: 8F: 33.1 years	Stem completion task (errorful-told target straight away or errorless-allowed wrong guesses then told correct target)	Memory impaired SCZ worse than others when allowed to guess target, but improved when prevented from guessing. Unable to differentiate between correct & incorrect responses during learning (untagged?)-similar to source monitoring concept		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
				of Frith.		
Paulsen 1995	175 SCZ 229 C 79 C (age matched)	94M: 81F: age 40.1 years 118M: 111F: age 54.6 years 48M: 31F: age 41.9 years	CVLT Vocabulary	SCZ worse at recall than recognition. Residual recognition impairment suggests encoding as well as retrieval deficit. No rapid forgetting means there is no storage deficit or loss of information over time. Cortical dementia (Alzheimers) subcortical dementia (Huntingtons & parkinsons) and c and SCZ showed 50% SCZ to have sub cortical, 35% normal, 15% cortical. Claim SCZ show mainly subcortical like dementia.		
Passerieux 1997 (abstract)	22 SCZ (TD & Non TD) 11 C		Semantic Priming: lexical decision task	C & NON-TDSCZ show priming effect for related word pairs compared with unrelated. TD SCZ do not. Problem with post lexical controlled info processing for integration of semantic info in Thought disordered patients.		
Perry 2000	30 SCZ 30 C	Age & education matched	Word stem priming (recall, recognition & priming)	Impaired recall in SCZ, but improved with recognition and normal priming. DECLARATIVE -NON DECLARATIVE DISSOCIATION		
Radant 1997 (abstract)	25 SCZ 24 C	Age matched	RAVLT trials 1-5, recall after distraction	SCZ worse than c on both memory measures.		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
Ragland 1996	30 SCZ 30 C	17M: 13 F: age 31 years 16M: 14F: age 28. 4 years	Paired associates recognition (using visual WCST) WMS Logical memory test Vocabulary of WAIS-R (C high average, SCZ low average)	Impaired on PART (also on WCST but not after controlling for intelligence). This is associative recognition so more difficult. WCST may also be affected by anti-cholinergic medication and practice effects.		
Ragland 2003	30 SCZ 30 C	19M: 11 F: age 22.9 years 17M: 13F: age 22 years (approx)	Shallow vs. deep classification (encoding) and recognition (Buckner et al 98) NART IQ Effect of pre-morbid IQ investigated in 2nd analysis by matching participants on estimate of IQ.	All groups fine on classification task, though SCZ slower than c. Both groups better recognition following deep relative to shallow encoding. No differences in recognition between groups. Group differences in response bias such that SCZ say no more with deep encoding-unsure? IQ didn't impact on recognition, but contributed to less accurate word classification at encoding.		
Riley 2000	40 FE SCZ 22 C	Age 24.6 years Age 26.7 years	Verbal fluency RAVLT WMS Visual Reproductions Letter-number auditory working memory test Visuo-spatial dot test WCST Stroop CPT Trail-making A WAIS Digit symbol Benton's line orientation judgement test	SCZ worse than c on delayed but not immediate recall. Also worse on verbal learning and verbal fluency for letters and categories.	No effect of medication on analyses	

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
Rizzo 1996	33 SCZ 33 C	21M: 12F: age 32.8 years 21M: 12F: age 31.3 years	Recency discrimination task-memory for temporal order/context of pictures WAIS-R IQ on Short form WAIS-R IQ-no difference in analyses after matching for IQ.	SCZ could recognise and recall items but were impaired in recall of when they were learned.	No effect of medication on performance	
Rushe 1999	58 SCZ 53 C	48M: 10F: age 33.6 years 45M: 8F: age 31 years	Verbal paired associates WMS Logical memory test Recognition memory Memory for temporal order Spatial and non-spatial associative learning WAIS-R IQ Schonell Reading Test NART IQ Significant difference in premorbid IQ-covariate	SCZ impaired relative to C on story recall &paired associates. Recognition and temporal order memory intact. Visual not as impaired as verbal.		
Saykin 1991	36 FE SCZ (medication naïve) 36 C	26M: 10F: age 28.8. years 18M: 18F: age 27 years	CVLT, WMS Paired associates = verbal learning WMS logical memory test =semantic memory Verbal fluency (COWA, Boston Naming), Comprehension of complex ideational material, Sentence repetition, Reading recognition = language WMS Visual Reproductions = visual memory WAIS information, vocabulary and similarities = verbal intelligence WAIS Picture completion, block design and object assembly = spatial org. WAIS Arithmetic, Digit Span, Rhythm test = auditory attention Trail-making A and B, WAIS Digit	General poorer performance across tests in SCZ relative to C. Semantic memory (Logical memory test), verbal learning (CVLT, paired associates) and visual memory (WMS visual reproductions) are selective deficits. Partialing out attention did not affect performance on memory tests. Abstraction on WCST was least impaired function in FEs. Suggests mainly LMTL		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
			Symbol, Stroop = visual attention CPT = vigilance WCST = abstraction Motor tests	dysfunction and possible some R (i.e. visual memory-but WMS not that sensitive to this RMTL)		
Saykin 1994	37 FE SCZ (medication naïve) 65 SCZ (previously treated) 131 C	23M: 14F: age 28.6 years 48M: 17F: age 31.3 years 76M: 55F: age 27.1 years	Same tests as in 1991(above). Added: Facial recognition test into visual memory (sensitive to RH TL) CPT attention & vigilance tests WAIS verbal scale combined with language functions Analyses with and without adjustments for age, sex and education	C > SCZ verbal memory tests. FEs show strengths in verbal intelligence and language, but deficits in verbal learning and memory Could represent left medial temporal disorder as suggested in 1991. Patients worse than FEs on spatial and motor tests and trends for worse performance on all other functions except attention/vigilance and abstraction.		
Schmand et al 1997	67 Psychotic in-patients (30 SCZ, 6 SCZffm, 10 SCZAaff, 3 Major Ds., 3 Bipolar, 3 reactive psychosis, 14 psychotic not specified) 19 Non-psychotic in-patients	38M: 29F: age 33. 2 years 7M: 12F: age 37.3 years	Word List Learning Tower of Hanoi/motor- & complex problem solving-procedural DART IQ	No differences in motor procedural learning, though psychotics less efficient in solving problem. Automatic processing intact in psychotics Psychotics worse on list learning.		Memory task did not correlate with psychotic symptoms

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
Schroder 1996	50 chronic SCZ (split into sub-syndromes) 50 C	Age 32 years Age 27 years	Declarative immediate and delayed recall Delayed recognition WCST (working memory) Tower of Toronto (Procedural memory) Attentional test	All SCZ worse than C on delayed recall and recognition, procedural memory and WCST. Immediate memory intact. Attention worse in chronic relative to remitted group.	No effect of chronicity, severity of illness or attention	Delusions associated with delayed recognition, negative symptoms associated with delayed recall and disorganisation associated with neurological soft signs and poor working memory.
Schwartz 1991	16 SCZ 16 C Significant differences in education. Verbal intelligence (WAIS-R IQ vocabulary) & age matched	15M: 1F: age 37 years 15M: 1F: age 34 years	Memory for temporal order-recency discrimination task Semantic ordering task Word recognition WCST	Memory for order of events impaired in SCZ relative to c in spite of intact recognition for items. Perseveration inversely correlated with recency discrimination task, but not with recognition. Most impaired in memory for spatial-temporal info had greatest WCST scores/executive deficits-failure of effortful processing?	Anti-cholinergic medication did not affect memory performance in SCZ	
Seidman 1998	35 SCZ 30 TLE 25 C	19M: 16F: age 28.7 years 13M: 17F: age 34 years 19M: 6F: age 30.2 years	WMS-logical memory test WMS paired associates WMS Visual reproductions Digit symbol incidental recall WAIS-R Block Design, Vocabulary and Digit Span ANCOVAs controlling for sex and education & IQ did not impact on performance	Savings scores in SCZ and TLE same and not poor. IQ also normal in SCZ-so deficits cannot be due to global intellectual deficit. Impaired incidental recall-suggests need for instruction. i.e. Paired associates learning in SCZ benefits from cues and repetition. Impairment in SCZ evident in non-verbal measures, but		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
				forgetting more for verbal than non-verbal.		
Seidman 2002	87 SCZ 15 Bipolar 94 C	68M: 19F: age 43.3 years 7M: 8F: age 40.7 years 43M: 51 F: age 42.3 years	WMS Logical stories WAIS-R Vocabulary & WRAT Reading WAIS-R Block Design, Hooper Visual organisation, line orientation judgement test Perseveration WCST WAIS-R Digit Span, Arithmetic Trail making A & B, WAIS-R Digit Symbol CPT & Dichotic Listening	SCZ < C on all functions except verbal ability (vocabulary and reading). SCZ < BP on abstraction, motor speed and vigilance.		
Shallice et al 1991	5 chronic SCZ (individual case study approach)		WMS Logical memory WMS visual reproductions WMS paired associates Warrington's recognition for words and faces Coughlan and Hollow's figure and story recall battery WMS Digit Span Cued recall tests NART WAIS FSIQ Ravens Progressive Matrices Peabody Vocabulary Spelling Arithmetic Token test Naming from descriptions Graded naming	All patients performed badly on tests supposed to be sensitive to frontal function, irrespective of differences in other areas of performance. 2/5 patients showed WAIS-NART IQ discrepancy suggestive of decline. Hence apparent only in some patients?		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
			Verbal Fluency WCST Stroop Other executive function tests Perceptual tests			
Sonntag 2003	21 SCZ 21 C	17M: 4F 17M: 4F	Word list (explicitly to learn some & forget others), recognition Remember/Know/Guess decision.	C remembered more to be learned than forgotten words-directed forgetting effect success, regardless of remembered, known or guessed recognitions decision. Gardiner found this in c for only remember (more sure) but not know responses. SCZ showed same degree directed forgetting but for know but not remember responses only. Deficit in noetic awareness in SCZ.		
Stirling 1997	27 SCZ 19 C	22M: 5 F: age 39 years 12M: 7F: age 40 years	Memory for action test (source memory: self generate 5 animals, fruits and body parts and remember them. Then given other 5 exemplars from experimenter also to be remembered- NART & 5 mins later – Recognition test-identify as old new-if old identify source as self or experimenter) and Serial position curve Free recall Priming False responses Ammons/Ammons IQ test (covariate in repeat analysis-no effect)	SCZ less effective than c on immediate and long term memory, and source memory independent of IQ. Primed recall is intact. Overall performance associated with negative symptoms. See Frith 1991 for same test in SCZ.		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
Stone 1998	18 SCZ 15 C	All M	Free recall (FW & BW digit span) Temporal order Self ordered pointing Recognition	SCZ worse than C. Reduced working memory accounted for strategic but not recognition memory performance (additional MTL deficit?). Education, verbal intelligence & immediate memory capacity don't account for working memory deficits in SCZ		
Stratta et al 1997	30 SCZ 25 C	Age 36.9 years Age 34.7 years	WCST WAIS Digit Span WAIS Digit Symbol Visuo-spatial working memory test	SCZ worse than C WCST did not correlate with any of the working memory measures		
Sullivan 1994	34 SCZ 67 C 47 age matched C	All M: age 36.9 years All M: age 45.1 years All M: age 37.9 years	WMS Logical stories and paired associates (LMTL) WMS drawings and design recognition (RMTL) Brown Peterson Distractor task-verbal and non-verbal (orbito-frontal?) WCSYT perseveration WMS self ordered pointing no. correct Letter search task time (RDLPFC?) Motor ability	SCZ worse than C. No modality or laterality specific deficit. May be multiple selective deficits as opposed to overall general deficit.		Declarative memory predicted symptom severity. Executive function could be related to disease duration-chronicity/medication?

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
Sullivan 1997 (abstract)	27 SCZ 52 ALCOHOLICS 66 C	Age and IQ covariates	(1) Content and context memory	SCZ impaired in item and order recognition of verbal and non-verbal material Alcoholics impaired only in order recognition. Similar deficit to parkinsonians.		
Sumiyoshi 2001	57 SCZ 33 C Early onset SCZ<20 years vs. Late onset SCZ >20 years High vs. low WAIS-R vocabulary SCZ	28M: 30F: age 27.2 years 18M: 15F: age 25.8 years	Animal Category Fluency Test Used multidimensional scaling to investigate structure of semantic memory.	Late onset or high vocabulary SCZ retain semantic memory structure, compared with others. Age of onset and verbal intelligence may be related to structure degradation in SCZ.		
Tamlyn 1992	60 SCZ (from which 5 SCZ with v. poor RBMT screening scores were excluded)	Age 44.4 years	RBMT (inc. prose recall) Word list recall Forward Digit Span Corsi blocks Warrington recognition memory Silly sentences Remote memory test Famous personalities test Autobiographical memory interview NART WAIS MMSE MEAMS	Memory impairments apparent irrespective of intellectual function levels (MMSE and MEAMS showed 80 and 82% above cut off for mild dementia and at normal level respectively) Memory inversely correlated with NART. Short term memory preserved-evidence for amnesic syndrome? Semantic memory not affected in classic amnesia, but disturbed in these SCZ.	No correlation between memory and medication	Memory impairment associated with negative symptoms and thought disorder and with severity of illness.

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
Titone 2004	29 SCZ 29 C	No difference in age & parental education. Significant difference in education (C>SCZ) & sex (SCZ less F than C)	Transitive Interference task: relational memory task A>B B>C C>D D>E & 2 new pairs (4 visual patterns, one at time, one hiding smiling face-to remember which one hides face-initially guess, then see-higher patterns hide it)	SCZ less accurate than c in responding to relational pairs. Impairment in binding for relational memory discussed.		
Tracy 2001	28 SCZ 28 C	Results significant after adjustments for age, sex and education	CVLT Non-verbal recall test	Equivalent impairment for both verbal and non-verbal material. Learning and recall more impaired than storage and maintenance followed by recognition. Proactive interference least impaired. Poor encoding and not forgetting maybe responsible for impaired recognition and recall. Encoding deficit for verbal and non-verbal suggests bilateral prefrontal deficit. Only retrieval deficit for verbal (though could mean non-verbal was easier?)		
Van Oostrum 2003	20 SCZ 20 PARKINSONS 20 C	As equivalent as possible on age, sex and education.	CVLT	After recognition, SCZ had more false positives, less semantic clustering and lower recall consistency than c. No abnormal forgetting in any group. Both patient groups less recall than C. All better at recognition than recall. SCZ show problems discriminating old from new items. Goldberg and Paulsen also shown benefit of recognition over retrieval in SCZ. Suggests sub cortical or		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
				frontal-striatal pathology deficit & not temporal lobes problem? Why striatum? Also seen in PD patients-retrieval deficit & preserved recognition. DAT temporal deficit shows encoding problems marked by intrusions and forgetting rate, not seen in SCZ.		
Vinogradov 1997	26 SCZ (medication less 7 days prior to experiment) 21 C	Matched on age, sex and education	Source monitoring (40 sentences-noun, verb and target which is blank-subjects to read out/self generate their completion word. Next test includes targets generated by experimenter plus new list of associated target words Recognition memory-to decide whether target word is new, old, self or experimenter generated. Shipley IQ	SCZ had normal recognition memory, but deficient in identifying source of target word. More errors in identifying source of items that were new and self-generated. Assoc between executive-motor dysfunction & source monitoring errors mediated by low IQ. Low IQ associated with source discrimination errors for self-generated items, but new ones (this was lost in SCZ with normal IQs though they still had more discrimination errors than C: Source memory impaired in old & frontal lesion patients. Frontal lobes essential for associating memories with context in which they are learned. SCZ more problems remembering source of items that were self generated (unusual in normal people). If item is familiar but source info is not available, they will say		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
				it was externally generated.		
Watanabe 2002 Letter to editors	15 SCZ (mild symptomatic out patients) 15 C	10M: 5F: age 27.6 years 10M: 5F: age matched	RAVLT Perceptual Mirror Reading Task-Implicit memory	Verbal learning impaired in SCZ compared to C. Effect of repetition same for both groups. Implicit learning intact in SCZ.		
Waters 2003	43 SCZ 24 C	No difference in age, sex, education or pre-morbid NART IQ	Context memory task-self pairing of objects or exp pairing of objects x2 tests Recognition for true pair combinations and source of pairing NART IQ	SCZ less accurate in recall of source and temporal order of events than C. Contextual binding impaired?		

Author	Sample	Demographics (M= male, F =female)	Task	Details	Medication Correlations	Symptom Correlations
Weiss 2002	20 SCZ (pictures) 20 SCZ (words) 16 C (pictures) 16C (words)	All M: age 44.6 years All M: age 43.9 years All M: age 42.3 years All M: age 37.4 years Ran analyses to control for parental education, encoding, and medication	Incidental encoding of words (& audio) Recognition old or new All items presented as words plus foils and foils then presented for second time-participants told to label foils still as 'new'	SCZ greater false recognition of new items. Greater false alarms for words than pictures encoding group. Also SCZ greater false recognition for repeated foils than C-this is due to equal familiarity of repeated foils and previous targets-pressure on using source memory to discriminate. Both SCZ and C suppress false recognition after picture better than after word encoding. Greater delay lead to greater false recognition in SCZ		
Wexler 2000	8 SCZ	4M: 4F: age 46 years	Auditory verbal serial position task (PET)	After 10 weeks of training verbal memory improved-associated with normalisation of activation of LIFC		

Table 1B: Literature reviews of memory in schizophrenia

Authors	Review title	Review Type	Number of studies	Results
Henrichs & Zakzanis 1998	Neuropsychological deficits in schizophrenia	Quantitative	204	Global neuropsychological deficit. Largest effect size in global verbal memory (d=1.41)
Aleman 1999	Memory Impairment in schizophrenia	Meta-analysis	70	Stable memory impairment in SCZ, independent of age, medication, illness duration, patient status, severity of symptoms or positive symptoms.
Danion et al, 2001	Treatment of cognitive dysfunction in schizophrenia	Theoretical/qualitative	8	Evidence to suggest that autonoetic awareness is impaired in SCZ
Cirillo & Seidman 2003	Verbal declarative memory dysfunction in schizophrenia: from clinical assessment to genetics and brain mechanisms	Qualitative	110	Of 110, 101 found impairment in SCZ on at least 1 VDM measure! This may be due to encoding deficits, due to mild rates of forgetting. Attention, medication, and symptoms don't account for this deficit. Similar but milder deficit in relatives and FE SCZ.
Achim and Lepage 2003	Is associative recognition more impaired than item recognition?	Meta-analysis	23	20% greater impairment for associative than for item recognition.

Table 1C: Studies investigating development and stability of cognitive impairment in schizophrenia

(for abbreviations and acronyms see 'Abbreviations and acronyms table')

Author	Sample	Demographics	Type of study	Tasks	Details	Medication & Symptoms	Outcome
Longitudinal studies of NP change							
Addington 1991	38 acute SCZ Test (1): 38 medicated Test (2): 36 medicated	25M: 13F: age 30.9 years	Longitudinal follow-up Initial assessment and 6 month follow up in remission.	Word fluency Category fluency RCFT Design fluency WCST WMS WAIS	(1) Performance on most tests improved over the 6 months. (2) No change seen in word fluency or WCST	(1) Higher medication related to low IQ but not cognition. (2) Cognitive impairment may be worse in those less responsive to medication, hence it may impact on performance. (3) General IQ, WCST and word fluency associated with negative symptoms & persist during remission-trait? (4) Delusions don't interfere with performance but associate with higher IQ. (5) Info processing deficits in positive symptoms could be state but in negative could be trait related. (6) positive symptoms improved along with cognitive function (except word	Improvements in cognition over 6 months could be related to change in positive symptoms

Author	Sample	Demographics	Type of study	Tasks	Details	Medication & Symptoms	Outcome
						fluency & WCST)- could be deficit of state	
Albus 2002	50 FE SCZ Test (1): 50 medicated Test (2): 23 medicated 50C	23M: 27F: age 31.6 years 26M: 24F: age 29 years	Longitudinal follow-up Tested at remission period and then 2 years later	WMS CVLT WCST Trail-making Stroop WAIS Digit Symbol	(1) All SCZ performed less well than controls on all NP scores. (2) Visuo-motor processing improved over time in both groups, and verbal learning in the FE SCZ (trials 1-5) (3) visual memory deterioration in SCZ due to improvement in C-bigger diff between 2.	(1)Symptomatology had no effect on NP scores (2) Medication impacted on scores at 2 year follow up.	Improvements NP impairment is evident at index and follow up, but is stable.
Censits 1997	30 FE SCZ (ill mean 3 years) (2 previously medicated) 30 previously treated SCZ (ill mean 9 years) Test (1): All groups no medication 2 weeks prior Test (2): All groups medicated 38 controls	17M: 13F: age 30.3 years 21M: 9F: age 27.1 years 25M: 13F: age 31 years	Longitudinal follow-up Tested at intake and 19 months later	WMS-R Logical memories CVLT trials 1-5 Word fluency Semantic fluency Boston naming test WRAT-Reading Benton line orientation WAIS-R Block Design WMS-R Design Reproduction (immediate and delayed) WCST Stroop Test CPT Trail-making WAIS-R Digit Span WAIS-R Digit Symbol Reitan-Klove sensory-perceptual exam Thumb-finger sequential touch-motor test	Results don't support neurodegeneration. Stability in NP of both groups over time.	(1) No correlations between medication dose and NP on eight domains of function (2) No difference on NP between first episode medication naïve and previously treated patients.	Clinical improvement seen in all domains except anhedonia. Clinical improvement positively correlated with NP improvement. Negative symptoms correlated consistently with NP. Account for most improvement in cognitive function (see Bilder 1985; Andreasen 1990) Bizarre ideation and language showed largest correlation coefficient
DeLisi et al 1995	25 FE SCZ	15M: 5F: age 27.3	Longitudinal follow-up Hospitalisation and	Language Executive function Verbal memory Spatial memory	NP did not worsen over time Greater the decrease in	No correlation between structural change and NP	Improvement in some tests

Author	Sample	Demographics	Type of study	Tasks	Details	Medication & Symptoms	Outcome
			4 yrs later	Concentration/speed Sensory/Perceptual Left & right hemisphere Global factor Structural MRI scans	brain size, the less an improvement in left hemisphere function. Improvement in concentration/speed and right hemisphere function		
Gold 1999	54 FE SCZ Negative Positive Disorganised Test (1): 45 medicated Test (2): 40 medicated		Longitudinal follow-up Hospitalisation and follow-up 5 yrs later (6 monthly interval assessments)	WMS Logical Memory free recall Verbal associative fluency delayed Visual search and attention WCST flexibility Trail-making B WAIS-R FSIQ Finger-tapping test	Verbal IQ and memory stable over time. Slight improvements over 5 years in performance IQ and FSIQ (not practice-too long a period in-between).	All symptom groups improved over time and FSIQ improved but verbal IQ stable. Attention, free recall and WCST categories improved. Motor function deteriorated in both hands (neuroleptics?). Verbal and FSIQ correlated with negative symptoms and changes in negative symptoms. Core feature? Medication not controlled so variable and fluctuating!	Improvements Cognitive function does not deteriorate over time
Heaton 2001	142 SCZ (outpatients) 206 C Split into short (< 36 months) and long follow up periods (>36 months)		Longitudinal follow-up Baseline FE & 6months –10 years later (mean 3 years)	WMS-R Logical memory CVLT Boston naming test Word fluency WAIS-R Block design WAIS-R Object assembly Trail-making WCST Finger tapping Grooved pegboard Hand dynameter	No change in differences between SCZ & C over time. Any improvements likely reflected practice effects as in controls.	Unaffected by symptoms change. No progressive decline after onset.	
Hill 2004	45 FE SCZ	28M: 17F: age	Longitudinal	WMS-R	SCZ but not C decline		Stable

Author	Sample	Demographics	Type of study	Tasks	Details	Medication & Symptoms	Outcome
	33 C	23M: 10F: age Age, sex & education matched	follow-up FE prior to medication and over 2 years SCZ completed 4/5 assessments at least, C 3/5 at least	CVLT	after 6 weeks of treatment in verbal memory. This returns to baseline level by 6 month follow up.		
Hoff 1992	56 SCZffm 57 C Test (1): All medicated Test (2): All medicated	41M: 15F: age 25.6 years 39M: 18F: age 29.1 years	Longitudinal follow-up Baseline 2 –4 weeks after hospital admission and 2 years later	Language Verbal memory Executive function Concentration/speed Sensory/perception Spatial memory Global score MRI scan	Not all patients and C had both scans and testing. Only 17 SCZ had follow ups. Performance on all measures appears to improve over time-specifically attention and speed and executive function. Improvement could be due to it being after discharge. A tested sub-group prior to discharge showed stability of function.		
Hoff 1999	42 FE SCZ 16 C Test (1): 39 medicated Test (2): 39 medicated 7/42 in remission at test (2) of which 4 were medicated Split into short (2/3 years) and long follow up groups (4/5 years)	31M: 11F: age 26.3 years 11M: 5F: age 26.1 years	Longitudinal follow-up Baseline FE & 2-5 yrs later	WRAT-R Boston naming test Word attack Word fluency (COWA) CVLT WMS-R Logical memory WMS-Visual reproductions WCST Trail-making Finger tapping Structural MRI scans	Dysfunction in first 5 years remains stable at 1 or 2 SD below C. Some aspects of function improved over time, although less verbal memory improvement over time relative to C.	Improvement in positive symptoms correlated (but not brain measurements) with cognitive improvement. Lack of improvement in verbal memory not related to medication	
Hughes 2002	62 SCZ (or SCZaff)	39M: 23F: age	Longitudinal	WMS logical memory	Significant	Improvement in	Significant

Author	Sample	Demographics	Type of study	Tasks	Details	Medication & Symptoms	Outcome
	25 C Test (1): All medicated Test (2): All medicated	37.7 years 15M: 10F: age 34.9 years	follow-up Baseline FE & 6 months later	WMS Visual reproductions HVLT Word fluency (FAS) WCST Tower of London Trail-making B WAIS-R Digit symbol Executive golf test CPT NART (test (1) only WAIS-R FSIQ test (1) only	improvement over 6 months in both groups on verbal memory measures, trails B, CPT errors, Digit symbol. SCZ also improved on trials A, WCST and delayed visual memory. Cognition relatively stable aside from obvious learning effect over time (practice)	symptoms predicted only better motor speed. No relationship between symptoms and cognitive ability. Negative symptoms predicted low IQ.	improvement over 6 months in both groups on verbal memory measures.
Landro 1994	22 SCZ 8 AFF 14 C	16M: 5F: age 32 years 4M: 4F: age 38 years 8M: 6F: 33 years	Longitudinal follow-up Tested x 3 1year intervals	STM task-Peterson & Peterson Auditory Trigram Procedure(3 consonants read aloud, then 3 digits read BW as a distractor 15 sec retention interval). LTM task-Continuous Distractor Paradigm. (3 different word pairs in 5 trials read aloud, with distractors between pair presentation. Recall).	SCZ performed significantly worse than C on STM and LTM task.		All groups improved/learned over time.
Morrison 2000	45 SCZ Test (1): All medicated Test (2): All medicated	28M: 17F: age 35 years	Longitudinal follow up Baseline and 7 years later	NART baseline NART 7 years later	NART does not decline over time. May be stable pre-morbid estimate of crystallised verbal intelligence	2 SCZ had large changes over time (-16: +18) but mean change small across group (1.4)	No change in NART
Nopoulous 1994	35 SCZ Test (1): 28 medicated Test (2): 29 medicated 2 not on medication at test (10 or (2)	29M: 6F: age 24 years	Longitudinal follow -up Baseline and 2 yrs later	RAVLT WMS-Logical memory WMS-R Paired associated Word fluency (COWA) Stroop test CPT Trail-making Benton visual retention	Cognitive function stable. Attention may be state dependent.	Improvements in complex attention (Stroop test, trails B) correlated with clinical symptom change.	Improvements in complex attention (FE-2yrs later SCZ)
Rund 1989	14 SCZ 8 NONPSYCHC 20 C		Longitudinal follow-up Baseline and 4	Digit span with neutral and distractor condition strings	Stable deficit in STM recall at both assessments in SCZ (esp non paranoid).		

Author	Sample	Demographics	Type of study	Tasks	Details	Medication & Symptoms	Outcome
			years later		Para better at distractor strings vs. neutral at first but not second assessment. Non-para & C stable impact of distractibility over time, but paranoids changed over time. Trait but impacted by changing psychopathology?		
Stirling et al (2003)	49 SCZ 41 SCZ, 8 SCZaff	28M: 21F: age 26 years	Longitudinal follow-up Baseline and 10-12 years later	Word fluency NART Warrington recognition test Memory for Design test WAIS-R Objects assembly, picture completion and arrangement, block design WCST	Decline over time in picture completion, object assembly and memory for designs-fronto-parietal tests? No improvement on WCST Verbal fluency, recognition of faces showed non-significant improvement-	Persistent negative symptoms prdict poor outcome. No relation to NP though.	
Sweeney 1991	39 SCZ (29 SCZ; 4 SCZffm; 6 SCZaff) Test (1): All medicated Test (2): All medicated	24M: 15F: age 28.6 years	Longitudinal follow-up Clinical discharge and 1 year later	RAVLT WMS-R Visual Reproductions Word fluency (COWA & FAS) WCST Trail-making WAIS-R Digit Symbol WAIS-R Digit Span WAIS-R Block Design Bentons Line Orientation Judgement Test Finger-tapping test	Psycho-motor function improved over time-trials, finger-tapping, digit symbol. Verbal memory (RAVLT recognition) improved with time. WCST improved preseveration errors and categories achieved-impaired to normal range in 59% patients. No change on digit span, block design, visual memory, verbal recall or fluency.		

Author	Sample	Demographics	Type of study	Tasks	Details	Medication & Symptoms	Outcome
Cross-sectional studies of age-related NP change							
Fucetola 2000	87 SCZ 94 C	Young (age 30 years) N=23 Middle (age 41 years) N=38 Old (age 58.3 years) N=26	NP across discrete age groups	WMS Logical Memory test Visual-Verbal test WCST WAIS-R Vocabulary WAIS-R Digit Span WAIS-R Block Design WAIS-R Digit Symbol Trail-making WRAT-R Arithmetic WRAT-Reading and Spelling Dichotic listening	Age related decline in NP same in SCZ & C. More accelerated decline though in abstraction (WCST) in SCZ.		No change
Goldberg 1993	Review of studies investigating stability of cognitive function in SCZ						
Heaton 1994	143 SCZ 38 C 42 Alzheimer's patients (AD)	Of 143 SCZ = 85 early onset young SCZ 36 early onset old SCZ 22 late onset SCZ	NP across discrete age groups	Story memory Figure memory WAIS-R Specifically % retention after 4 hour delay	All 3 SCZ groups like one another, but diff from AD & C. Impairments not related to AGE, CHRONICITY or TIME of ONSET. AD show forgetting after a delay, which reflects neuropathological process: this was not seen in SCZ.		
Hyde et al 1994	74 SCZ (medicated)	5 age cohorts: 18-29, 30-39, 40-49, 50-59 years	NP across discrete age groups	MMSE List Learning Dementia Rating Scale Category fluency Boston naming WCST WRAT	Boston naming test performance declined with age. No difference between cohorts in performance on all other tests (tests used to detect a		SCZ appears to have static course across age groups.

Author	Sample	Demographics	Type of study	Tasks	Details	Medication & Symptoms	Outcome
					progressive dementia)		
Mockler 1997	62 SCZ	5 age cohorts: 18-29, 30-39, 40-49, 50-59 years 2 age cohorts: 18-39 years (young), 40-69 years (old)	NP across discrete age groups	RBMT WAIS-R FSIQ NART WAIS-NART discrepancy score	No differences between 5 and 2 age cohorts in verbal, performance or WAIS-FSIQ No decline from pre-morbid to current IQ across groups.	Differences on digit symbol & picture completion, but unrelated to age or duration of illness.	SCZ has a static neuropsychological course. Must occur prior to onset: BUT WHEN?

Table 1D: Studies investigating premorbid cognitive function in schizophrenia

(For abbreviations and acronyms see 'Abbreviations and acronyms table')

Authors	Sample	Age groups	Design	Cognitive measures	Results	Differences
Ambelas (1992)	18 adult SCZ 18 C	10-15 year olds	Follow-back case-control study (premorbid IQ in SCZ and C kids seen at child guidance clinic)	IQ	C higher IQ, speech, language and reading than kids seen at same clinic who in adulthood developed SCZ.	Premorbid difference (C and premorbid SCZ children)
Ang et al 2004	30 FE SCZ (M) 30 C (M)	12 years & 16 years-/	Follow-back case-control study From 20 years old SCZ military service men to premorbid school assessment	Standardised English and Maths PSLE (primary: 12 years) Standardised English and Maths and GCE (secondary: 16 years)	Both groups showed reduction in marks on maths between 12 and 16 years assessments, but significantly bigger drop in those who are now SCZ	Change < (premorbid 12-16 years)
Fuller 2002	70 SCZ	57M: 13F 9, 13 and 16 years (premorbid)-/	Follow-back From approx. age 30 years to premorbid school assessment) (using mental health centre + prospective	Iowa tests of educational development and basic skills (Percentile ranks for 6 domains of function) Vocabulary Reading comprehension Language	School scores at 9 and 13 non-significantly below the state average. Scores increased 9-13. A statistically significant drop in scores (below state average) occurred between	Change < (premorbid 13-premorbid 16 years)

Authors	Sample	Age groups	Design	Cognitive measures	Results	Differences
			longitudinal participants (Iowa recent onset psychoses study)	Maths Sources of information (i.e. maps) Composite (total scores)	13 and 16 years, specifically no inc seen at any point in language scores (applying rules of grammar to writing& organisation of ideas to make text more coherent and understandable) Scores at 16 positively correlated with RAVLT, WAIS-R & VF	
Guerra 2002	189 psychiatric patients	16-50 years	Follow-back To premorbid measures	OC's Family history of mental illness Development delays Social function IQ NART	Early illness onset predicted by genetic loading and developmental delays Psychotic symptoms predicted by poor school function in adolescence and family history, in spite of 'normal' NART scores	
Isohanni 1998	383 psychiatric diagnosis	16-28 years	Follow-back (school assessment premorbid)	Age inappropriate school class level at 14 Class marks at 16	Not being in right class at 14 predicted later hospitalisation. But low marks at 16 predicted only non-psychotic disorders.	
Jones 1994	50 (children with psychiatric care contact)		Follow back case – control study (school assessment premorbid)	IQ	Differences between those who developed SCZ and those who developed affective disorder. SCZ had lower IQs-could this be related to behavioural difficulty?	Premorbid difference (Premobid children SCZ and premorbid children affectives)
Lane and Albee 1964	36 SCZ 36 siblings of SCZ 35 C 35 siblings of C	7-8 years-2nd grade (premorbid)	Follow back case-control study (school assessments pre-morbid-matched scores between SCZ and C grps)	Kulhman-Anderson Cleveland IQ test	Those who became SCZ significantly lower IQ (9 pts) than their siblings, but no difference between controls and their siblings.	Premorbid difference

Authors	Sample	Age groups	Design	Cognitive measures	Results	Differences
Munro 2002	51 SCZ	Premorbid children-/	Follow-back From 21 years later	IQ Clinical, social and service utilisation	Low IQ predicted inc service utilisation & poor social outcome.	
Russell 1997	34 SCZ		Follow-back From 19.4 yrs later	IQ	Mean child & adult IQ 1sd< C. Suggests stable deficit in IQ predating psychosis and lasting lifetime. (Note: were seen at child psychiatry clinic-could be cohort with early developmental decline?)(adult IQs in these SCZ lower than other literature reports for adult SCZ)	
Russell 2000	24 adult SCZ	Premorbid children	Follow-back	Childhood IQ, Adulthood NART Adulthood WAIS-R	No differences between child and adult IQ scores. NART differed from other 2 IQ measures, and may not be good indicator of premorbid intellect, esp. where IQ is not average.	Stable IQ (premorbid childhood-SCZ adulthood)
Conscript and birth cohorts						
Cannon 2000	72 SCZ (or SCZaff) 63 siblings 7941 C	4-7 years (premorbid)-/	Birth cohort study Follow up to ascertain morbidity	Standardised cognitive tests	SCZ and siblings worse on verbal and non-verbal tests compared to non-psychiatric C at 4-7years old.	Difference between groups (premorbid 4-7 years SCZ and 4-7 years siblings)
Caspi 2003	44 FE SCZ 44 C	16-17 years (premorbid)-/	Cohort study (Israeli draft) follow up 2 years later	Arithmetic, Similarities (verbal reasoning) Raven's progressive matrices (abstract reasoning) OTIS-R (verbal IQ)	No change in IQ between premorbid and first episode SCZ. Decline on Raven's and OTIS relative to C. Most cognitive decline may be prior to first psychotic episode	No change (premorbid 17 –FE 19 years)
Crow et al 1995	57 broad category SCZ 40 narrow category SCZ	Premorbid-7, 11, 16 and 23 years	National Child Development Study	(Bristol Social Adjustment Guide Physical and neurological	Greatest academic impairment in pre-SCZ,	

Authors	Sample	Age groups	Design	Cognitive measures	Results	Differences
	35 Affective Psychosis 79 Neurosis Compared to total (12-15,000 at different stages) or random 10% of sample (Done et al)			development Reading Maths General ability including verbal and non-verbal IQ Tests differed for different age groups	then pre-neurotics, then pre-affectives. Pre-SCZ lowest on reading (i.e. word recognition) at all age groups, maths at 7 and 11 but not 16, relative to others. General ability also worse than all at 11 years. Pre SCZ hostile and deviant in behaviour at 7, more so in M than F. No evidence of social withdrawal. This appears by age 11. Pre-SCZ slow to develop continence, poor coordination and vision at 7 and clumsy at 16 years.	
David 1997	50,000 Swedish conscripts, of which 195 later SCZ.	18 years (premorbid)	Cohort study (Swedish conscripts)	Verbal Visuo-spatial, General knowledge Mechanical knowledge	195 conscripts later treated for SCZ. Low IQ (specifically verbal and mechanical knowledge) associated linearly with increased risk for SCZ. Risk for other disorders too, but less linear relationship.	
Gunnell 2002	109643 Swedish conscripts, of which (over 5 years) 60 later SCZ and 92 other psychoses.	18 years (premorbid)-/	Cohort study (Swedish conscripts) follow up 5 years later	Verbal intelligence Performance/non-verbal intelligence. Controlled for low birth weight, birth related exposures and parental education.	Over 5 yrs, 60 developed schizophrenia & 92 other psychoses. Poor test scores associated with later psychosis, esp. SCZ. Other controlled factors did not affect results.	
Jones 1994	30 SCZ	From birth and at 8,	Prospective Birth	Non-verbal	Deficit of 3.1 for	

Authors	Sample	Age groups	Design	Cognitive measures	Results	Differences
	4716 C	11 and 15 years (premorbid)	cohort study (British National Birth Cohort)	Verbal Arithmetic Vocabulary Reading Sociability Aggression Emotional stability Attitudes to others	vocabulary and 9.5 for non-verbal test scores, increasing with age. Linear association between low IQ and increased risk for SCZ. SCZ walked later than C (difference of 1.2 months) Solitary play at 4 yrs was predictor for SCZ	
High-Risk Studies						
Erlenmeyer and Kimling	79 adult offspring schizophrenic patients {12 schizophrenia-related psychoses 28 major affective disorders 13 major axis I disorder 13 no disorder} 57 adult offspring of affectively ill patients {4 schizophrenia related psychoses 26 major affective disorders 12 major axis I disorders 15 no disorder} 133 adult offspring of normal parents {1 schizophrenia related psychosis 40 major affective disorders 37 major axis I disorders 55 no disorder}	Mean age (SADS-interview) 19.7 years Assessed from age of 9.3 years 6 assessments 3 year intervals.	High-risk study (New-York)	CPT Attention span WISC Digit Span FW and BW Visual Aural Digit Span Neuromotor assessment (2 regression equations (1) relates parental status and control variables to NP (2) relates parental status, control variables and NP to adult psychiatric outcome)	Sensitivity of prediction of schizophrenia related psychoses greatest for memory model in offspring of SCZ (83.3%) and lowest for attention deviance – although also lowest false positives for this factor (58.3%). NP could phenotypic indicator. Affectives offspring also showed greater memory and motor than attention impairments, so less specific for SCZ perhaps? Combining 3 models gave better prediction, accuracy and lowest False Positives than either model individually.	
Goldstein 2000	Offspring of 182 SCZ	7 years (premorbid)	High-Risk study/ Birth cohort	IQ OC's	Low IQ at 7 significantly associated with developing	

Authors	Sample	Age groups	Design	Cognitive measures	Results	Differences
			Follow up to ascertain morbidity	Sex Age, Hypoxic-aschemic insult.	SCZ/other psychoses.	
Griffith 1980	17 adult SCZ 190 High-risk (HR)	HR Children (premorbid)	High-risk study (Copenhagen) Follow-up to adulthood	WISC	No difference in IQ scores between HR who did and did not develop SCZ.	No difference between groups (HR and HR now SCZ)
Kremen 1998	693 offspring (later developed SCZ)	Birth-4-7 (premorbid)	High-Risk study (National Collaborative Perinatal Project) Follow-up at 23years	Stanford Binet IQ test (4 years old) WISC (7years old). Looked at IQ change between 4 and 7 years-regressed standardised age 7 scores on age 4 scores and residuals (observed – predicted) tells you amount of change in comparison to expected predicted score.	Those showing declines between 4 and 7 were more likely to develop psychotic symptoms by age 23. IQ between 4 and 7 raw score did not predict alone, but at age 7 low raw IQ did predict psychotic	Change < (premorbid 4-premorbid 7 years)

Table 1E: Meta-analysis: included studies of learning and memory in unaffected relatives of schizophrenics and controls

(For abbreviations and acronyms see 'Abbreviations and acronyms table')

Reference	Relatives (age)	Gender	Controls (age)	Gender	Neuropsychological Test	IQ[1]	
Appels, M et al 2003	74 parents (53.6)	37M: 37F	56 C (53.7)	28M: 28F	CVLT Trials 1-5 CVLT Long delay recall, Verbal Fluency for letters (N & A) and category (animals and professions) WAIS Digit Span FW & BW	Groningen Intelligence Test: NS	1
Byrne, M, et al 1999[2]	104 1st & 2nd degree (21.1)	57M: 47F	33 C (21.2)	17M: 16F	WMS Visual reproductions immediate and delayed WAIS Digit Span FW & BW	NART IQ WAIS-R FSIQ: S Covaried for IQ and retained differences on delayed Visual memory	2
Byrne, M, et al 2003[3]	157 1st & 2nd degree (21.2)	77M: 80F	34 C (21.3)	17M: 17F	RBMT Story recall Verbal Fluency for letters (F, A & S) and category (animals) RAVLT (complete test)	NART IQ & WAIS-R FSIQ: S Not inc. as covariate	3
Chen Y, et al, 2000	21 siblings (30.5)	6M: 15F	26 C (30.5)	11M: 15F	Verbal Fluency for category (animals, transport and food)	WAIS Comprehension, Similarities, & Information: S Not inc. as covariate	4
Docherty, N, et al,	59 parents (62)	31M: 28	24 C (61)	13M: 11F	Matched Task Digit Span		5
Dollfus, S, et al, 2002	23 parents (58.1)	7M: 16F	23 C (55.7)	7M: 16F	Verbal Fluency for letters (P) and category (animals)	RAVEN IQ & WAIS-R IQ: S Covaried for IQ and retained differences in VF	6
Egan, M, et al 2001	193 siblings (36.1)	83M: 110F	47 C (33.3)	16M: 31F	WMS Logical Memory WMS Visual Reproductions CVLT (Trials 1-5 Learning) Verbal Fluency for letters (and category	WAIS-R IQ: NS WRAT: NS	7
Faraone, S, et al 2000[4]	41 simplex (I close affected relative) (18-59)	29M: 12F	100 C (18-59)	58M: 42F	WMS Logical Memory WMS Visual Reproductions	WAIS Block Design & Vocabulary: S	8

[1] NS = non-significant difference between relatives and controls, S = significant difference between relatives and controls

[2] Byrne et al (1999) includes a subset of sample in Byrne et al (2003). WMS visual reproductions and WAIS-R Digit span data was not available in Byrne et al (2003), therefore data was extracted from Byrne et al (1999)

[3] Byrne et al (1999) uses a subset of sample in Byrne et al (2003)

Reference	Relatives (age)	Gender	Controls (age)	Gender	Neuropsychological Test	IQ[1]	
						Corrected for IQ differences and retained significant differences in performance	
Franke, P, et al 1999	49 siblings (26.9)	ND[5]	53 C (28.1)	ND	Recurring Digit Span Task	NA[6]	9
Gochman et al (2004)	24 siblings (19.3)	12M: 12F	38 C (17.8)	21M: 17F	WAIS Digit Span FW & BW	WAIS-R/WISC-R Vocabulary: NS	10
Goldberg, et al 1993[7]	48 (24 Discordant MZ twins) (30.9)	28M: 20F	14 C (7 MZ twins) (30.6)	6M: 8F	WAIS Digit Span FW & BW		11
Goldberg, et al 1995	40 (20 Discordant MZ twins) (30.9)	20M: 20F	14 C (7 MZ twins) (30.6)	6M: 8F	WMS Logical Memory WMS Visual Reproductions Paired Associate Learning Verbal Fluency for letters (F, A & S)	WMS IQ & WRAT Reading: NS	12
Harris, J, et al 1996	28 parents of schizophrenics (Probands average age 35 years)	14M: 14F	18 C (29)	9M: 9F	Story Memory test (Heaton et al, '99), CVLT trials 1-5 WAIS-Digit Span	WAIS Vocabulary + Block design: NS	13
Ismail 2000	21 siblings (37.9)	9M: 12F	75 C (35.9)	59M: 16F	Digit Span Verbal Fluency for letters	NA[8]	14
Keefe, R, et al 1994	54 1st degree (34.8)	22M: 32F	18 C (35.9)	15M: 3F	VF letters (t) & category (animal)	WAIS Vocabulary & Block design: NS	15
Keri, S, et al, 2001	25 1st degree relatives (31.2)	15M: 10F	20 C (33.4)	12M: 8F	Verbal recall & Recognition of List (Short & Long delays) Digit Span Forwards & Backwards Verbal Fluency for letters (F, A & S)	WAIS-R IQ: NS	16
Kremen , W, et	39 1st degree	All F	44 C (35.9)	All F	WMS Logical Memory	WRAT Reading Performance	17

[4] Only simplex relatives from this study are included in the meta-analysis. See Seidman et al (2002)
[5] ND = Not detailed
[6] NA = Not applicable (IQ not measured within this study)
[7] Goldberg et al (1995) uses a subset of sample in Goldberg et al (1993). WAIS Digit span FW and BW were not available Goldberg et al (1995), so extracted data from Goldberg et al (1993)
[8] NA = Not applicable (IQ not measured in this study)

Reference	Relatives (age)	Gender	Controls (age)	Gender	Neuropsychological Test	IQ[1]	
al 1998	relatives (38.4)				WMS Visual Reproductions	(covariate) WAIS Vocabulary & Block Design (covariate) Only visual memory differences lost after adjustment for both IQ and visual copy score.	
Laurent, A, et al, 1999	37 1st degree relatives (46.1)	14M: 23F	37 C (45.4)	14M: 23F	WMS Logical Memory, WMS Visual Reproductions (immediate & % loss) Paired Associate Learning, Digit Span FW & BW	Estimated FSIQ (Brooker & Cyr, 1986) (WAIS Vocabulary & Block Design): NS	18
Lyons, M, et al, 1995	18 1st degree relatives (42.8).	ND[9]	11 C (39.5)	Groups matched for gender	CVLT (complete test)	NA	19
O'Driscoll, G, et al, 2001	20 1st degree relatives (18-50)	9M: 11F	14 C (18-50)	5M: 9F	WMS Logical Memory test	General IQ>80 all subjects. WAIS Block Design & Vocabulary (Trend correlation with delayed verbal memory)	20
Roxborough et al 1993	30 (38.7)	12M: 18F	30 C (28.7)	23M: 7F	Verbal Fluency for letters (F, A & S) and categories (animals, fruit and flowers)	NART (est. FSIQ) WAIS (est. FSIQ) Covaried for NART in VF letters but not Categories	21
Seidman et al 2002[10]	28 simplex (41.9)	10M: 18F	48 C (40.1)	27M: 21F	WMS Logical Memory Immediate & Delayed	(WAIS-R Vocabulary &Block design): S WRAT-R Reading: NS	22
Shedlack, K, et al 1997	14 siblings (33.1)	5M: 9F	17 C (31.9)	9M: 8F	WMS Logical Memory Immediate & Delayed WMS Visual Reproductions Immediate & Delayed WAIS Digit Span FW & BW	WRAT Word Attack (Woodcock, 1987)): NS	23
Toomey et al	54 (39.1)	33M: 21F	72 C (36.0)	40M: 32F	WMS Logical memory	WRAT-R Reading:	24

[9] ND = Not detailed

[10] Only simplex relatives in this study are included in the meta-analysis for WAIS IQ. Uses subset of sample used in Faraone et al (2000). Multiplex sample in Faraone et al (2000) showed worse performance compared to both simplex and control group on Logical memory measure.

Reference	Relatives (age)	Gender	Controls (age)	Gender	Neuropsychological Test	IQ[1]	
1998						NS	
Toulopoulou, T et al, 2003	115 relatives (1st & 2nd degree) (49.4)	44M: 71F	66 C (38.8)	33M: 33F	WMS Logical Memory Immediate & Delayed, Paired Associates WMS Visual Reproductions Immediate & Delayed	WAIS-R IQ	25
Wittorf 2004	26 1st degree relatives (43.8)	11M: 15F	21 C (37.8)	10M: 11F	RAVLT Verbal Fluency for letters WAIS Digit Span FW & [11]BW	NA	26
Zalla et al 2003	22 1st degree relatives (35.8)	11M: 11F	20 C (35.1)	7M: 12F	Verbal Fluency for letters, categories and associations	WAIS-R FSIQ: S	27

[11] RCFT score not included in meta-analysis due to different format from WMS Visual Reproductions

Table 1F: Meta-analysis: excluded studies of learning and memory in unaffected relatives of schizophrenics and controls

(For abbreviations and acronyms see 'Abbreviations and acronyms table')

Reference	Relatives (age)	Controls (age)	Neuropsychological Test		IQ [12]	Results [13]	Reason for exclusion
Asarnow et al 2002	11 1st or 2nd degree relatives (11.7) + Parents[14] 4M: 7F	47 C (12.3) + Parents 26M: 21F	Verbal memory-	CVLT Trial 1			Participants < 16 years old
Cannon et al 1994	16 siblings (31)	31 C (28)	Verbal memory- Spatial Memory- Language- Attention-	CVLT Trials 1-5 + WMS-Logical Memory Passages + Paired Associate Learning WMS Visual Design Reproduction + Facial Recognition COWA letters + Animal & Boston Naming + Comprehension + Sentence Repetition + Reading + Recognition + Vocabulary, Token test WAIS-R Digit Span + Digit Symbol + Stroop Test + Trail Making A + CPT vigilance	NA[15]	Verbal Memory: C > Sibs ** Spatial Memory: C > Sibs ** Language: C > Sibs * Attention: C > Sibs *	Aggregated scores
Cannon et al 2000	18 (36 Discordant MZ twins) (49) 60 (30 Discordant DZ twins) (48)	110 C (49)	Verbal working memory- Spatial working memory- Verbal fluency- Verbal episodic memory	WAIS-R Digit Span WMS Visual Span Verbal fluency animal names CVLT trials 1-5 Learning + Short & Long Delayed List Recall CVLT intrusions score	Estimated IQ (WAIS-R Vocabulary, Similarities, Block design & Digit Symbol): S	Verbal Working Memory: NS Genetic Liability: Spatial Working Memory, divided attention, choice	Aggregated scores

[12] NS = non-significant, S = significant difference
[13] * $p<0.05$, ** $p<0.001$, NS = non-significant
[14] Parents only assessed on WAIS-R Vocabulary
[15] NA = Not applicable (IQ not measured in this study)

Reference	Relatives (age)	Controls (age)	Neuropsychological Test		IQ [12]	Results [13]	Reason for exclusion
				CVLT clustering score		reaction time, recall intrusions, (less significant semantic clustering ability): MZ twins < DZ twins < controls	
			Story memory- Visual episodic memory-	WMS Logical Memory Test WMS Visual Reproductions		Diagnosis effect: Verbal Episodic, Visual Episodic, Spatial Working Memory predictive of schizophrenia	
						Genetic liability may impact prefrontal cortical systems	
Condray et al	12 1st degree relatives (35.9)	18 C (31.9)	Language-	Luria Nebraska Language Comprehension-Relational Concepts Factor Scale	WAIS-R Information & Block Design	No difference between SCZ and brothers on language comprehension, but brothers less able on language measures than C	Memory tests not compatible
Conklin et al 2000	56 1st degree relatives (42.3)	73 C (35.7)	Attention	WAIS Digit Span FW & BW	NA [16]	Backwards span C > rels *	No available statistics. F values reflect comparison across 3 groups (relatives, controls and schizophrenic patients)
Chazan et al 1986	23 1st & 2nd degree relatives (20-63 years)	NA [17]	Memory-	Full WMS Memory Quotient (MQ)	N/A	Significant correlation	No control Group/

[16] NA = Not applicable (IQ not measured in this study)

Reference	Relatives (age)	Controls (age)	Neuropsychological Test		IQ [12]	Results [13]	Reason for exclusion
						between MQ of SCZ and relatives	Only MQ presented
Davalos et al 2004	51 children (10.2)	51 C (10.9)	Verbal working memory- Visual working memory-	Sentence Span Counting Span	Estimated IQ (WAIS Block Design): NS	Sentence Span: C > offspring * Counting Span: C > offspring *	Memory tests not compatible
Driscoll et al 1984	1st degree relatives	C	Memory-	Intentional and incidental memory		C> rels on intentional learning with distraction	Participants < 16 years
Edelstyn et al 2003	2 1st degree relatives (parents)	16 C (31)	Memory-	Word and Face Recognition Memory	N/A		Memory tests not compatible/ relative sample < 10 participants
Erlenmyer and Kimling 2000	269 offspring	NA[18]	Attention-	Digit span FW & BW CPT Attention span task			
Faraone et al 1995	35 1st degree relatives (36.7)	72 C (35.5)	Verbal memory- Visual memory- Learning- Mental control/encoding	WMS Logical WMS Visual Reproductions - Paired Associate Learning - WAIS Digit Span + mental control +arithmetic	NA	WMS Logical Memory Immediate: C > rels ** WMS Logical Memory Delayed: C > rels ** WMS Visual Reproductions Copy: C > rels * WMS Visual Reproductions Immediate: C > rels * WMS Visual Reproductions Delayed: C > rels T	Aggregated scores

[17] NA = Not applicable (No control group)
[18] NA = Not applicable (no control group data included)

Reference	Relatives (age)	Controls (age)	Neuropsychological Test		IQ [12]	Results [13]	Reason for exclusion
Faraone et al 1996	22 1st degree relatives (68)	14 C (68)	Memory-	WMS Logical Memory WMS Visual Reproductions (copy & immediate)	NA	NS	Later studies used
Faraone et al 1999	39 1st degree relatives (42)	45 C (41)	Memory-	WMS Logical Memory WMS Visual Reproductions	NA	WMS Logical Memory Immediate: C > rels * WMS Logical Memory Delayed: C > rels * Stable differences over 4 years	Later studies used
Gilvarry et al 2001	72 1st degree relatives of schizophrenics (47.5) (Obstetric Complications Rels scz:- OC-= 43; OC+ =9		Verbal fluency-	Thurstone's Word Fluency test (C & S)	NART IQ Scz < affectives ** Rels scz < rels manics * Rels scz OC+ > Rels OC- *	Word Fluency: Rels scz OC+ > Rels cz OC- (+ after NART adj.) ** Obstetric comp rels scz better IQ and fluency than those without?	No control group
Johnson et al 2003	19 MZ discordant for schizophrenia twins (48.6) 31 DZ discordant for schizophrenia twins (48.4)	56 C (45.5)	Episodic memory- Working memory- Attention- Executive function-	WMS Logical Memory WMS Visual Reproductions CVLT (Trials 1-5) Digit Span BW, Visual Span FW & BW Digit Span FW, Trail Making A & B, Stroop interference Lexical & semantic verbal Fluency, WCST, Block Design	Estimated IQ (WAIS Vocabulary)	Schizoptypal symptoms related to verbal memory, visual memory, attention & executive function. Genetic risk and symptoms interact for most functions Spatial Working memory only related to genetic risk and not symps	
Krabbendam et al	50 1st degree relatives of	50 C (35)	Episodic memory	RAVLT	Estimated FSIQ	Speed Info	

Reference	Relatives (age)	Controls (age)	Neuropsychological Test		IQ [12]	Results [13]	Reason for exclusion
2001	schizophrenics (36.9)		Semantic fluency- Working memory-	Word Fluency (animals & professions) WAIS-R Digit Span + Trail Making (Modified to Concept Shifting test)	(Groningen Short Form) Rels higher IQ than controls, esp when controlling for independent cognitive deficits	Processing, Working Memory, Episodic Memory: (order of magnitude of deficit seen): C > rels	
Kremen et al 1997	39F & 15M 1st degree relatives of schizophrenics (38.4, 40.8) Looking for GrpXSex Interaction i.e. Male rels differ from female rels more than male controls from female controls	44F & 28M (35.9, 36.7)	Verbal memory- Visual memory- Learning- Mental control/encoding-	WMS Logical Memory WMS Visual Reproductions Paired Associate Learning WAIS Digit Span + mental control + arithmetic	WRAT-Reading (est IQ)	Logical Memories Immediate & Delayed GrpXsex interaction * F worse than M scz	Aggregated scores
Macdonald et al (2003)	24 siblings 24 Scz	36 C	Context processing	CPT AX task (expectancy and context processing)		C > rels * in context processing task, but not expectancy	
Mirsky et al 1988	1st degree relatives (25?)	C?	Attention/memory-	WAIS-R Digit span		C > rels *	Combined DS score?
Rutschmann et al 1980	46 1st degree relatives (NYHRP)	53 C	Verbal memory-	Auditory short term recognition memory test (for words and consonant vowel trigrams)	N/A		Memory tests not compatible
Sponheim et al 2004	22 1st degree relatives	23 C	Verbal memory-	Encoding (Size judgement task) – free recall - priming (lexical decision task about word or non-word presenting old words, new words and non words – speed of response to new and old shows priming effect)and recognition task of original old words	WAIS short from IQ vocabulary and Block Design	Encoding: SCZ < Rels & C Rels and C did not differ. Free recall: SCZ < C & Rels Rels < C Priming SCZ slower than C & Rels All grps benefited from previous	Memory tests not compatible

Reference	Relatives (age)	Controls (age)	Neuropsychological Test		IQ [12]	Results [13]	Reason for exclusion
						word exposure (get faster), so all show priming effects Recognition SCZ < Rels and C Rels and C did not differ. A correlation analysis showed depth of encoding to predict explicit recall in C but not rels, whereas priming was associated with encoding in rels	
Staal et al 2000	15 1st degree relatives (41.5)	32 C (40.3)	Verbal memory- Visual/spatial memory- Attention- Language- Executive function-	CVLT total test Rey CFT + WMS Visual reproductions Immediate Recall Digit span + self ordering task + Stroop test + missing item scan Vocabulary + Verbal and category fluency + Stroop Colour naming Tower of London planning and initiation on motor planning task	N/A	Executive function C > siblings *	Aggregated scores
Tuulio-Henriksson et al 2002	264 1st degree relatives (from cohort of 131/397 ascertained families)	NA [19]	Attention- Verbal memory-	WMS-R Digit span FW & BW CVLT	WAIS-R Vocabulary, similarities, block design and digit symbol	Using Quantitative Trait Loci: Traits for verbal encoding &	No control group

[19] NA = Not applicable (no control group)

Reference	Relatives (age)	Controls (age)	Neuropsychological Test		IQ [12]	Results [13]	Reason for exclusion
					(covariate)	verbal working memory: semantic clustering, recognition memory, intrusions. Poor semantic categorization to facilitate encoding. Slowed encoding?? Block design-rels slower than c. Visual working memory & concept formation too All reflect frontal lobe deficits Apparently long & short term recall, and verbal total recall are non genetically mediated	
Tuulio-Henriksson et al 2003	31singleton family1st degree relatives (46.3) vs. 67 multiplex family 1st degree relatives (48.5)	NA	Attention- Verbal memory-	WMS-R Digit span FW & BW CVLT	WAIS-R Vocabulary, similarities, block design and digit symbol	Simplex vs. multiplex families differ only in visual BW span	No control group

APPENDIX 2: Tables and figures to accompany chapter 2

Table 2A: Edinburgh High Risk Study sample numbers over time

Table 2B: Baseline neuropsychological test means, standard deviations and results of Univariate Analyses in the high-risk participant group

Table 2C: Comparison of verbal memory test performance over time (baseline to latest assessment) in high-risk participants who have (HR+), and have not (HR-) experienced a psychotic symptom over time, those who have subsequently developed schizophrenia (Scz) and controls (C)

Table 2D: Comparison of executive function test performance over time (baseline to latest assessments) in high-risk participants who have (HR+), and have not (HR-) experienced a psychotic symptom over time, those who have subsequently developed schizophrenia (Scz) and controls (C)

Table 2E: Comparison of general intellectual and perceptual motor speed performance over time (baseline to latest assessments) in high-risk participants who have (HR+), and have not (HR-) experienced a psychotic symptom over time, those who have subsequently developed schizophrenia (Scz) and controls

Table 2F: Comparison of neuropsychological performance over time (baseline to latest assessments) in groups classified according to qualitative genetic liability (proximity of affected relative)

Table 2G: Results of regression analysis of quantitative genetic liability and mean difference in performance between first and last neuropsychological assessments

Table 2H: Neuropsychological Assessments used across phases of the EHRS (see abbreviations and acronyms)

Figure 2A: Informed consent form

Table 2A: Edinburgh High Risk Study sample numbers over time

	Edinburgh High Risk Project 1994-2004 ⇓	
	Potential Sample identified (1994) ⇓ ⇓	
High Risk (N)		Control (N)
(229)		(43)
	Phase 1 Round 1 (Preliminary data only) (Johnstone et al 2000)	
	⇓ ⇓	
(162)		(36)
	Baseline Full Neuropsychological data available	
	(Byrne et al 2003) ⇓ ⇓	
(157) ⇓		(34) ⇓
(-4) No PSE		(- 2) Withdrawn
(+ 1) Phase 2 Round 1		(+ 4) Phase 2 Round 1
	Baseline Full Clinical & Neuropsychological data available ⇓ ⇓	
(154)		(36)
⇓	Clinical & Neuropsychological data for analysis of changes over time (At least 2 assessments required)	⇓
(- 35) Only 1 neuropsychological assessment		(-6) Only 1 neuropsychological assessment
(- 1) Developed schizophrenia at 2nd assessment ⇓	⇓	
(118)		(30)

Table 2B: Baseline neuropsychological test means, standard deviations and results of Univariate Analyses in the high-risk participant group

Task (Baseline assessment)	*HR- (PSE1) (N=107)*	*HR+ (PSE1) (N=28)*	*Now SCZ (N=18)*	*Main effect of Group*		*Planned HR- & HR+ >SCZ*		*Contrasts HR->HR+*	
	Mean (SD)	Mean (SD)	Mean (SD)	F	p	t	p	t	P
General Intelligence	(N=100)	(N=25)	(N=17)						
NART est. FSIQ	98.9 (9.0)	97.8 (10.4)	97.1 (13.1)	0.3	0.7				
WAIS-R FSIQ	99.0 (13.0)	93.3 (11.2)	96.8 (13.7)	2.0	0.1				
WAIS-R VIQ	97.8 (11.7)	92.9 (9.8)	94.2 (11.4)	2.3	0.1				
WAIS-R PIQ	100.4 (14.0)	95.8 (13.2)	101.8 (17.4)	1.2	0.3				
Spot the Word Test	45.7 (4.9)	45.1 (4.2)	43.4 (5.4)	1.6	0.2				
WAIS-R Digit Symbol	10.2 (2.8)	9.5 (2.2)	9.3 (2.6)	1.1	0.3				
WAIS-R Block Design	11.0 (2.8)	10.4 (2.5)	11.1 (3.4)	0.5	0.6				
Speed of Comprehension	63.5 (18.2)	58.3 (17.2)	61.2 (19.7)	0.8	0.4				
Memory	(N=97)	(N=25)	(N=17)						
RBMT Immediate Story Recall	9.4 (3.2)	7.6 (3.3)	8.3 (3.2)	3.5	0.03			1.7	0.01
RBMT Delayed Story Recall	8.2 (3.2)	6.8 (3.5)	7.0 (2.8)	2.5	*0.08*			1.4	0.05
RAVLT Total trials 1-5	51.3 (8.9)	52.5 (7.7)	47.0 (7.8)	2.3	0.1	4.9	0.03		
RAVLT Long Delay Recall	10.5 (2.8)	11.3 (2.7)	9.8 (2.3)	1.3	0.3				
WMS-R Total Immediate Visual Recall	35.2 (3.8)	36.0 (3.9)	34.1 (4.8)	1.2	0.3				
WMS-R Total Delayed Visual Recall	32.6 (5.8)	33.6 (4.4)	32.1 (5.4)	0.4	0.6				
Verbal Fluency for Categories	15.7 (4.7)	14.1 (4.3)	16.2 (4.4)	1.5	0.2				
Executive function	(N=98)	(N=28)	(N=16)						
HSCT Time Sect. 1 *	5.3 (1.1), 6 (5.0, 6.0)	4.9 (1.4), 6 (5.0, 6.0)	4.9 (1.3), 6 (5.0, 6.0)	1.7, 0.1	0.2, 0.9				
HSCT Time Sect. 2	5.6 (0.9), 6 (6.0, 6.0)	5.5 (1.1), 6 (5.0, 6.0)	5.5 (1.0), 6 (5.5, 6.0)	0.3, 1.1	0.7, 0.6				
HSCT Type A errors	3.6 (5.2), 3 (0.0, 6.0)	3.0 (3.9), 0 (0.0, 6.0)	4.8 (4.8), 3 (1.5, 10.0)	0.8, 2.4	0.5, 0.3				
HSCT Type B errors	4.7 (6.5), 2 (0.75, 4.0)	5.4 (8.2), 2 (1.0, 4.0)	5.2 (7.2), 2 (0.0, 9.0)	0.1, 0.1	0.9, 0.1				
Stroop Time suppression condition	23.4 (5.6)	23.7 (4.8)	24.1 (6.3)	0.1	0.9				
Stroop Time suppression-control	13.5 (5.3)	13.2 (5.4)	14.2 (5.4)	0.1	0.8				

* All Hayling Sentence Completion (HSCT) data not normally distributed. Medians and 25th and 75th percentiles presented along with means and standard deviations. Chi-squared value (Kruskal-Wallis test) and significance, presented after F value (ANOVA) and significance.

Table 2C: Comparison of verbal memory test performance over time (baseline to latest assessment) in high-risk participants who have (HR+), and have not (HR-) experienced a psychotic symptom over time, those who have subsequently developed schizophrenia (Scz) and controls (C)

Task[20]	*Controls*		*HR-*		*HR+*		*Scz*		*Group effect at first and latest assessment*[21]	*Contrasts for first and latest assessment*	*Overall Group Effect*	*Effect Size*[22]	*Group Contrasts*[23]	*Group effect (+ NART-IQ)*[24]	*GrpXTime Interaction*
	Mean	SE[25]	Mean	SE	Mean	SE	Mean	SE			F			F	F
RBMT Immediate Story Recall															
Baseline	11.7	(0.6)	9.4	(0.5)	9.0	(0.5)	8.5	(0.9)	5.7 **	(1) **	5.1 **	0.12	(1) **	3.4*	0.9
Latest	10	(0.6)	9.1	(0.5)	7.9	(0.4)	7.6	(0.9)	3.1 *	(1) * (3)^{T}					
RBMT Delayed Story Recall															
Baseline	10.7	(0.6)	8.1	(0.5)	8.1	(0.4)	7.3	(0.9)	5.6 **	(1) **	5.0 **	0.12	(1) **	3.3*	0.7
Latest	9.0	(0.6)	7.4	(0.5)	7.3	(0.4)	6.6	(0.9)	2.5^{T}	(1) *					
RAVLT Total trials 1-5															
Baseline	55.8	(1.9)	52.4	(1.5)	54.5	(1.6)	46.8	(2.9)	2.8 *	(1) * (3) *	2.4	0.08	(1) *(3) *	2.0	0.8
Latest	52.8	(1.7)	50.5	(1.3)	50.4	(1.4)	46.4	(2.6)	1.5						
RAVLT Long Delay Recall															
Baseline	12.3	(0.5)	10.7	(0.4)	11.2	(0.4)	9.3	(0.8)	3.2 *	(1) ** (3)^{T}	3.3 *	0.10	(1) *(3) *	2.6*	0.3
Latest	13.4	(0.5)	12.5	(0.3)	12.9	(0.4)	11.4	(0.7)	2.1						

[20] Means adjusted for time between assessments and number of assessments: * $p<0.05$, **$p<0.01$ significant after Bonferroni correction, ^{T}Trend for significance
[21] Results of Univariate Analysis of Variance for first and for latest assessments
[22] Partial Eta Squared (proportion of the effect + error variance attributable to the effect)
[23] Planned Helmert contrasts: (1) C > HR; (2) HR- > HR+ & SCZ; (3) HR+ > SCZ
[24] Effect after co-varying for NART IQ
[25] Standard error

Table 2D: Comparison of executive function test performance over time (baseline to latest assessments) in high-risk participants who have (HR+), and have not (HR-) experienced a psychotic symptom over time, those who have subsequently developed schizophrenia (Scz) and controls (C)

Task[26]	*Controls*		*HR-*		*HR+*		*Scz*		*Group effect at first and latest assessment*[27]	*Contrasts for first and latest assessment.*[4]	*Overall Group Effect*	*Effect size*[28]	*Group Contrasts*[29]	*Group effect (+ NART-IQ)*[30]	*GrpXTime Interaction*
	Mean	SE[31]	Mean	SE	Mean	SE	Mean	SE	F		F			F	F
Verbal Fluency for Letters															
Baseline	41.4	(2.2)	41.3	(1.7)	37.0	(1.6)	38.2	(3.5)	1.4		2.0	0.04		1.8	0.9
Latest	45.3	(2.6)	45.6	(2.0)	40.2	(1.8)	37.5	(4.1)	2.3						
Verbal category fluency															
Baseline	18.2	(1.0)	16.1	(0.8)	14.9	(0.7)	18.0	(1.5)	3.1 *	(1) *	3.0 *	0.06		1.9	1.3
Latest	18.9	(0.9)	18.4	(1.9)	16.4	(1.7)	17.5	(3.5)	2.2						
Stroop Test Suppression															
Baseline	21.5	(1.0)	23.0	(0.8)	23.6	(0.7)	22.6	(1.6)	1.5		1.6	0.04		0.5	0.7
Latest	19.9	(0.9)	20.7	(0.7)	22.1	(0.7)	19.6	(1.5)	1.6						
Stroop Suppression-control															
Baseline	11.4	(0.9)	13.1	(0.8)	13.7	(0.7)	12.6	(1.5)	1.1		1.9	0.04		0.8	0.4
Latest	9.2	(0.8)	9.8	(0.7)	11.2	(0.6)	9.3	(1.4)	1.4						
HSCT Time Sect. 1 [32]															
Baseline	5.6	(0.8) (1.4, 2.4)	5.3	(1.1) (1.5, 2.7)	5.3	(1.2) (1.4, 2.7)	5.5	(0.9) (1.1, 2.5)	1.0		1.5	0.03		0.7	0.4
Latest	6.2	(1.1) (0.5, 1.9)	5.9	(0.6) (0.7, 2.1)	6.0	(0.7) (1.0, 2.4)	5.5	(0.9) (0.9, 2.3)	2.4						
HSCT Time Sect. 2															

[26] Means adjusted for time between assessments and number of assessments; * $p<0.05$ **$p<0.006$ significant after Bonferroni correction
[27] Results of Univariate Analysis of Variance for first and for latest assessments
[28] Partial Eta Squared (proportion of the effect + error variance attributable to effect)
[29] Planned Helmert contrasts: (1) C > HR; (2) HR- > HR+ & SCZ; (3) HR+ > SCZ
[30] Effect after co-varying for NART IQ
[31] Standard error
[32] HSCT measures log transformed to achieve a normal distribution. Only two measures were successfully transformed and therefore included. Means, standard errors, and 25th and 75th percentiles presented for these measures.

Baseline	6.0	(0.2) (2.0, 3.4)	5.7	(0.1) (2.9, 3.7)	5.5	(0.1) (2.3, 3.9)	5.5	(0.3) (2.6, 3.9)	1.3		2.5 *	0.06	(1) *	2.1	0.5
Latest	6.2	(0.1) (1.6, 3.3)	6.1	(0.1) (1.8, 3.5)	5.8	(0.1) (1.6, 3.6)	5.7	(0.2) (2.2, 3.7)	2.6[1]						

Table 2E: Comparison of general intellectual and perceptual motor speed performance over time (baseline to latest assessments) in high-risk participants who have (HR+), and have not (HR-) experienced a psychotic symptom over time, those who have subsequently developed schizophrenia (Scz) and controls

Task[33]			*Controls*		*HR-*		*HR+*		*Scz*		*Group effect at first and latest assessment*[34]	*Group contrasts for first and latest assessment.*[4]	*Overall Group Effect*	*Effect Size*[35]	*Group Contrasts*[36]	*Group effect (+ NART-IQ)*[37]	*GrpXTime Interactions*
			Mean	SE[38]	Mean	SE	Mean	SE	Mean	SE	F		F			F	F
Spot the Word																	
Baseline			47.9	(0.8)	45.8	(0.7)	46.0	(0.6)	45.4	(1.5)	3.2 *	(1) **	1.7	0.04		0.2	0.3
Latest			49.6	(0.9)	48.1	(0.7)	47.5	(0.7)	46.8	(1.7)	1.3	(1)^{T}					
Speed of Comprehension																	
Baseline			69.0	(3.7)	62.2	(2.9)	62.7	(2.6)	66.0	(5.8)	1.0		1.1	0.02		1.3	0.4
Latest			75.1	(3.4)	68.3	(2.7)	67.8	(2.4)	67.0	(5.3)	1.2						
WAIS-R Block Design																	
Baseline			12.7	(0.5)	11.4	(0.4)	10.7	(0.4)	11.9	(0.9)	4.1 **	(1) **	4.2 **	0.08	(1) **	2.3	0.6
Latest			14.2	(0.6)	12.6	(0.5)	11.9	(0.4)	13.9	(0.9)	4.3 **	(1) * (3) *					
WAIS-R Digit Symbol																	
Baseline			11.5	(0.5)	10.7	(0.4)	9.7	(0.4)	10.1	(0.8)	3.5 **	(1) **(2)^{T}	3.3 **	0.07	(1) **	1.7	1.2
Latest			12.6	(0.5)	11.1	(0.4)	10.6	(0.4)	11.1	(0.9)	2.9 *	(1) **					

[33] Means adjusted for time between assessments and number of assessments; * $p<0.05$ **$p<0.01$ significant after Bonferroni correction, ^{T} Trend for significance
[34] Results of Univariate Analysis of Variance for first and for latest assessments
[35] Partial Eta Squared (proportion of the effect + error variance attributable to effect)
[36] Planned Helmert contrasts: (1) C > HR; (2) HR- > HR+ & SCZ; (3) HR+ > SCZ
[37] Effect after co-varying for NART IQ
[38] Standard error

Table 2F: Comparison of neuropsychological performance over time (baseline to latest assessments) in groups classified according to qualitative genetic liability

Task[39]	*2nd degree*		*1st & 2nd degree*		*X2 1st degree*		*Group effect*	*Effect size*[40]	*Group Contrasts*[41]	*Group effect (+ NART-IQ)*[42]	*Group X Time interaction*
	Mean	SE[43]	Mean	SE	Mean	SE	F			F	
RBMT Immediate Story Recall											
Baseline	10.0	0.6	8.8	0.4	8.4	0.8	1.5	0.03	NS	1.0	0.3
Latest	8.9	0.6	8.1	0.4	8.1	0.8					
RBMT Delayed Story Recall											
Baseline	9.2	0.6	7.7	0.4	7.0	0.8	3.1*	0.06	(1)*	2.6	0.5
Latest	8.1	0.6	6.9	0.4	6.9	0.8					
RAVLT Long Delay Recall											
Baseline	11.3	0.6	10.6	0.4	10.0	1.0	0.6	0.02	NS	1.2	0.6
Latest	12.0	0.5	12.2	0.3	11.2	0.8					
Verbal category fluency											
Baseline	16.6	1.3	15.7	0.8	13.6	2.1	0.5	0.01	NS	0.6	0.8
Latest	18.1	1.2	16.8	0.8	17.1	2.0					
HSCT Time Sect. 2											
Baseline	5.8	0.1	5.5	0.1	5.5	0.2	1.3	0.02		1.1	1.6
Latest	5.9	0.1	5.9	0.1	5.8	0.2					
WAIS-R Block Design											
Baseline	12.0	0.5	10.4	0.3	11.6	0.7	4.7*	0.08	(1)*	3.3*	0.5
Latest	13.6	0.5	11.6	0.4	12.7	0.8					
WAIS-R Digit Symbol											
Baseline	10.4	0.4	10.0	0.3	10.0	0.7	1.0	0.02	NS	0.5	1.5
Latest	11.6	0.5	10.4	0.3	11.2	0.7					

[39] Means adjusted for time between assessments and number of assessments; *p<0.05, **p<0.007 significant after bonferroni correction
[40] Partial Eta Squared (proportion of the effect + error variance attributable to effect)
[41] Planned Helmert contrasts: (1) C > HR; (2) HR- > HR+ & SCZ; (3) HR+ > SCZ
[42] Effect after co-varying for NART IQ
[43] Standard error

Table 2G: Results of regression analysis of quantitative genetic liability and mean difference in performance between first and last neuropsychological assessments

Task	*Significance of overall model*		*Regression coefficient for genetic liability*		*Regression coefficient for psychopathology*		R^2	*Genetic liability Correlation with mean difference score*	
	F	p	t	p	t	p		r	p
RBMT immediate recall	0.71	0.59	-0.84	0.400	1.10	0.29	0.026	-0.08	0.21
RBMT delayed recall	0.99	0.41	-1.69	0.093	0.11	0.91	0.036	-0.15	0.055
RAVLT 1-5	0.29	0.88	-0.11	0.91	-0.32	0.97	0.017	0.013	0.45
RAVLT long delay	2.07	0.094	-0.92	0.36	-0.16	0.87	0.11	-0.10	0.19
VF animals	1.30	0.27	-1.63	0.11	1.33	0.18	0.047	-0.16	0.043
HSCT time section 2	2.05	0.093	-0.89	0.37	0.35	0.73	0.039	-0.13	0.096
Block design	0.71	0.59	0.44	0.66	-0.56	0.58	0.026	0.083	0.19
Digit symbol	0.32	0.87	0.34	0.73	-1.00	0.32	0.012	0.043	0.33
Spot the word	1.4	0.24	-0.43	0.67	0.38	0.71	0.054	0.017	0.43

Table 2 H: Neuropsychological Assessments used across phases of the EHRS (see abbreviations and acronyms)

Domains of function	*Baseline Phase 1*	*Phase 1 Round 2*	*Phase 1 Round 3*	*Phase 2 Round 1*	*Phase 2 Round 2*	*Phase 2 Round 3*
Current IQ	Full WAIS-R					
	SCOLP	SCOLP	SCOLP	SCOLP	SCOLP	SCOLP
Premorbid IQ	NART					
	SCHONELL					
Executive Function	HSCT	HSCT	HSCT	HSCT	HSCT	HSCT
	STROOP	STROOP	STROOP	STROOP	STROOP	STROOP
	VF (FAS) & CAT	VF (FAS) & CAT	VF (FAS) & CAT	VF (FAS) & CAT	VF (FAS) & CAT	VF (FAS) & CAT
		Trails A & B	Trails A & B	Trails A & B	Trails A & B	Trails A & B
Perceptual Motor Speed	WAIS-R Digit Symbol	WAIS-R Digit Symbol	WAIS-R Digit Symbol	WAIS-R Digit Symbol	WAIS-R Digit Symbol	WAIS-R Digit Symbol
Mental Control/Encoding	WAIS-R Digit Span (FW & BW)	WAIS-R Digit Span (FW & BW)	WAIS-R Digit Span (FW & BW)	WAIS-R Digit Span (FW & BW)	WAIS-R Digit Span (FW & BW)	WAIS-R Digit Span (FW & BW)
	WAIS-R Arithmetic					
Sustained Attention	CPT			CPT	CPT	
Language	Token Test					
	WAIS-R Vocabulary					
Learning & Memory	RBMT	RBMT	RBMT	RBMT	RBMT	RBMT
	RAVLT	RAVLT	RAVLT	CVLT	CVLT	
	WMS-R Visual Reps	WMS-R Visual Reps	WMS-R Visual Reps	RCFT	RCFT	RCFT
				CANTAB	CANTAB	CANTAB
Handedness	Hand Preference					

Table 2I: Levene's test of homogeneity of variance of groups(C, HR-, HR+ & Scz) for all executive and intellectual function test measures

Test measures	Levene Statistic	df1	df2	Sig.
STROOP time in seconds; colour words in black and white (Condition 1) Phase 1 Rd1 (MV = 1)	.683	3	136	.564
STROOP blocks of colour; time in seconds (Condition 2) Phase 1 Rd1 (MV = 1)	.487	3	136	.692
STROOP colour words in incongruent ink; time in seconds (Condition 3) Phase 1 Rd1 (MV = 1)	1.763	3	136	.157
Stroop time for condition 1 last visit	.519	3	135	.670
Stroop time for condition 2 last visit	.332	3	135	.802
STroop time for condition 3 last visit	.239	3	135	.869
WAIS-R block design subtest (scaled scores) First visit	.888	3	144	.449
WAIS-R block design (Calc; standardised score; MV = 99) Last visit	2.653	3	139	*.051*
WAIS-R digit symbol subtest (scaled scores) First visit	.243	3	144	.866

WAIS-R digit symbol substitution (Calc; standardised score; MV = 99) Last visit	.861	3	142	.463
SCOLP spot the word raw score First visit	2.544	3	137	.059
SCOLP speed of comprehension raw score - total no attempted First visit	.788	3	137	.502
SCOLP spot the word score (MV = 101) Last visit	2.173	3	138	.094
SCOLP speed of comprehension total no attempted (MV = 101) Last visit	.297	3	143	.827
HSCT TIME A1-LN TRANSFORM	.686	3	140	.562
HSCT TIME A2-LN TRANSFORM	.102	3	119	.959
HSCT TIME B1-LN TRANSFORM	1.235	3	140	.299
HSCT TIME B2-LN TRANSFORM	1.030	3	139	.381
NART estimated full scale IQ (usually Phase 1; MV = 1)	1.854	3	140	.140
Full scale I.Q. (scaled scores) (MV = 1)	.158	3	143	.924

Table 2J: Levene's test of homogeneity of variance of groups (C, HR-, HR+ & Scz) for all memory test measures

Test measure	Levene Statistic	df1	df2	Sig.
First ravlt 1-5	.216	3	137	.885
First ravlt interference	.288	3	137	.834
First ravlt short delay	1.997	3	137	.117
First ravlt long delay	.444	3	137	.722
Last ravlt 1-5	1.244	3	90	.299
Last ravlt interf	.912	3	91	.439
Last ravlt short delay	.225	3	91	.878
Last ravlt long delay	1.932	3	92	.130
RBMT immediate story recall first assessment	.314	3	135	.815
RBMT immediate story recall last asessment	.672	3	135	.571
RBMT delayed story recall first assessment	.649	3	135	.585
RBMT delayed story recall last assessment	1.023	3	135	.385
VF first assessment	1.231	3	142	.301
VF last assessment	.317	3	141	.813
VF animals first assessment	.665	3	140	.575
VF animals last assessment	1.366	3	141	.256

Table 2K: Tests of normality at each level of the independent variable (C, HR-, HR+ & Scz) for each executive and intellectual test measure

Test measure	Psychotic group by PSE overall	Kolmogorov-Smirnov(a)		
		Statistic	df	Sig.*
STROOP time in seconds; colour words in black and white (Condition 1) Phase 1 Rd1 (MV = 1)	Cont	.105	21	.200
	HR-	.127	33	.191
	HR+	.157	38	.019
	Scz	.211	10	.200
STROOP blocks of colour; time in seconds (Condition 2) Phase 1 Rd1 (MV = 1)	Cont	.135	21	.200
	HR-	.089	33	.200
	HR+	.111	38	.200
	Scz	.247	10	.084
STROOP colour words in incongruent ink; time in seconds (Condition 3) Phase 1 Rd1 (MV = 1)	Cont	.157	21	.192
	HR-	.171	33	.015
	HR+	.097	38	.200
	Scz	.252	10	.071
Stroop time for condition 1 last visit	Cont	.107	21	.200
	HR-	.085	33	.200
	HR+	.105	38	.200
	Scz	.220	10	.185
Stroop time for condition 2 last visit	Cont	.107	21	.200
	HR-	.105	33	.200
	HR+	.076	38	.200
	Scz	.241	10	.104
STroop time for condition 3 last visit	Cont	.130	21	.200

	HR-	.107	33	.200
	HR+	.090	38	.200
	Scz	.180	10	.200
SCOLP spot the word raw score First visit	Cont	.077	21	.200
	HR-	.112	33	.200
	HR+	.094	38	.200
	Scz	.232	10	.137
SCOLP speed of comprehension raw score - total no attempted First visit	Cont	.083	21	.200
	HR-	.095	33	.200
	HR+	.064	38	.200
	Scz	.218	10	.196
SCOLP spot the word score (MV = 101) Last visit	Cont	.112	21	.200
	HR-	.107	33	.200
	HR+	.165	38	.010
	Scz	.148	10	.200
SCOLP speed of comprehension total no attempted (MV = 101) Last visit	Cont	.143	21	.200
	HR-	.072	33	.200
	HR+	.147	38	.037
	Scz	.176	10	.200
WAIS-R block design subtest (scaled scores) First visit	Cont	.104	21	.200
	HR-	.153	33	.049
	HR+	.138	38	.064
	Scz	.187	10	.200
WAIS-R block design (Calc; standardised score; MV = 99) Last visit	Cont	.138	21	.200
	HR-	.166	33	.022
	HR+	.106	38	.200
	Scz	.313	10	.006
WAIS-R digit symbol subtest (scaled scores) First visit	Cont	.200	21	.028
	HR-	.124	33	.200
	HR+	.119	38	.197

	Scz	.270	10	.037
WAIS-R digit symbol substitution (Calc; standardised score; MV = 99) Last visit	Cont	.176	21	.090
	HR-	.126	33	.200
	HR+	.187	38	.002
	Scz	.185	10	.200
HCST - Time (seconds) section A First visit (New)	Cont	.236	30	**.000**
	HR-	.221	44	**.000**
	HR+	.233	52	**.000**
	Scz	.170	13	.200
HCST - Time (seconds) section B First visit (New)	Cont	.169	30	.029
	HR-	.176	44	.002
	HR+	.153	52	.004
	Scz	.127	13	.200
HSCT time for section A Last visit (MV = 200)	Cont	.245	30	**.000**
	HR-	.179	44	**.001**
	HR+	.185	52	**.000**
	Scz	.215	13	.104
HSCT time for section B Last visit (MV = 200)	Cont	.210	30	.002
	HR-	.129	44	.062
	HR+	.214	52	**.000**
	Scz	.207	13	.132
HSCT TIME A1-LN TRANSFORM	Cont	.166	21	.134
	HR-	.087	33	.200
	HR+	.090	38	.200
	Scz	.198	10	.200
HSCT TIME A2-LN TRANSFORM	Cont	.141	21	.200
	HR-	.147	33	.066
	HR+	.128	38	.116
	Scz	.132	10	.200
HSCT TIME B1-LN TRANSFORM	Cont	.160	21	.167

	HR-	.154	33	.045
	HR+	.103	38	.200
	Scz	.216	10	.200
HSCT TIME B2-LN TRANSFORM	Cont	.133	21	.200
	HR-	.135	33	.131
	HR+	.082	38	.200
	Scz	.176	10	.200
NART predicted full scale IQ	Cont	.175	21	.093
	HR-	.113	33	.200
	HR+	.136	38	.074
	Scz	.272	10	.035
WAIS actual full scale IQ	Cont	.145	21	.200
	HR-	.100	33	.200
	HR+	.202	38	.000
	Scz	.155	10	.200

* Critical value of p is <0.001

Table 2L: Tests of normality at each level of the independent variable(C, HR-, HR+ & Scz) for each memory test measure

Test measure	Psychotic Symp Grp	Kolmogorov-Smirnov		
		Statistic	df	Sig.*
VF first assessment	Control	.093	20	.200
	HR-	.111	31	.200
	HR+	.099	29	.200
	SCZ	.185	9	.200
VF last assessment	Control	.120	20	.200
	HR-	.138	31	.139
	HR+	.092	29	.200
	SCZ	.153	9	.200
VF animals first assessment	Control	.161	20	.185

	HR-	.110	31	.200
	HR+	.102	29	.200
	SCZ	.131	9	.200
VF animals last assessment	Control	.116	20	.200
	HR-	.113	31	.200
	HR+	.127	29	.200
	SCZ	.181	9	.200
First ravlt 1-5	Control	.172	20	.122
	HR-	.171	31	.022
	HR+	.099	29	.200
	SCZ	.205	9	.200
First ravlt interference	Control	.224	20	.010
	HR-	.249	31	**.000**
	HR+	.195	29	.006
	SCZ	.260	9	.081
First ravlt short delay	Control	.474	20	**.000**
	HR-	.130	31	.194
	HR+	.130	29	.200
	SCZ	.201	9	.200
First ravlt long delay	Control	.161	20	.187
	HR-	.175	31	.017
	HR+	.165	29	.042
	SCZ	.136	9	.200
last ravlt 1-5	Control	.117	20	.200
	HR-	.125	31	.200
	HR+	.191	29	.008
	SCZ	.194	9	.200
last ravlt interf	Control	.159	20	.200
	HR-	.153	31	.063

	HR+	.208	29	.003
	SCZ	.189	9	.200
last ravlt short delay	Control	.181	20	.086
	HR-	.117	31	.200
	HR+	.159	29	.059
	SCZ	.199	9	.200
last ravlt long delay	Control	.210	20	.020
	HR-	.185	31	.008
	HR+	.155	29	.073
	SCZ	.223	9	.200
RBMT immediate story recall first assessment	Control	.119	20	.200
	HR-	.073	31	.200
	HR+	.114	29	.200
	SCZ	.170	9	.200
RBMT immediate story recall last asessment	Control	.137	20	.200
	HR-	.096	31	.200
	HR+	.154	29	.078
	SCZ	.180	9	.200
RBMT delayed story recall first assessment	Control	.125	20	.200
	HR-	.094	31	.200
	HR+	.120	29	.200
	SCZ	.099	9	.200
RBMT delayed story recall last assessment	Control	.226	20	.008
	HR-	.159	31	.045
	HR+	.118	29	.200
	SCZ	.163	9	.200

* Critical value of p is <0.001

Table 2M: Levene's test of homogeneity of variance of groups (no history, 2nd degree, x1 1st degree, x2 1st degree) for all executive and intellectual function test measures

	Levene Statistic	df1	df2	Sig.*
HSCT TIME A1-LN TRANSFORM	1.925	3	140	.128
HSCT TIME A2-LN TRANSFORM	1.623	3	119	.188
HSCT TIME B1-LN TRANSFORM	.567	3	140	.637
HSCT TIME B2-LN TRANSFORM	1.122	3	139	.342
SCOLP spot the word raw score First visit	2.157	3	137	.096
SCOLP spot the word score (MV = 101) Last visit	3.148	3	138	.027
SCOLP speed of comprehension raw score - total no attempted First visit	.566	3	137	.638
SCOLP speed of comprehension total no attempted (MV = 101) Last visit	.507	3	143	.678
STROOP time in seconds; colour words in black and white (Condition 1) Phase 1 Rd1 (MV = 1)	.600	3	136	.616

STROOP blocks of colour; time in seconds (Condition 2) Phase 1 Rd1 (MV = 1)	.688	3	136	.561
STROOP colour words in incongruent ink; time in seconds (Condition 3) Phase 1 Rd1 (MV = 1)	1.089	3	136	.356
STROOP time condition 3 - time condition 1 Phase 1 Rd1 (MV=200)	1.511	3	136	.214
Stroop time for condition 1 last visit	.326	3	135	.807
Stroop time for condition 2 last visit	.652	3	135	.583
Stroop time for condition 3 last visit	.270	3	135	.847
Stroop difference between times for conditions 1 and 3 last visit	.183	3	135	.908
WAIS-R block design subtest (scaled scores) First visit	1.019	3	144	.386
WAIS-R block design (Calc; standardised score; MV = 99) Last visit	.452	3	139	.716
WAIS-R digit symbol subtest (scaled scores) First visit	.824	3	144	.483

WAIS-R digit symbol substitution (Calc; standardised score; MV = 99) Last visit	.284	3	142	.837

* Critical value of p is <0.001

Table 2N: Levene's test of homogeneity of variance of groups (no history, 2nd degree, x1 1st degree, x2 1st degree) for memory test measures

	Levene Statistic	df1	df2	Sig.*
VF first assessment	3.435	3	142	.019
VF last assessment	2.785	3	141	.043
VF animals first assessment	1.356	3	140	.259
VF animals last assessment	.719	3	141	.542
First ravlt 1-5	.304	3	137	.823
First ravlt interference	.654	3	137	.582
First ravlt short delay	1.992	3	137	.118
First ravlt long delay	.698	3	137	.555
last ravlt 1-5	1.023	3	90	.386
last ravlt interf	.605	3	91	.613
last ravlt short delay	.298	3	91	.827
last ravlt long delay	.045	3	92	.987
RBMT immediate story recall first assessment	.351	3	135	.788
RBMT immediate story recall last asessment	1.479	3	135	.223
RBMT delayed story recall first assessment	.516	3	135	.672

RBMT delayed story recall last assessment	1.117	3	135	.345

* Critical value of p is <0.001

Table 2O: Tests of normality at each level of the independent variable (no history, 2nd degree, x1 1st degree, x2 1st degree) for each executive and intellectual function measure

	New family history	Kolmogorov-Smirnov		
		Statistic	df	Sig.*
HSCT time for section A Last visit (MV = 200)	no family history	.240	21	.003
	2nd degree relative/s	.215	25	.004
	x 1 1st degree relative	.157	40	.015
	x 2 1st degree relatives	.229	16	.024
HSCT time for section B Last visit (MV = 200)	no family history	.185	21	.058
	2nd degree relative/s	.232	25	.001
	x 1 1st degree relative	.160	40	.011
	x 2 1st degree relatives	.167	16	.200
HSCT number of type A errors Last visit (MV = 200)	no family history	.539	21	.000
	2nd degree relative/s	.364	25	.000
	x 1 1st degree relative	.315	40	.000
	x 2 1st degree relatives	.429	16	.000
HSCT number of type B errors Last visit (MV = 200)	no family history	.395	21	.000
	2nd degree relative/s	.289	25	.000
	x 1 1st degree relative	.338	40	.000
	x 2 1st degree relatives	.281	16	.001
HCST - Time (seconds) section A First visit (New)	no family history	.233	21	.004

	2nd degree relative/s	.255	25	.000
	x 1 1st degree relative	.291	40	.000
	x 2 1st degree relatives	.143	16	.200
HCST - Time (seconds) section B First visit (New)	no family history	.212	21	.015
	2nd degree relative/s	.188	25	.022
	x 1 1st degree relative	.136	40	.062
	x 2 1st degree relatives	.196	16	.103
HSCT - Number of category A errors First visit (new)	no family history	.357	21	.000
	2nd degree relative/s	.478	25	.000
	x 1 1st degree relative	.229	40	.000
	x 2 1st degree relatives	.280	16	.002
HSCT - Number of category B errors First visit (new)	no family history	.272	21	.000
	2nd degree relative/s	.202	25	.010
	x 1 1st degree relative	.216	40	.000
	x 2 1st degree relatives	.160	16	.200
HSCT TIME A1-LN TRANSFORM	no family history	.166	21	.134
	2nd degree relative/s	.104	25	.200
	x 1 1st degree relative	.104	40	.200
	x 2 1st degree relatives	.088	16	.200
HSCT TIME A2-LN TRANSFORM	no family history	.141	21	.200
	2nd degree relative/s	.108	25	.200
	x 1 1st degree relative	.127	40	.106
	x 2 1st degree relatives	.161	16	.200
HSCT TIME B1-LN TRANSFORM	no family history	.160	21	.167
	2nd degree relative/s	.133	25	.200
	x 1 1st degree relative	.109	40	.200
	x 2 1st degree relatives	.133	16	.200
HSCT TIME B2-LN TRANSFORM	no family history	.133	21	.200
	2nd degree relative/s	.105	25	.200
	x 1 1st degree relative	.118	40	.168

	x 2 1st degree relatives	.122	16	.200
WAIS-R block design subtest (scaled scores) First visit	no family history	.104	21	.200
	2nd degree relative/s	.125	25	.200
	x 1 1st degree relative	.100	40	.200
	x 2 1st degree relatives	.172	16	.200
WAIS-R block design (Calc; standardised score; MV = 99) Last visit	no family history	.138	21	.200
	2nd degree relative/s	.167	25	.069
	x 1 1st degree relative	.104	40	.200
	x 2 1st degree relatives	.227	16	.027
WAIS-R digit symbol subtest (scaled scores) First visit	no family history	.200	21	.028
	2nd degree relative/s	.115	25	.200
	x 1 1st degree relative	.102	40	.200
	x 2 1st degree relatives	.177	16	.191
WAIS-R digit symbol substitution (Calc; standardised score; MV = 99) Last visit	no family history	.176	21	.090
	2nd degree relative/s	.163	25	.086
	x 1 1st degree relative	.146	40	.031
	x 2 1st degree relatives	.121	16	.200
SCOLP spot the word raw score First visit	no family history	.077	21	.200
	2nd degree relative/s	.099	25	.200
	x 1 1st degree relative	.071	40	.200
	x 2 1st degree relatives	.136	16	.200
SCOLP spot the word score (MV = 101) Last visit	no family history	.112	21	.200
	2nd degree relative/s	.199	25	.012
	x 1 1st degree relative	.073	40	.200
	x 2 1st degree relatives	.142	16	.200
SCOLP speed of comprehension raw score - total no attempted First visit	no family history	.083	21	.200
	2nd degree relative/s	.135	25	.200
	x 1 1st degree relative	.089	40	.200
	x 2 1st degree relatives	.174	16	.200
SCOLP speed of comprehension total no attempted (MV = 101) Last visit	no family history	.143	21	.200

	2nd degree relative/s	.136	25	.200
	x 1 1st degree relative	.117	40	.180
	x 2 1st degree relatives	.143	16	.200
STROOP time in seconds; colour words in black and white (Condition 1) Phase 1 Rd1 (MV = 1)	no family history	.105	21	.200
	2nd degree relative/s	.110	25	.200
	x 1 1st degree relative	.194	40	.001
	x 2 1st degree relatives	.146	16	.200
STROOP blocks of colour; time in seconds (Condition 2) Phase 1 Rd1 (MV = 1)	no family history	.135	21	.200
	2nd degree relative/s	.139	25	.200
	x 1 1st degree relative	.054	40	.200
	x 2 1st degree relatives	.156	16	.200
STROOP colour words in incongruent ink; time in seconds (Condition 3) Phase 1 Rd1 (MV = 1)	no family history	.157	21	.192
	2nd degree relative/s	.171	25	.058
	x 1 1st degree relative	.126	40	.108
	x 2 1st degree relatives	.206	16	.068
Stroop time for condition 1 last visit	no family history	.107	21	.200
	2nd degree relative/s	.131	25	.200
	x 1 1st degree relative	.081	40	.200
	x 2 1st degree relatives	.083	16	.200
Stroop time for condition 2 last visit	no family history	.107	21	.200
	2nd degree relative/s	.087	25	.200
	x 1 1st degree relative	.066	40	.200
	x 2 1st degree relatives	.112	16	.200
STroop time for condition 3 last visit	no family history	.130	21	.200
	2nd degree relative/s	.139	25	.200
	x 1 1st degree relative	.087	40	.200
	x 2 1st degree relatives	.107	16	.200
STroop difference between times for conditions 1 and 3 last visit	no family history	.187	21	.053
	2nd degree relative/s	.109	25	.200

x 1 1st degree relative	.103	40	.200
x 2 1st degree relatives	.107	16	.200

* Critical value of p is <0.001

Table 2P: Tests of normality at each level of the independent variable (no history, 2nd degree, x1 1st degree, x2 1st degree) for each memory test measure

	Qualitative genetic liability	Kolmogorov-Smirnov		
		Statistic	df	Sig.*
VF first assessment	no family history	.093	20	.200
	2nd degree rel/s	.140	17	.200
	x1 1st degree rel	.101	45	.200
	x2 1st degree rels	.209	7	.200
VF last assessment	no family history	.120	20	.200
	2nd degree rel/s	.134	17	.200
	x1 1st degree rel	.100	45	.200
	x2 1st degree rels	.161	7	.200
VF animals first assessment	no family history	.161	20	.185
	2nd degree rel/s	.137	17	.200
	x1 1st degree rel	.100	45	.200
	x2 1st degree rels	.177	7	.200
VF animals last assessment	no family history	.116	20	.200
	2nd degree rel/s	.138	17	.200
	x1 1st degree rel	.109	45	.200
	x2 1st degree rels	.225	7	.200
First ravlt 1-5	no family history	.172	20	.122
	2nd degree rel/s	.143	17	.200
	x1 1st degree rel	.145	45	.018

	x2 1st degree rels	.245	7	.200
First ravlt interference	no family history	.224	20	.010
	2nd degree rel/s	.202	17	.064
	x1 1st degree rel	.133	45	.045
	x2 1st degree rels	.246	7	.200
First ravlt short delay	no family history	.474	20	.000
	2nd degree rel/s	.139	17	.200
	x1 1st degree rel	.125	45	.076
	x2 1st degree rels	.278	7	.111
First ravlt long delay	no family history	.161	20	.187
	2nd degree rel/s	.139	17	.200
	x1 1st degree rel	.133	45	.044
	x2 1st degree rels	.301	7	.055
last ravlt 1-5	no family history	.117	20	.200
	2nd degree rel/s	.160	17	.200
	x1 1st degree rel	.133	45	.045
	x2 1st degree rels	.157	7	.200
last ravlt interf	no family history	.159	20	.200
	2nd degree rel/s	.160	17	.200
	x1 1st degree rel	.117	45	.140
	x2 1st degree rels	.205	7	.200
last ravlt short delay	no family history	.181	20	.086
	2nd degree rel/s	.166	17	.200
	x1 1st degree rel	.150	45	.013
	x2 1st degree rels	.191	7	.200
last ravlt long delay	no family history	.210	20	.020
	2nd degree rel/s	.216	17	.034
	x1 1st degree rel	.166	45	.003
	x2 1st degree rels	.279	7	.107
RBMT immediate story recall first assessment	no family history	.119	20	.200

	2nd degree rel/s	.135	17	.200
	x1 1st degree rel	.101	45	.200
	x2 1st degree rels	.134	7	.200
RBMT immediate story recall last asessment	no family history	.137	20	.200
	2nd degree rel/s	.109	17	.200
	x1 1st degree rel	.118	45	.136
	x2 1st degree rels	.138	7	.200
RBMT delayed story recall first assessment	no family history	.125	20	.200
	2nd degree rel/s	.114	17	.200
	x1 1st degree rel	.085	45	.200
	x2 1st degree rels	.226	7	.200
RBMT delayed story recall last assessment	no family history	.226	20	.008
	2nd degree rel/s	.136	17	.200
	x1 1st degree rel	.104	45	.200
	x2 1st degree rels	.155	7	.200

* Critical value of p is <0.001

Figure 2A: Informed consent form

Consent form for subjects

THE EDINBURGH HIGH RISK STUDY

I agree/do not agree (please circle as appropriate) to participate in this study.

I have read the consent form and participant information sheet and had the opportunity to ask questions about them.

I agree to the provision of any clinically significant information to my General Practitioner.

I understand that I am under no obligation to take part in this study.

I understand that I have the right to withdraw from this study at any stage.

I understand that this is non-therapeutic research from which I cannot expect to derive any benefit.

.....	.....
Signature of Participant	Date of Birth
.....	.....
Please print name	Address: Street name
	.....
	Town/City
	Post Code .....

.....
Signature of Investigator

GP Name and address:

.....

.....

.....

Date .....

Three copies to be made: one each for investigator, participant and any relevant general practice/hospital case notes.

APPENDIX 3: Tables and figures to accompany chapter 4

Table 3A: Tests of homogeneity of variance for each measure of the CVLT and RCFT

Table 3B: Tests of normality at each level of the independent variable for each measure of the CVLT and RCFT

Table 3C: Means, standard deviations and results of univariate analyses for CVLT measures of verbal memory in high risk participants with (HR+) and without psychotic symptoms (HR-) at the time of the first fMRI scan and controls (C)

Table 3D: Means, standard deviations and results of univariate analyses for RCFT measures of non-verbal memory in high risk participants with (HR+) and without psychotic symptoms (HR-) at the time of the first fMRI scan and controls (C)

Table 3A: Tests of normality at each level of the independent variable for each measure of the CVLT and RCFT

CVLT MEASURE	*C*		*HR-*		*HR+*	
	Kolmogorov-Smirnov statistic (df)	*p*	*Kolmogorov-Smirnov statistic (df)*	*p*	*Kolmogorov-Smirnov statistic (df)*	*p*
IMMEDIATE RECALL						
List A Trial 1	0.20 (19)	**0.01**	0.30 (35)	0.07	0.18 (23)	0.02
List A Trials1-5 total	0.11 (19)	0.20	0.80 (35)	0.20	0.12 (23)	0.20
List A Learning slope 1-5	0.10 (19)	0.20	0.16 (35)	0.20	0.17 (23)	0.09
List B Immediate recall	0.16 (19)	0.20	0.13 (35)	0.10	0.25 (23)	**0.01**
List B Trial 1-List A trial 1	0.21 (19)	0.03	0.22 (35)	**0.001**	0.11 (23)	0.20
DELAYED RECALL						
List A Short-delay free recall	0.11 (19), 0.20	0.20	0.15 (35)	0.04	0.14 (23)	0.20
List A Short-delay cued recall	0.19 (19)	0.06	0.18 (35)	**0.007**	0.21 (23)	**0.01**
List A Long-delay free recall	0.19 (19)	0.20	0.17 (35)	**0.002**	0.21 (23)	0.03
List A Long-delay cued recall	0.18 (19)	0.11	0.14 (35)	0.06	0.15 (23)	0.18
RETENTION						
List A Short delay free recall – trial 5 recall	0.14 (23)	0.20	0.15 (38)	0.05	0.20 (36)	**0.01**
List A Long delay free recall – trial 5 recall	0.15 (23)	0.20	0.23 (38)	**0.001**	0.12 (36)	0.20
List A Long delay free recall-short-delay recall	0.19 (23)	0.05	0.14 (38)	0.08	0.19 (36)	0.03

CVLT MEASURE	*C*		*HR-*		*HR+*	
	Kolmogorov-Smirnov statistic (df)	*p*	*Kolmogorov-Smirnov statistic (df)*	*p*	*Kolmogorov-Smirnov statistic (df)*	*p*
RECOGNITION						
Recognition hits	0.26 (19)	**0.01**	0.28 (35)	**<0.001**	0.25 (23)	**0.01**
Recognition misses	0.25 (19)	**<0.001**	0.29 (35)	**<0.001**	0.27 (23)	**<0.001**
Recognition false positives	0.40 (19)	**<0.001**	0.32 (35)	**<0.001**	0.34 (23)	**<0.001**
Response bias	0.38 (19)	**<0.001**	0.36 (35)	**<0.001**	0.39 (23)	**<0.001**
Total Recognition discriminability	0.24 (19)	**0.006**	0.30 (35)	**<0.001**	0.29 (23)	**<0.001**
ORGANISATION						
Total observed semantic clustering	0.22 (19)	0.02	0.16 (35)	0.02	0.08 (23)	0.20
Total chance adjusted semantic clustering	0.21 (19)	0.02	0.18 (35)	0.04	0.10 (23)	0.20
Total serial clustering forwards	0.17 (19)	0.12	0.18 (35)	**0.004**	0.28 (23)	**<0.001**
Total serial clustering backwards	0.13 (19)	0.20	0.23 (35)	**0.001**	0.15 (23)	0.14
Combined total chance adjusted serial clustering	0.08 (19)	0.20	0.12 (35)	0.20	0.17 (23)	0.90
RCFT MEASURES						
Copy trial	0.27 (23)	**<0.001**	0.24 (44)	**0.004**	0.20 (29)	**<0.001**
Copy time (seconds)	0.25 (23)	**0.001**	0.22 (44)	**<0.001**	0.15 (29)	0.08
Immediate recall	0.20 (23)	0.02	0.11 (44)	0.20	0.09 (29)	0.20
Delayed recall	0.16 (23)	0.11	0.15 (44)	0.02	0.11 (29)	0.20

CVLT MEASURE	*C*		*HR-*		*HR+*	
	Kolmogorov-Smirnov statistic (df)	*p*	*Kolmogorov-Smirnov statistic (df)*	*p*	*Kolmogorov-Smirnov statistic (df)*	*p*
Total correct recognition	0.26 (23)	**<0.001**	0.17 (44)	**0.002**	0.14 (29)	0.15
True positives	0.22 (23)	**0.006**	0.19 (44)	**<0.001**	0.14 (29)	0.12
True negatives	0.45 (23)	**<0.001**	0.36 (44)	**<0.001**	0.46 (29)	**<0.001**
False positives	0.45 (23)	**<0.001**	0.36 (44)	**<0.001**	0.46 (29)	**<0.001**
False negatives	0.22 (23)	**0.006**	0.19 (44)	**<0.001**	0.14 (29)	0.12

Table 3B: Tests of homogeneity of variance for each measure of the CVLT and RCFT

TEST MEASURE	LEVENE STATISTIC	df1	df2	SIG.
Total observed semantic clusters (trials 1-5) MAX = 12X5=60	3.719	2	78	**.029**
Total chance adjusted semantic clustering (all trials chance adj tog)/ (no.trials with at least 2 correct words recalled)	3.656	2	78	**.030**
VERBAL LEARNING: Total recall trials 1-5	1.034	2	86	.360
TEST MEASURE	LEVENE STATISTIC	df1	df2	SIG.

TEST MEASURE	LEVENE STATISTIC	df1	df2	SIG.
TOTAL OBSERVED SERIAL CLUSTERING FW	1.832	2	77	.167
TOTAL OBSERVED SERIAL CLUSTERING BW	2.477	2	77	.091
TOTAL OBSERVED SERIAL CLUSTERING FW & BW combined	.381	2	97	.684
CAVLTList B trial 1: interference trial (MV = 99) Phase 2 Rd1	.020	2	86	.980
CAVLT short delay list A: immediate recall time VI (MV = 99) Phase 2 Rd1	1.231	2	86	.297
CAVLT long delay recall score (MV = 99) Phase 2 Rd1	.330	2	85	.720
CAVLT immediate cued recall (MV = 99) Phase 2 Rd1	.327	2	84	.722
CAVLT long delay cued recall (MV = 99) Phase 2 Rd1	.438	2	86	.647
CAVLT recognition hits (MV = 99) Phase 2 Rd1	1.450	2	85	.240
CAVLT recognition misses (Calc) (MV = 99) Phase 2 Rd1	1.450	2	85	.240

CAVLT recognition false positives (MV = 99) Phase 2 Rd1	.185	2	85	.832
CAVLT discriminability (MV = 101) Phase 2 Rd1	.045	2	85	.956
CAVLT STORAGE INDEX (long delayed recall-short delay recall)	.120	2	85	.887
CAVLT STORAGE INDEX 2 (short delay recall-trial5 recall)	.481	2	86	.620
CAVLT STORAGE INDEX 2 (long delay recall-trial5 recall)	.089	2	85	.915
CVLT List B vs LIst A trial 1 contrast measure-% changes raw score: (#C List B trial-#C List A trial 1/#C List A trial 1) X 100	.571	2	86	.567
learning slope1-5 trials (Exy-((Ex)(Ey)/n)/Ex2-(EX)2/n)=f1/10	1.357	2	86	.263
Rey copy trial score (MV = 99) Phase 2 Rd1	1.155	2	95	.319
Rey copy trial time (Phase 2 round 1)	.307	2	97	.736
Rey immediate recall trial (Phase 2 round 1)	2.454	2	95	.091
Rey immediate recall standardised score T (Phase 2 round 1)	4.158	2	95	**.019**
rey delayed recall trial (Phase 2 round 1)	3.460	2	94	**.035**

rey delayed recall standardised T score (Phase 2 round 1)	5.551	2	94	**.005**
rey number true positives (Phase 2 round 1)	.650	2	93	.525
rey number false positives (Phase 2 round 1)	2.068	2	93	.132
rey number true negatives (Phase 2 round 1)	2.068	2	93	.132
reyfn	.650	2	93	.525
rey total score (Phase 2 round 1)	.088	2	93	.916

Table 3C: Means, standard deviations and results of univariate analyses for CVLT measures of verbal memory in high risk participants with (HR+) and without psychotic symptoms (HR-) at the time of the first fMRI scan and controls (C)

CVLT MEASURE	*C MEAN (SD)*	*HR- MEAN (SD)*	*HR+ MEAN (SD)*	*BETWEEN GRP EFFECT (ANOVA)*	*SIGNIFICANCE*[44]	*BETWEEN GRP EFFECT (KRUSKAL-WALLIS)*	*SIGNIFICANCE*[45]
IMMEDIATE RECALL				F	p	χ^2	p
List A Trial 1	6.86 (1.0)	6.64 (2.1)	6.96 (1.8)	0.3	0.7	1.1	0.6
List A Trials1-5 total	55.91 (8.1)	53.46 (9.6)	54.15 (8.1)	0.6	0.6		
List A Learning slope 1-5	1.54 (0.6)	1.54 (0.5)	1.46 (0.4)	0.2	0.8		
List B Immediate recall	7.57 (1.9)	6.13 (2.1)	5.96 (2.3)	4.3	0.02 T		
List B Trial 1-List A trial 1 (z scores)	0.47 (0.8)	-0.06 (1.07)	-0.31 (1.1)	3.6	0.03 T		
DELAYED RECALL							
List A Short-delay free recall	11.52 (2.7)	11.59 (2.5)	11.33 (2.0)	0.09	0.9		
List A Short-delay cued recall	12.86 (2.1)	12.18 (2.3)	11.88 (2.1)	1.2	0.3	2.9	0.2
List A Long-delay free recall	12.83 (2.4)	11.82 (2.6)	11.65 (2.2)	1.7	0.2	5.0	0.08
List A Long-delay cued recall	13.57 (2.1)	12.41 (2.4)	12.00 (2.2)	3.2	0.05 T		
RETENTION							
List A Short delay free recall – trial 5 recall (z scores)	-0.09 (0.8)	0.09 (0.6)	-0.12 (0.6)	0.9	0.4	1.6	0.4

[44] * = Significant after Bonferroni correction; T = trend for significance after Bonferroni correction
[45] * = Significant after Bonferroni correction; T = trend for significance after Bonferroni correction

CVLT MEASURE	*C MEAN (SD)*	*HR- MEAN (SD)*	*HR+ MEAN (SD)*	*BETWEEN GRP EFFECT (ANOVA)*	*SIGNIFICANCE*[44]	*BETWEEN GRP EFFECT (KRUSKAL-WALLIS)*	*SIGNIFICANCE*[45]
List A Long delay free recall – trial 5 recall (z scores)	0.2 (0.8)	-0.02 (0.7)	-0.2 (0.7)	2.5	0.08	5.8	0.06
List A Long delay free recall-short-delay recall (z scores)	0.34 (0.6)	-0.11 (0.6)	-0.13 (0.6)	4.4	0.01 *		
RECOGNITION							
Recognition hits	15.17 (0.9)	14.89 (1.5)	15.04 (1.0)	0.4	0.7	0.1	0.9
Recognition misses	0.83 (0.98)	1.11 (1.5)	0.96 (1.0)	0.4	0.7	0.1	0.9
Recognition false positives	0.74 (1.6)	0.87 (1.8)	0.96 (1.8)	0.09	0.9	0.5	0.8
Response bias	0.01 (0.2)	-0.03 (0.2)	-0.001 (0.2)	0.2	0.8	0.4	0.8
Total Recognition discriminability	96 .44 (4.8)	95.5 (6.5)	95.6 (4.8)	0.2	0.8	0.7	0.7
ORGANISATION							
Total observed semantic clustering	18.6 (11.5)	14.5 (8.9)	13.3 (5.9)	2.1	0.1	2.5	0.3
Total chance adjusted semantic clustering	1.46 (1.7)	0.77 (1.3)	0.86 (0.9)	1.6	0.2		
Total serial clustering forwards	5.5 (3.6)	6.1 (6.0)	6.6 (5.2)	0.2	0.8	0.8	0.7
Total serial clustering backwards	3.9 (2.60	4.1 (3.9)	4.1 (2.2)	0.01	0.9		
Combined total chance adjusted serial clustering	3.2 (3.8)	4.3 (6.7)	4.5 (5.4)	0.3	0.7		

Table 3D: Means, standard deviations and results of univariate analyses for RCFT measures of non-verbal memory in high risk participants with (HR+) and without psychotic symptoms (HR-) at the time of the first fMRI scan and controls (C)

RCFT MEASURE	C	HR-	HR+	*BETWEEN GRP EFFECT (ANOVA)*	*SIGNIFICANCE*[46]	*BETWEEN GRP EFFECT (KRUSKAL-WALLIS)*	*SIGNIFICANCE*[47]
	Mean (SD)	Mean (SD)	Mean (SD)	F	P	χ^2	P
Copy trial	34.2 (1.7)	33.4 (3.5)	33.1 (2.6)	0.9	0.4	1.0	0.60
Copy time (seconds)	159.0 (114.2)	170.0 (110.5)	161.7 (75.0)	0.1	1.0		
Immediate recall	24.4 (5.3)	21.3 (6.7)	20.9 (7.0)	2.3	0.1		
Delayed recall	23.7 (5.1)	20.6 (7.1)	20.2 (5.9)	2.3	0.1	1.0	0.60
Total correct recognition	21.9 (1.7)	20.8 (1.7)	20.2 (1.7)	5.2	0.007 *	11.2	0.004 *
RECOGNITION RESPONSES							
True positives	10.2 (1.3)	9.4 (1.7)	8.8 (1.6)	5.4	0.006 *	10.7	0.005 *
True negatives	11.7 (0.7)	11.4 (0.9)	11.6 (0.9)	1.2	0.3	3.4	0.20
False positives	0.3 (0.7)	0.6 (0.9)	0.4 (0.8)	1.2	0.3	3.4	0.20
False negatives	1.8 (1.3)	2.5 (1.7)	3.2 (1.6)	5.4	0.006 *	10.7	0.005 *

[46] * = Significant after Bonferroni correction; T = trend for significance after Bonferroni correction
[47] * = Significant after Bonferroni correction; T = trend for significance after Bonferroni correction

APPENDIX 4: Tables and figures to accompany chapter 6

Table 4A: Structural MRI in relatives of schizophrenic patients

Table 4B: Functional neuroimaging studies of memory in schizophrenia

Table 4A: Structural MRI in relatives of schizophrenic patients

Study	Sample[48]	Gender (age)	MRI Magnet and slices thickness[49]	Brain regions investigated	Findings
Cannon et al (1998)	63 SCZ+12 SCZaff 60 1st degree RELS 56 C	40M: 35F (40) 27M: 33F (40) 25M: 31F (40)	1 T 5mm contiguous slices	Cortical gray and white matter Sulcal and ventricular cerebro-spinal fluid (CSF)	Fetal hypoxia correlates with increased ventricle volume in SCZ and with mainly temporal lobe gray matter reduction and CSF increase bilaterally in SCZ and RELS.
Cannon et al (2002)[50]	64 SCZ 51 1st degree RELS 54 C	32M: 32F (40) 22M: 29F (40) 23M: 32F (40)	1.5 T 5mm contiguous slices	Cortical gray matter and CSF	Temporal gray matter loss in SCZ & RELS predicted by fetal hypoxia Sulcal enlargement and increased CSF is associated with hypoxia in SCZ. Fetal hypoxia and sulcal enlargement in RELS only.
Chua et al (2000)	27 SCZ 53 1st degree RELS 35 C	17M: 10F 26M: 27F 20M: 15F	1.5 T 3mm contiguous slices	Corpus callosum	No differences between groups
Harris et al (2002)	6 SCZ 6 + ve history parents 6 –ve history parents 6 C	5M: 1F (38) 4M: 2F (69) 2M: 4F (69) 5M: 1F (38)	1.5 T 1.5/1.7 mm contiguous slices	Whole brain Hippocampus	+ ve parents larger hippocampus volume than SCZ. Compensatory mechanism?
Keshavan et al (1997 & 2000)	17 1st degree RELS 22 C	8M: 9F (13-22) 11M: 11F (9-22)	1.5 T 5 mm contiguous slices	Amygdala-hippocampal comples & Dorsolateral Prefrontal cortex	Reduced amygdala-hipocampus volume and increased left asymmetry of anterior amygdala hippocampus (see also Schreiber et al (1999)
Lawrie et al (1999)	20 1st episode SCZ 100 1st and 2nd degree RELS (High-risk) 30 C	15M: 5F 54M: 46F 15M: 15F	1T 5 mm contiguous slices	Whole brain Prefrontal lobes Temporal lobes Amygdala-hippocampal complex Caudate nuclei	HR smaller amygdala-hippocampal complex and thalamus relative to C

[48] C = controls; DZ = dizygotic; HR = high-risk; MZ = monozygotic; RELS = unaffected relatives; SCZ = schizophrenic patients ; SCZaff = schizoaffective disorder

[49] T = tesla

[50] Cannon et al (2002) used same sample as used previously by same authors in 1998 and Van Erp et al (2002)

Study	Sample[48]	Gender (age)	MRI Magnet and slices thickness[49]	Brain regions investigated	Findings
				Lentiform and thalamic nuclei Lateral, third and fourth ventricles	
Lawrie et al (2002)	66 1st & 2nd degree RELS (High-Risk) 20 C	34M: 32F (23.1) 13M: 7F (22.9)	1T 1.88 mm contiguous slices	Temporal lobes	Scanned at baseline and at 2-year follow up. No change over time in HR temporal lobe or amygdala-hippocampal gyrus (although at baseline in latter region was reduced in RELS). Reduced right temporal lobe in 19 RELS (12 had at first assessment) with psychotic symptoms
Marcelis et al (2003)	31 SCZ 32 1st degree RELS 27 C	15M: 16F (18-55) 14M: 18F (18-55) 14M: 13F	1.5 T 3 mm slices	Whole brain	Voxel based morphometry-reduced cerebellum and fusiform gyrus , and Increased superior temporal gyrus in RELS. SCZ greater pallidum and putam and less frontal (superior and inferior), fronto-limbic, and cingulated than RELS.
Narr et al (2002)	20 MZ discordant twins 20 DZ discordant twins 20 C MZ twins 20 C DZ twins	10M: 10F (48.3) 10M: 10F (49) 10M: 10F (48.3) 10M: 10F (47.9)	1T 1.2 mm contiguous slices	Lateral and third ventricles Corpus callosum	Affected and unaffected MZ had upward bowing (displacement) of corpus callosum, associated with ventricle volume
O'Driscoll et al (2001)	20 1st degree RELS 14 C	9M: 11F (35.4) 5M: 9F (36.2)	1.5 T 1mm contiguous slices	Posterior hippocampus Amygdala-anterior hippocampus	Verbal memory and amygdala-anterior hippocampus correlated. Reduced amygdala-hippocampus volume and delayed verbal memory in RELS.
Schreiber (1999)	15 1st degree RELS 15 C	(11.7-18.9) (11.5-19.1)	1.5T 5 mm contiguous slices	Corpus callosum, frontal lobes, amygdala-hippocampus, lateral and third ventricles	Reduced right amygdala-hippocampus and increased left asymmetry of anterior amygdala-hippocmapus in

Study	Sample[48]	Gender (age)	MRI Magnet and slices thickness[49]	Brain regions investigated	Findings
					RELS
Seidman et al (2002)	18 SCZ 28 1st degree simplex [51] RELS 17 1st degree multiplex RELS 48 C	10M: 8F (43.2) 17M: 28F (44.6) 27M: 21F (40.1)	1.5 T 3mm contiguous slices	Total cerebrum and hippocampus	Positive correlation between verbal memory and left hippocampus volume. Smaller left hippocampi in multiplex RELS, but no differences between SCZ and RELS. Vulnerability to SCZ?
Seidman et al (2003)	40 simplex SCZ 48 multiplex SCZ 28 1st degree simplex RELS 17 1st degree multiplex RELS 48 C	27M: 13F (44.9) 32M: 16F (44.3) 17M: 28F (44.6) 27M: 21F (40.1)	1.5 T 3mm contiguous slices	Total cerebrum and anterior and posterior parahippocampal gyrus (PHGa and PHGp)	No difference in total cerebrum volume between groups. SCZ and multiplex RELS smaller left PHGa than C. RELS & SCZ smaller right PHGa than C. RELs greater left and right PHGp than C. No correlation between volumes and verbal memory-although PHGa moderate correlation with memory in multiplex RELS
Sharma (1998) & (1999)	29 SCZ 55 1st degree RELS 39 C	18M: 11F 24M: 31F 20M: 19F	1.5 T 1.5 mm contiguous slices	(1998)-Whole brain, cortical gray matter, temporal lobe, lateral ventricles, cerebellum (1999)-cerebral asymmmetry	Greater ventricle volume in SCZ than RELS or C. Reduced whole brain and cerebellum in SCZ than RELS or C. SCZ and obligates abnormal asymmetry in PFC, sensorimotor & occiptio-parietal. Non-obligates also lack symmetry in occipito-parietal.
Shulze et al (2003)	35 multiplex SCZ 31 non psychosis family SCZ 63 1st degree RELS 68 C	17-70 years old	1.5 T 1.5 mm contiguous slices	Hippocampus	Smaller left hippocampus in SCZ, but not significant in RELS, to C
Staal et al (1998) & (2000)	32 1st degree RELS (discordant	24M: 8F	1.5 T	(1998)- Thalamus, total brain,	Lower thalamic volume in

[51] Simplex is a family with only one member affected by schizophrenia, multiplex is a family with more than one affected member

Study	Sample[48]	Gender (age)	MRI Magnet and slices thickness[49]	Brain regions investigated	Findings
	siblings) 32 C	24M: 8F	2mm slices	intracranium (2000)-lateral and third ventricles, frontal lobe, caudate nucleus, amygdala-hippocampus, parahippocampal gyrus, cerebellum	SCZ than RELS or C, and lower in RELS than C.
Steele (2002)	6 SCZ 6 obligate carrier 1st degree RELS 6 non-carrier 1st degree RELS	2M: 4F (46.2) 2M: 4F (49) 3M: 3F (45.2) 3M: 3F	1T/or 1.5T 1.5 mm slices	Whole brain, third, fourth and lateral ventricles, prefrontal and temporal lobes, caudate nuclei, lentiform, thalamus, amygdala-hippocampal complex	Greater whole brain and gray matter loss in RELS than SCZ, but smaller ventricles and smaller amygdala-hippocampus in carriers and SCZ than non-carriers
Tepest et al (2002)	12 SCZ (no affected RELS) 13 SCZ 1st degree RELS 12 unaffected 1st degree RELS 10 C	8M: 4F (29.8) 6M: 7F (30.5) 7M: 6F (31.1) 5M: 5F (24.4)	1.5 T	Hippocampus	RELS significantly smaller hippocampi than C (smaller still in multiply affected family SCZ)
Toulopoulou et al (2004)	51 SCZ & 5 SCZaff 90 1st degree RELS	39M: 17F 27M: 28F	1.5 T 1.55 mm slices	Whole brain, prefontal lobes, lateral and third ventricles, temporal lobes, hippocampus, cerebellum	SCZ enlarged third ventricle, reduced left temporal lobe and hippocampi.
Van Erp et al (2002)[52]	60 SCZ & 12 SCZaff 58 1st degree RELS 53 C	39M: 33F (40) 25M: 33F (40) 24M: 29F (40)	1.5 T 1.3 mm slices	Hippocampus	RELS less bilateral hippocampus than C. SCZ less than RELS and C. Fetal hypoxia correlates with reduced hippocampus in SCZ only.

[52] Same sample as in Cannon (2002) and (1998)

Study	Sample[53]	Gender (age)	Task	Imaging technique	Activations[54]	Behavioural performance
					bilateral insula, bilateral occipital SCZ > C Bilateral APFC (BA 10) & L BA 6	Words familiar due to performing task before scanning.
(Jennings et al 1998)	8 SCZ (med) 8 C	M (37) M (37)	Shallow & deep encoding (T junction count & semantic decision living vs. non living)	PET $^{15}OH_2O$ (rCBF)	During semantic processing: Both groups SCZ & C > L IFG (BA 45) BA9, BA6, STG (BA22), BA47, BA40/43, bilateral AC (BA32) SCZ & C < LBA 25, BA8/6 R BA 37, BA39, BA40, BA21, BA24, Bilateral BA 18, 19 Within groups SCZ (opposite pattern to controls) > LBA10, RBA21, BA43 SCZ < L BA18 & 19, Thalamus, R superior parietal (BA7), BA10, BA22, BA19 Path Analysis: LBA45 (IFG), BA32 (Dorsal AC), BA22 (STG) & Bilateral BA 10 (AC on left) (Areas chosen where activation significant & previous activity in other studies) C-Positive reciprocal connections between LBA 45 - L22 LBA 22 - L32 LBA 45 - R 10 RBA 10 - L10 SCZ-Negative reciprocal connections of above	No difference in shallow or deep task RT No difference in shallow task accuracy Small difference in deep task accuracy
(Jessen et al 2003)	12 SCZ 12 C	9M: 3F (27.4) 9M: 3F (27.7)	Verbal deep encoding & recognition (Enc: X 50 words in 5 blocks every 3 seconds. To internally associate with a chosen noun 3 minutes between tasks (Recognition: 50 old & 50 new & 50 null 2 sec presentation + 1.5 fix = 3.5 ISI)	EPI (BOLD) FMRI 1.5T (Blocked & event related designs)	Only R & L hippocampal activation analysed according to anatomical masks Encoding: Bilateral hippocampus in both, L anterior greater in C than SCZ Recognition: Old & new words- Bilateral hippocampus in both. Correct old bilateral in C, but only R in SCZ Correct new SCZ > C R hippocampus (anterior)	FMRI for false alarms & misses too low for comparison RT encoding NS Recognition correct old less in SCZ than C, but correct new NS Recognition RT NS

Study	Sample[53]	Gender (age)	Task	Imaging technique	Activations[54]	Behavioural performance
					Could be R hippocampus due to difficulty in novelty detection in SCZ during recognition of new words (see Weiss 2004)	
(Kubicki et al 2003)	9 SCZ 9 C	M (39.7) M (43.2)	Deep & shallow encoding & recognition Repetition priming Deep: words abstract or concrete. Shallow: words upper or lower case Repeated presentation to assess priming effect	EPI (BOLD) FMRI 1.5T Blocked design	Semantic encoding: within groups C > Bilateral IFG, R SPFC, bilateral AC & occipital lobes SCZ > LIFG, RmidFC, L posterior STG, L parietal, cingulate & occipital. Between groups C > SCZ bilateral IFG (52 28 –2-BA45) SCZ > C LSTG-L inferior parietal and cingulate. Perceptual: within groups C > cingulate & occipital only. SCZ-same activations as in semantic condition. SCZ- No repetition/priming effect behaviourally or as decrease in LIFG	Expected depth of processing effect (better recognition for deep vs. shallow encoded words) C show priming effect (faster RT on repetitions) but not SCZ in semantic encoding
VERBAL FLUENCY						
(Artiges et al 2000)	14 SCZ (negative) 14 C	M (29) M (30.7)	Verbal fluency (phonological) Vs. Spontaneous word production Vs. Rest	PET $H_2O^{15}O$ (rCBF)	C show mainly left lateralised (language dominant) activity in IFC, DLPFC, precentral and inferior parietal. SCZ show less activation in L frontal, and increases in R IFG, & R inferior parietal=diminished laterality balance. R hemisphere activity negatively correlates with verbal fluency performance. Right hemisphere may be compensatory but ineffective recruitment	Verbal IQ not correlated with word production
(Bullmore et al 1999)	5 SCZ 5C	Age & IQ matched	Covert verbal fluency (Phonological) Covert semantic decision task (living vs. non-living)	EPI (BOLD) FMRI 1.5T Blocked design	Hypofrontality apparent only in verbal fluency, not semantic decisions task. Cannot attribute to different scanning techniques or disorder heterogeneity-function of task alone. Is verbal phonological fluency harder or is it due to task specific processes in PFC?	N/A
(Curtis et al 1998)	5 SCZ 5 C	M (31.6) M (29.6)	Covert verbal fluency (phonological) Vs. Silent repetition of 'rest'	EPI (BOLD) FMRI 1.5T Blocked design	Reduced activity in LDLPFC, IFG, insula Inc activity in medial parietal	No differences in performance prior to scanning
(Dye 1999)	6 SCZ	3M: 3F	Verbal Fluency	PET	Bilateral STG activity < in SCZ & BPD	N/A

Study	Sample[53]	Gender (age)	Task	Imaging technique	Activations[54]	Behavioural performance
	6 BPDs[55] 10 C	(48.8) 3M: 3F (46.5) 6M: 4F (51.5)	(phonological) Vs. Repetition	$H_2O^{15}O$ (rCBF)	No differences in frontal activity.	
(Fletcher et al 1996)	12 SCZ (med free 6 months, 9 med naïve) 12 C	(26) Age matched C	Verbal fluency Paced (phonological) vs. control word repetition task; after scan half given apomorphine (acts on dopamine receptors) and half a placebo	PET $H_2O^{15}O$ (rCBF)	SCZ: > Bilat PFC, AC, Linferior pariet, STG, posterior cingulate gyrus SCZ > Same as above, AC, R midFC, Lfusiform gyrus. C: > PFC, AC, thalamic/sub thalamic C: < STG, bilateral and posterior cingulate gyrus SCZ vs. C SCZ no anterior cingulate and don't deactivate sup temp gyrus.	SCZ slower than C- non significant Apomorphine-dopaminergic antagonist modifies brain activity (anti psychotic) anterior cingulate widespread heterogeneity-attention, coordination with other areas STG. No diff between apomorphine and placebo on task performance.
(Frith et al 1995)	18 SCZ (Poor VF performance Odd VF performance Normal VF performance) 6 C	5M:2F (57.9) 4M: 1F (53) 5M: 1F (47.7) 5M: 1F (57.2)	Paced verbal fluency (phonological) Vs. Word classification (semantic categorisation: man made vs. natural) Vs. Word repetition	PET Inhaled $C^{15}O_2$ (rCBF)	Within groups: Fluency vs. repetition All groups > LDLPFC, AC and thalamus < posterior cingulate, RSTG Repetition vs. fluency Only C > L STG (i.e. less STG in fluency). This was not apparent in SCZ.	No differences between groups. Activity in semantic categorisation fell between repetition and VF, but appeared greater in SCZ than C on sight.
(Spence et al 2000)	10 OBLIGs 10 SCZ 10 C	4M: 6F (55.4) (41.7) 6F: 4M (51.5)	Verbal fluency (phonological)	PET $H_2O^{15}O$ (rCBF)	SCZs didn't deactivate precuneus & showed disconnectivity between LDLPFC and AC. AC connected to PFC and thalamus and attention/motor control role.	
(Sommer et al 2003a)	12 F SCZ 12 F C Compared to previous. 12 M SCZ	(33.6) (32)	Verb generation task (cued with noun) Vs. Reverse mirror read semantic decision task (reduced orthographic	EPI (BOLD) FMRI 1.5T Blocked design	Investigated language lateralisation VOIs. SCZ F inc right hem activity hence decreased language lateralisation relative to F C. Compared to M SCZ lower lateralisation than C	N/A

[55] BPDs = bipolar disorder patients

Study	Sample[53]	Gender (age)	Task	Imaging technique	Activations[54]	Behavioural performance
			processing) Vs. Rest			
(Weiss et al 2004b)	9 M SCZ 9 M C	(31.4) (26.8)	Covert verbal fluency (phonological) Vs. Rest	EPI (BOLD) FMRI 1.5T Blocked design	Fluency vs. rest: within groups C > PFC, AC, L parietal, L thalamus SCZ > PFC, AC, L parietal, L Thalamus. No between group differences, but-Broca's lateralisation index= C > L IFG (BA44) SCZ > bilateral BA44 = Reduced language lateralisation of IFG	
(Yurgelun-Todd et al 1996)	12 SCZ 11 C	10M: 2F (34.4) 6M: 5F (28.2)	Verbal fluency (phonological) Vs. Counting (rest)	EPI (BOLD) FMRI 1.5T Blocked design	Fluency vs. rest: between groups C > SCZ DLPFC SCZ > C STG	All groups performed satisfactorily.
WORD/ STORY RECALL						
(Andreasen et al 1996)	14 SCZ 13 C	10M: 4F (30.7) 6M: 7F (28.6)	Prose recall (Wechsler logical story memory test)	PET $H_2O^{15}O$ (rCBF)	Practiced: SCZ < fronto-thalamic-cerebellar regions and L motor area. REST: SCZ < Medial frontal, lateral right frontal, left thalamus and left cerebellum. Novel: SCZ < fronto-thalamic-cerebellar region, anterior cingulate, bilat lentic nuclei, anterior temp, mammillary bodies.	Practiced: SCZ and C equal performance Unpracticed: poorer performance from SCZ
(Barch and al 2002)	38 SCZ 48 C	63% M (36.3) 46% M (36.5)	Word list and picture encoding and recognition (& N-Back WM task)	EPI (BOLD) FMRI 1.5T Blocked design	LTM & WM (irrespective of material type) SCZ < C RDLPFC, brain stem, bilateral parietal cortex Enc & WM C > SCZ brain stem, basal ganglia, thalamus, medial PFC SCZ > C somatosensory cortex WM C > SCZ Rant&post hippocampus, bilateral DLPFC, bilateral SPFC, bilateral precuneus. SCZ didn't show greater L response in IFC, parietal or temporal during words over faces, as seen in C-reduced laterality?	SCZ worse on recognition of words and faces than C, but all better on words. SCZ slower on recognition of words than C
(Crespo-Facorro et al 1999)	14 med free SCZ 13 C	10M: 4F (28.6) 6M: 7F (30.7)	Word list recall (15 items RAVLT) Auditory encoding (i.e. practiced words learned 1 week prior to recall & novel words seen I minute prior to recall)	PET $H_2O^{15}O$ (rCBF) + MRI scan	SCZ Novel: dec rCBF in R anterior cing, R thalamus, bilat cerebellum SCZ Practiced: Dec rCBF in LDLPFC, bilat medial frontal, LSMA, L thalamus, L cerebellar regions, anterior vermis,R cuneus SCZ fail to activate cortical cerebellar-thalamic-cortical circuitry	No diffs in performance sig.

Study	Sample[53]	Gender (age)	Task	Imaging technique	Activations[54]	Behavioural performance
			Spoken recall Vs. Rest		during recall of practiced and novel lists.	
(Fletcher et al 1998)	12 med SCZ 7 C	M 6M: 1F	Word list recall (1-12 item lists -graded list memory task)	PET $H_2O^{15}O$ (rCBF) Fixed effects GLM	DLPFC: C active throughout task SCZ (U) and (I) active then decrease with inc task difficulty of task (beyond 4 words) LSTG: C task related decrease SCZ linear and unrelated to task INF PARIETAL: as above POSTERIOR PARIETAL: C active throughout retrieval SCZ (I) not active SCZ (U) highly active No medial temp activations seen-maybe hippocampus, sensitive to novelty. Not in here due to repetition of material.	All groups showed perfect recall up to 4 words-after 4, performance declined
(Fletcher et al 1999)	12 SCZ 7 C	M 6M: 1F	Word List Recall (1-12 item lists -graded list memory task)	PET $H_2O^{15}O$ (rCBF)	PFC and ACC activity in C predicted STG decrease, but not seen in SCZ. Reflects modulation of ACC and PSC on STG function i.e. PFC suppresses STG activity/or modulating ACC which then suppresses STG. ACC associated with response inhibition	
(Ganguli et al 1997)	8 SCZ (remission) 8 C	5M: 3F (39.6) 5M: 3F (36.9)	Word list recall (Supra span task: 12 word free recall 15 seconds after each auditory list presentation- x 6 lists) Vs. Visual fixation	PET $H_2O^{15}O$ (rCBF) + MRI scan	SCZ < C bilateral frontal and STG Less activation decrease in LOFC, L temporor-occipital, inferior parietal in SCZ than C SCZ: No left sup temp or putamen activation	Participants practiced procedure prior to scanning and asked not to use serial recall on day. Recency and primacy effects in both groups. Patients perform more poorly in recency aspect of task
(Gur et al 1994)	18 SCZ 18 C	12M: 6F (26.7) 12M: 6F (26.6)	Word recognition (Word recognition task-Kimura) (also face recog)	PET Xenon injection (rCBF)	SCZ didn't show laterality changes shown by C, L-R verbal, R-L visual in mid temp region SCZ less global >, especially in left & for verbal, than C	Sensitivity (identify as seen before) was less affected than specificity (reject items as non targets) in SCZ -lower than C both verbally and facially
(Hazlett et al 2000)	20 SCZ (med free) 32 C	14M: 6F (38.3) 25M: 7F (41.8)	Word list recall (16 words-Serial Verbal Learning Test) Presented 30 minutes before tracer uptake	PET (FDG) (rGMR)	Dec in rGMR in frontal cortex & inc in temporal cortex in SCZ (assoc with serial order) Dec in frontal & temporal areas but not parietal & occipital	SCZ recalled fewer words in semantic clusters and showed greater use of serial ordering compared to C

Study	Sample[53]	Gender (age)	Task	Imaging technique	Activations[54]	Behavioural performance
(Kayser et al 1999)	24 SCZ 19 C	15M: 9F (29) 9M: 10F (30)	Word recognition (continuous word recognition paradigm: old vs. new words decision. No words repeated > than once)	ERP (EEG recordings at 4 midline & 13 homologous sites	Normal old new effect is greater positivity to old than new, which could signify normal MTL function. SCZ and C both show old-new effect. Reduced -ve potentials in SCZ, specifically in the left inferior temporo-parietal areas-early in word processing (200-400ms). May not require MTL in this task.	Longer RT for old than new. SCZ less accurate than C, but both perform above chance. Word recognition worse in SCZ.
(Nohara et al 2000)	10 SCZ 9 C	M (27.2) M (25.8)	Word list recall (Verbal learning task)	SPECT (rCBF)	No inc frontal activity in SCZ as seen in C During learning: SCZ lower rCBF in bilateral IFG, L AC, R SPFC, bilateral midFC	C generally generate more words than SCZ
(Ragland et al 2001)	23 SCZ 23 C	18M: 5F (35.2) 12M: 11F (30.7)	Word encoding & recognition (Penn word recognition test-20 word list presented 15 minutes prior to recognition)	PET $H_2O^{15}O$ (rCBF)	Same activation in sensorimotor cortex for both groups in motor task ENCODING: C maximal activation in LIFG & additional bilateral effect in inferior temporal gyrus, L SMA, R insula, R occipital cortex, R cerebellum. SCZ activation in bilateral superior frontal regions, L superior temporal gyrus, L cerebellum, R thalamus. C greater LiPFC, L middle and superior frontal gyrus and L superior temporal gyrus activation than SCZ RECOG: C bilateral PF, L anterior cingulate gyrus, L middle frontal and superior gyrus, L inferior temporal gyrus and bilateral fusiform gyrus activation. SCZ showed L middle frontal gyrus, R superior frontal gyrus, L middle temporal gyrus, bilateral inferior temporal gyrus, L cingulate gyrus, L middle occipital gyrus & bilat inferior occipital regions. = C greater activation than SCZ in L PFC and L AC, L midFC, L mesial temporal lobe, R thalamus. L PFC involved in episodic memory processing and improved by encoding word associations semantically. Degree of PFC activation related to strategic encoding processes. Recognition can be successful with shallow processing (noetic	Recognition high for both groups (SCZ non significantly less accurate than C, with more guesses) RTs same for both groups Motor task high for both groups

Study	Sample[53]	Gender (age)	Task	Imaging technique	Activations[54]	Behavioural performance
					awareness-familiarity over conscious recollection). Recall (source memory) would probably put more pressure on frontal activations and performance may be impaired. Future depth of processing/imaging studies needed.	
Ragland 2004	14 SCZ 15C	(32.7) (28.4)	Word encoding & N-back working memory task (prevents verbal rehearsal)& Recognition task	EPI (BOLD) FMRI 4T Event related design	Encoding: within groups C > LBA10, LDLPFC, RSMA (BA6), posterior cingulate and visual areas. SCZ > LBA10, LBA44, visual areas, LSTG, L parietal, LAC, R thalamus BUT, No L DLPFC in SCZ Between groups C > LBA9 & 46, L insula, R putamen, LBA7. SCZ > C L inferior temporal, R middle temporal (BA21), bilateral PHG, motor and visual areas. Recognition: within groups C > LBA10, 9, 46, bilateral BA7, L thalamus. SCZ > as above + BA10/11 (OFC) but not 9 or 46. Between groups C > SCZ LDLPFC, insula, thalamus and superior parietal. SCZ >C sensorimotor areas, LOFC, L middle temporal and R precuneus. Retrieval success: C > SCZ LDLPFC SCZ > C OFC, LPHG, RBA40	8 c and 1SCZ made word associations to recall. Rest used rehearsal or didn't know. No differences in RT. SCZ difficulty in recognition (targets) greater than C. Looked at correct recognition only.
(Weiss et al 2004a)	15 M SCZ 16 M C	M (46) M (48.2)	Shallow encoding & recognition (Stark & Squire's Old/New Recognition Memory test-for hippoc activity in controls) Enc-80 words presented x2-to read aloud only 15 minute delay Rec -160 words (80 old & 80 new)	EPI (BOLD) FMRI 1.5T Blocked design	Bilat hippocampus in both groups during 'old' vs. baseline. New vs. baseline bilateral hippocampus in both groups Old>New in C- no hippocampus activity, but SCZ showed R posterior hippoc activity (NS) New>Old in C- R anterior hippoc, but not in SCZ ROI analysis: C > R than L in new>old, but SCZ opposite Correlation between R hippoc and false alarm rate in SCZ but not c	Correct old NS Incorrect old (false alarm rate) sig greater in SCZ than c Hots & correct new quicker RT than misses & false alarms C faster for correct new vs incorrect new but Sz RT similar for new (correct rej)& old (false alarm) Difficulty in correctly rejecting New items, hence inc false alarm rate. R anterior activity in C during new items, but not SCZ. R ant important in

Study	Sample[53]	Gender (age)	Task	Imaging technique	Activations[54]	Behavioural performance
						novelty detection & familiarity? 2ndry to prefrontal abnormalities
(Yurgelun-Todd et al 1997) Abstract only	12 SCZ 12 C		Word list recall List 15 words presented x3	FMRI 1.5T	ROIs frontal, temporal & parietal SCZ>C temporal C>SCZ DLPFC	Hypofrontality Suggests disconnectivity in fronto-temporal networks
WORKING MEMORY						
(Artiges et al 2000)	8 SCZ 8 C	(28) (25)	Random number generation: (Avoid sequences and repetitions) Executive control task.	PET $H_2O^{15}O$ (rCBF)	SCZ: No covariation between anterior cingulate and ability to do task. No superior parietal activation in respect of task pacing. C: the more random the responses, the greater the activation of the superior anterior cingulate. Superior parietal activation inc with difficulty and hence task speed. Cingulo-parietal dysfunction	SCZ: Slower responding than controls, and less random responses-i.e found it hard to inhibit previously spoken response and generate brand new ones. C: The more random the number responses, the greater the control. Responded faster than patients and had more random responses.
(Barch and al 2002)	38 SCZ 48 C	63% M (36.3) 46% M (36.5)	Word list and picture encoding and recognition (& N-Back WM task)	EPI (BOLD) FMRI 1.5T Blocked design	SCZ: LTM & WM Impaired activity of RDLPFC, brain stem, basal ganglia, thalamus, parietal cortex SCZ: Enc & WM Impaired activity in Lhippo/parahippo SCZ: WM only Impaired activity in bilateral DLPFC and R medial temporal cortex	SCZ worse than controls on WM task. No effect of verbal & non verbal material.
(Callicott et al 1998)	10 SCZ 10C then 6 SCZ (2 med free) 6C	M (34.1) M (33.3)	N-back & Motor control task	EPI (BOLD) FMRI 1.5T 9 runs with 30second epochs of alternating conditions	Some SCZ failed to show activation in SMA during control task. Matched then for voxel stability (PSD). SCZ: All but 1 of 6 failed to activate DLPFC with higher loads. Tendency for over activation of parietal cortex C: Activated DLPFC	No diffs on 0 back, but SCZ poorer on 2 back than C (the only SCZ activating DLPFC had performance well below C, but another patient who failed to activate DLPFC had performance equivalent to C) possible compensatory activation to improve performance hindered by ineffective usage of DLPFC in SCZ ?
(Callicott et al 2000)	37 SCZ 32 C		Parametric version of N-Back task	EPI (BOLD) FMRI 1.5T Blocked design (9 runs with	Both similar response across 0B-1B-2B SCZ: Greater dynamic response in BA 9-10, 46, 42 & cingulate 32	SCZ worse at higher levels of difficulty than C (i.e. 1B and 2B)

Study	Sample[53]	Gender (age)	Task	Imaging technique	Activations[54]	Behavioural performance
				30second epochs of alternating conditions)	Greater resp than C in intra parietal sulcus (BA 39) C: greater dynamic resp in regions outside PFC & ventral PFC, & in L BA 7, precuneus R BA 39 Also C greater CEREBELLUM resp than SCZ, LsupTemp G & post cingulate Linear deactivation in R Hippocampus with inc task difficulty	
(Holcomb et al 2000)	18 SCZ 12 C		Tone freq recognition (Trained to equivalent performance) Sensorimotor task & Rest	PET $H_2O^{15}O$ (rCBF)	SCZ: Less change in rCBF of anterior cingulate & SMA when switching from motor to decision task Lower rCBF to frontal areas with extended response times C: Inc rCBF to frontal areas with extended response times. SCZ ineffeicient use of fronto cingulate system in task.	SCZ: Performed as well in tone discrimination as C
(Honey et al 2002)	20 SCZ 20 C	M (34.6) M (39.3)	Low load verbal N-back task	EPI (BOLD) FMRI 1.5T Blocked design	SCZ: Similar activations in relevant areas to C. Robust fronto parietal activation as in C. No RT-funct response relationship found. May not be using phonological loop adequately. C: Activations in relevant areas (bilateral parietal & occipito-parietal, precuneus, bilateral DLPFC, inf frontal, lat PM, precent gyrus, occipital areas & cerebellum) similar to SCZ. A reaction time-functional response linear effect in posterior bilateral parietal cortex-inc parietal activation with inc resp latency.	SCZ and C performed equivalently, but a significant difference in RT, with SCZ slower than C in both exp and control cdts.
(Jansma et al 2004)	10 SCZ (med) 10 C		Spatial N-Back task (inc difficulty)	EPI (BOLD) FMRI 1.5T Blocked design	Normal in both groups. At 3 back DLPFC activity ceased in SCZ relative to Controls	Peak activation in DLPFC reached earlier in SCZ than C
(Kindermann et al 2004)	8 SCZ 2 SCZAff 12 C	 (58) (63)	Spatial Working Memory task (McCarthy et al)	FMRI 1.5T Blocked design	SCZ show normal working memory (spatial) activation Greater in fusiform gyrus, MFC, R cerebellum, middle occipital, supramarginal gyrus. C greater in STG and MFC areas.	Young and old SCZ show normal DLPFC when spatial working memory task demands are within their capacity.
(MacDonald and Carter 2003)	17 SCZ 17 C	71% M (34.2) (33.5)	CPT-AX task (To inhibit learned automatic response-	FMRI 1.5T Event-related design	C inc LDPFC during inhibition, but not SCZ	Context processing: ability to represent and maintain info to adaptively controls behaviour:

Study	Sample[53]	Gender (age)	Task	Imaging technique	Activations[54]	Behavioural performance
			respond to pre-specified probe (X) only when it follows context cue (A). 3 distractors BX, AY & BY.)			Assoc with top down support to overcome natural response in C only
(Manoach et al 1999)	13 SCZ 10 C	M M	Item (digit) recognition (Sternberg)	BOLD EPI FMRI 1.5T Blocked design	SCZ greater in L DLPFC (but not right) & inversely correlated with task performance	SCZ performed above chance but made more errors and had longer RT than C
(Manoach et al 2000)	9 SCZ 9 C	M (42.4) M (38.7)	Item (digit) recognition (Sternberg)	BOLD EPI FMRI 1.5T Blocked design	SCZ greater in L DLPFC (but not right) & inversely correlated with task performance. Also SCZ activated Thalamus & Basal ganglia despite matched performance	SCZ deficient WM performance
(Manoach et al 2001) Retest reliability	RETEST of ABOVE		Item (digit) recognition (Sternberg)	BOLD EPI FMRI 1.5T Blocked design	Cognitive activation not reliable across sessions in individual SCZ patients. Greater variation over time.	
(Menon et al 2001)	11 SCZ 13 C	M (44.5) M (42.6)	2-back Continuous Performance Task	BOLD EPI FMRI 1.5T Blocked design	ROI analysis-DLPFC, inferior and superior parietal, frontal operculum, STG & AC. Deficits in R & L DLPFC, inferior & superior parietal	Tested again several moths later-SCZ worse and slower than C
Mendrek 2004						
(Meyer-Lindenberg et al 2001)	13 SCZ (med free) 13 C	12M: 1F (32) 9M: 4F (30)	N-back (0 back and 2 back)	PET $H_2O^{15}O$ (rCBF) Functional Connectivity analysis	Half variance explained by PHG, cerebellar loadings for SCZ vs. C DLPFC & AC for C vs. SCZ	SCZ < C
(Perlstein et al 2001)	17 SCZ (med) 16 C	11M: 6F (36.5) 10M: 6F (36.5)	N-back (letters) Parametric 0,1,2,3 for C and 0,1, 2 for SCZ	BOLD FMRI 1.5T Blocked design	SCZ deficit in RDLPFC (BA 46/9) only where differing from C on task performance. SCZ with greater DLPFC have worst performance.	Sensitivity and response criterion (Beta) lower in SCZ than C at 2 back
(Perlstein et al 2003)	16 SCZ 15 C	11M: 5F (36.8) 9M: 6F (36.4)	N-back & AX-CPT (letters) N-back as above. CPT-respond to pre-specified probe (X) only when it follows context cue (A). 3 distractors BX, AY & BY.	BOLD FMRI 1.5T Blocked design	Tasks engaged overlapping networks. Inc load=inc activity Less RDLPFC in high WM load in SCZ DLPFC NOT correlated with cue maintenance (i.e. A trials) in groups-so not responsible for holding of cue information? DLPFC on R could be attention related is active with inc demand during cue related trials? Probably preparatory therefore.	Inc load associated with inc error rates-SCZ more so than C. SCZ made more 'wrong cue' responses than C (i.e. B) especially at short delay periods. More BX trial errors in SCZ than C. SCZ use cues less effectively than C.

Study	Sample[53]	Gender (age)	Task	Imaging technique	Activations[54]	Behavioural performance
			B cue activity may reflect intention to overcome response to target X			C showed greater activity during b than during A cue trials.
(Quintana et al 2003)	8 SCZ 8 C	6 M: 2F (29.2) 6 M: 2F (35.2)	Spatial & Visual working memory coloured circles and happy/sad faces presented-anticipating responses & remembering cues	FMRI 3T Blocked design	PFC & PPC (post parietal) specifically looked at. Retention task: SCZ>C DLPFC C>SCZ on faces in LBA47 Bilat PPC with both faces & dots. Only during faces in C, also bilat STG but only L in SCZ Anticipation task: C>SCZ DPFC (BA9), RDFC &IFC (BA44). Bilat IFC (BA 47) in C only.	
(Stevens et al 1998)	14 M SCZ 14 M C		Word & tone serial positions	BOLD FMRI 1.5T Blocked design	Both tasks=frontal, temporal, parietal activation in both groups WSPT: C=LinfFG (BA6,44, 45) Reduced activity in these areas in SCZ	
(Walter et al 2003)	15 SCZ (med) 15 C		N-back verbal & spatial	BOLD FMRI 1.5T Blocked design	No lateralisation effects in SCZ (i.e L for verbal & R for spatial) No hypofrontal in SCZ.	Medication effects may influence hypofrontality findings in past (atypical neuropleptics in particular)
(Weinberger et al 1996)	10 SCZ (7 med) 10 C	M	N-back	FMRI	Reduced PFC activation in (9/10 none in 2-back cdt.) SCZ, despite normal performance	More errors but otherwise normal performance
(Wexler et al 2000)	8 SCZ	4M: 4F (46)	Word serial position Over 10 weeks: 4 words same each trial; 5 words different each trial; 4 word visual different; 3 tone auditory different each trial On 2 occasions before & after verbal memory exercises	FMRI	SCZ task related activity in L inf FC with improved performance (in 9/10). 1 SCZ after 15 weeks showed normalised LinfFC.	Performance gains on verbal tests but not on tones.
(Wencel et al 2002) Abstract only	8 SCZ 12 C		N-back & cpt-x control task	FMRI	Patients activated left orbito- frontal (BA11) not seen in controls. All activated bilatDLPFC, bilat Inf Parietal (BA 40), LSTG, Ant Cing. C more than SCZ in these areas	All declined on 2 back, SCZ declined more than C. Equal performance on CPT task
VISUAL ENCODING & RECOGNITION						
(Eyler Zorrilla et al 2002)	8 SCZ 10 C	(5 F) (mean age 54) (2 F)(mean age 61)	Picture encoding & repeat presentation (control)	BOLD FMRI 1.5T Blocked design	SCZ with greatest PHG/hippocampus response during encoding were able to recognise after (+ve correlation) Only a –ve correlation in C	No differences in recognition
(Eyler Zorrilla et	9 SCZ		Picture encoding &	BOLD FMRI	4 search regions: Fusiform Gyrus, PHG, Hippocampus, IFG	-ve response in repeated relative to

Study	Sample[53]	Gender (age)	Task	Imaging technique	Activations[54]	Behavioural performance
al 2003)	10 C		repeat presentation (control)	1.5T Blocked design	Novel>repeated pictures C>SCZ hippocampus/PHG & fusiform gyrus	baseline? Failure of cognitive subtraction in SCZ?
(Gur et al 1994)	8 SCZ 18 C		Face & Word recognition	PET (xenon)	SCZ didn't show laterality changes shown by C, L-R verbal, R-L visual in mid temp region SCZ less global inc, esp in left & for verbal than C	Sensitivity (identify as seen before) was less affected than specificity (reject items as non targets) in SCZ -Lower than C both verbally and facially
(Heckers et al 2000)	9 SCZ 8 C		Visual object recog task (3D line drawings)	PET $H_2O^{15}O$ (rCBF)	New-Old: C>SCZ rCBF in RPFC (BA 10), R post Thalamus SCZ>C rCBF R post cing/precuneues Old-New SCZ>C L PFC (BA 8)	
(Leube et al 2003)	10 SCZ 10 C		Face Memory task: Scanned during Encoding only	FMRI 1.5T	Face Encoding (to be remembered later) C>SCZ: R hippoc (BA 27), R cerebellum	No differences

APPENDIX 5: Tables and figures to accompany chapter 7

Figure 5A: EHRS functional MRI information sheet

Figure 5B: Medical screening form

Figure 5C: Within scanner task instructions

Figure 5D: Post scan participant debriefing form

Figure 5A: EHRS functional MRI information sheet

Functional MRI in the Edinburgh High Risk Project

To be read with subjects before scanning

Thank you for agreeing to participate in this part of the study.

We will ask you to remove all metal objects from your person before going into the scanning room. You will then be asked to lie down on the scanner platform, when we will put head phones over your ears, put a hand-set on your dominant hand with buttons to press, and then slide the screen for giving you instructions in the scanner over your head. We will try to make sure that you can press all the buttons on the hand-set easily, that you are lying comfortably, and that you can clearly see the overhead screen. The scanner platform will then lift and slide into the scanner itself. You may hear a few clicking noises, and the scanner platform may move slightly at the beginning of each of the four scans we hope to conduct.

The first scan is simple and brief (localiser), so that the other scans can be positioned properly.

The second scan is a more detailed scan of the structure of your brain, and will last seven minutes. The scanner makes a noise rather like a fog horn at this time. It is important that you lie still, but relaxed, during the scan and in the scanner in general.

The overhead screen will give you some information and instructions at the beginning of the third scan. You will be asked to press the button to say that you are ready and then asked to press your thumb on the thumb button to start the task itself. During the task you will be asked to think of a word to finish off a sentence in which the last word is missing. We simply want you to think of a word that would finish the sentence – please do not speak while the scan is being done, as this will distort the image. Once you have thought of the first word that occurs to you press any button on the handset and wait for the next sentence. Do not worry if you cannot think of a word in time or if you do not think the word is appropriate – we are mainly interested in what you are doing when you try to think of the word, rather than the word you produce itself. Every now and then you will see a screen with circles on it, which is a rest period during which you don't have to do anything at all. This scan will take about 12 minutes in total.

The fourth and final scan is split into two stages. You will be given instructions and a brief practice session at the beginning of each stage. You will be shown a single word and asked to decide whether the object is 'living' or 'non-living'. Please press your thumb button or your first finger button (index, or pointing finger button) when you have made the decision about the word. If you are not sure about which button to press, please make a "best guess" and press the appropriate button. Again, do not worry if you are right or wrong, as we are mainly interested in what happens in the brain as you are making this decision, rather than if you get it right or wrong. The first stage of this fourth and final scans lasts about three minutes. You will then be given a practice session to get the hang of the second stage of this scan. You will be shown a word and asked to decide whether you saw it in the previous stage or not, and to press a button to indicate this. This part of the fourth and final scan will last about six minutes. Again, please make a response for each word, even if it is a 'best guess', and do not worry if you get it right or wrong.

In general, therefore, please lie still but relaxed, do not speak whilst a scan is being done, press the appropriate button when you have thought of a response and do not worry about how well you are doing. You can, of course, stop the scanning session at any time, if you wish, but the whole thing should last for less than an hour.

Figure 5B: Medical Screening Form

SHEFC BRAIN IMAGING RESEARCH CENTRE FOR SCOTLAND

SCREENING FORM #1(P)

SCREENING FORM FOR USE BY PATIENTS ENTERING THE SCANNER ROOM

Surname: First name(s):

Home address:

Date of birth: Home telephone number: Business telephone number:

Weight: Height:

CIRCLE THE CORRECT RESPONSE TO ALL OF THE QUESTIONS BELOW (IF YOU HAVE DIFFICULTY READING OR UNDERSTANDING THIS FORM, SOMEONE WILL HELP YOU):

- Do you have a cardiac pacemaker or artificial heart valve? YES/NO
- Have you ever had metal fragments in your eyes? YES/NO
- Do you have any vascular clips, a cochlear implant or a shunt *etc*? YES/NO
  If you have a shunt is it programmable?
- Have you ever had a shrapnel injury or any other injury involving metal? YES/NO
- Have you ever, at any time in your life, had any operations to your head? YES/NO
- Do you wear dentures, a dental plate, a brace, contact lenses or a hearing aid? YES/NO
- Have you had any joint replacements, Harrington rods *etc*? YES/NO
- Do you suffer from any heart disease or rhythm disorder? YES/NO
- Do you suffer from epilepsy or diabetes? YES/NO
- Have you had any recent surgery of any type (within the last six months)? YES/NO
- Are you wearing a nicotine/hormone or cardiac patch? YES/NO

Please turn over

LADIES:

- Could you be pregnant? YES/NO
- Are you breast-feeding? YES/NO
- Do you have an IUCD or sterilisation clips? YES/NO

- Reasons why it might not be safe for me to undergo Magnetic Resonance Imaging scanning have been explained to me, and I have been given the opportunity to ask questions about them. I am satisfied that I have all the information that I need to provide **informed consent.**
- I know of no reason why I should not undergo Magnetic Resonance Imaging scanning or take part in the study.
- I have removed all credit cards incorporating magnetic strips, and loose metallic objects (*e.g.* coins, keys, badges, hair grips, jewellery, hearing aids, watches, cell-phones, pagers *etc*, and documents held together with paper clips or staples), and have placed these in a secure locker or left them with a friend or relative before I enter the scanner room.

Signature of Patient (or Guardian):

Date:

Name of Radiographer:

CN Number (SBIRCS use only):

Figure 5C: Within Scanner Instructions (Flett 2000)

Word Classification Task:
You will see a list of words
Your task is to decide if the words refer to living things or nonliving objects
Press any button to continue...

To make a response press the THUMB button if the word is a LIVING thing and the INDEX FINGER button if the word is a NONLIVING object
You may respond at any point before the next word appears
Press any button to continue...

There now follows a PRACTICE run
During the practice you will be given feedback on your first response
Remember; press the Thumb button for a LIVING thing and the Index Finger button for a NONLIVING thing
Press any button to continue...

That was the end of the practice run
The real run will follow shortly
There will be a loud noise as the scan starts *(Presented for 5000 ms)*

Recognition Task:
This is a DIFFERENT task
In this task you will see another list of words
Some were presented on the screen in the living-nonliving task you have just done
Others are similar new words
Press any button to continue...

To respond press the THUMB button for YES, the word did appear in the previous list
Press the INDEX FINGER button for NO, the word did not appear in the previous list
If you are unsure then make your best guess
You may respond at any point before the next stimulus appears
Press any key to continue...

There now follows a PRACTICE run
During the practice run you will receive feedback for your response
Remember; press the Thumb button for a word you DID see in the previous list and the Index Finger button for a word you did NOT see
Press any key to continue...

That was the end of the practice run
The real run will follow shortly
There will be a loud noise as the scan starts *(Presented for 5000 ms)*

There now follows the actual task
Respond to each word as in the Practice Run
Press Thumb for an OLD, previously seen word and Index Finger for a NEW word, not previously seen
Press any button to continue... Thank you for you attention. This task is complete

Figure 5D: Post-test participant debriefing form

Edinburgh High Risk Study

Debriefing Questionnaire

To be completed by the participant and the researcher after the fMRI scan

Participant ..... Scan Date .....

1. Did you have any problems during the scan? – Yes/No (please circle)

If yes: Please state what were the main problems

.....

.....

2. Were you comfortable during the scan? – Yes/No (please circle)

If no: Please state if you were so uncomfortable as to make you move in the scanner- Yes/No (please circle)

3. **a)** In general, were you able to think of words during the Hayling sentence Completion Task? - Yes/No (please circle)

b) In general, were you able to press a button once you had thought of the words during the Hayling Sentence Completion Task? - Yes/No (please circle)

4. **a)** In general, were you able to decide whether a word was living or non living, during the Living/Non living Decision Task? - Yes/No (please circle)

b) In general, were you able to press a button once you had decided in which category a word belonged (living or non living)? Yes/No (please circle)

5. **a)** In general, were you able to decide whether you had seen a word before or not? - Yes/No (please circle)

b) In general, were you then able to press the correct button? - Yes/No (please circle)

Signature ..... Participant Date .....

Signature ..... Researcher

APPENDIX 6: Tables to accompany chapter 8

Table 6A- Random effects within group encoding contrast results

Table 6B - Random effects between group encoding contrast results

Table 6C- Random effects within group recognition versus rejection contrast results

Table 6D- Random effects between group recognition versus rejection contrast results

Table 6E- Random effects within group correct recognition versus baseline contrast results

Table 6F- Random effects between group correct recognition versus baseline contrast results

Table 6G- Random effects within group correct rejection versus baseline contrast results

Table 6H- Random effects between group correct recognition versus baseline contrast results

Table 6I- Random effects within group correct recognition versus correct rejection contrast results

Table 6J- Random effects between group correct recognition versus correct rejection contrast results

Table 6A: Maxima of significant within group differences in brain fMRI response which are greater during encoding relative to baseline experimental activation

Group comparison:	Anatomy	Hemisphere	Cluster size (K_E)	Talairach Tournoux x y z	MNI x y z	BA	Z	Cluster –level Significance (p corrected)[1]
C (+)	Medial frontal gyrus	L	222	-1 0 51	-2 –2 56	6	4.3	0.003
	Parietal lobe, pre-central gyrus	L	1922	-43 -18 59	-44 –22 64	4	4.7	<0.001
	Parietal lobe, post-central gyrus	R	199	61 –20 26	62 –22 28	2	4.4	0.006
	Superior temporal	L	243	-53 17 -9	-54 18 –10	21	5.4	0.002
	Cerebellum, declive	L	1213	-41 –61 –22	-42 –62 -30		5.3	<0.001
C (-)	Medial frontal gyrus (WM)	R	72	7 12 –15	8 14 -18	6/44	4.1	0.35/ 0.01 (unc)
	Parietal lobe, precuneus (WM)	R	28999	9 –44 46	10 –48 48	5/7	6.2	<0.001
	Middle temporal	R	75	53 –4 16	54 –4 20	21	4.4	0.32/ 0.01 (unc)
	Cerebellum, posterior, tonsil	L	304	-21 –48 -36	-22 –48 -46		4.6	<0.001
HR – (+)	Frontal lobe, sub-gyral (WM)	R	200	13 51 -22	14 54 –24	11	4.6	0.034
	Parietal lobe, post central gyrus	L	7507	-51 –28 53	-52 –32 56	2	6.6	<0.001
	Parietal lobe, post central gyrus	R	1282	65 –16 17	66 –18 18	43	5.5	<0.001
	Superior temporal gyrus	L	672	-59 13 -7	-60 14 –8	38	4.7	<0.001
	Superior temporal gyrus	R	444	57 13 -10	58 14 –12	38	4.8	<0.001
	Cerebellum, anterior, culmen	L	4408	-35 –51 -24	-36 –52 32		7.0	<0.001
	Cerebellum, posterior, tuber	R	6006	41 –59 -25	42 –60 –34		7.0	<0.001
HR - (-)	Frontal lobe, sub-callosal gyrus	L	518	-9 9 -12	-10 10-14	25	4.1	<0.001
	Limbic lobe, cingulate gyrus	R	73283	9 –42 40	10 –46 42	31	7.5	<0.001
	Cerebellum, posterior, tonsil	R	1822	5 –54 -54	6 –54 -54		4.8	<0.001
HR+ (+)	Medial frontal lobe	L	179	-1 0 55	-2 –2 60	6	4.3	0.010

[1] Results presented at height threshold p<0.001, spatial extent 20, z scores > 3, z statistic significant at p corrected for multiple comparisons, unless otherwise stated (i.e. unc = p uncorrected for multiple comparisons.

Group comparison:	Anatomy	Hemisphere	Cluster size (K_E)	Talairach Tournoux x y z	MNI x y z	BA	Z	Cluster –level Significance (p corrected)[1]
	Inferior parietal lobule	L	2908	-51 –28 47	-52 –32 50	40	5.8	<0.001
	Inferior parietal lobule	R	483	47 –40 53	48 –44 56	40	5.0	<0.001
	Superior temporal lobe	L	212	-59 11 -3	-60 12 –4	22	4.5	<0.001
	Cerebellum, anterior, culmen	L	3929	-37 –47 -26	-38 –48 -34		6.4	<0.001
	Cerebellum, posterior, tonsil	R	4071	35 –48 -32	36 –48 –42		5.6	<0.001
HR + (-)	Thalamus	R	358	9 –23 1	10 –24 0	13	5.5	<0.001
	Inferior frontal gyrus	R	115	39 23 8	40 24 10	45	4.7	0.080
	Inferior temporal gyrus	R	122	51 –23 -39	52 –22 -48	20/38	4.6	0.063
	Occipital lobe, cuneus (WM)	L	36950	-13 –82 29	-14 –86 28	19	6.2	<0.001
	Cerebellum, posterior, tonsil	L	265	-3 –54 -47	-4 -54 -60		4.4	<0.001

Table 6B: Maxima of significant between group differences in brain fMRI response which are greater during encoding relative to baseline experimental activation

Group comparison:	Anatomy	Hemisphere	Cluster size (K_E)	Talairach Tournoux x y z	MNI x y z	BA	Z	Cluster –level Significance (p corrected)[1]
C > HR	NSA							
C > HR-	NSA							
C > HR+	NSA							
HR > C	Inferior frontal gyrus	R	137	51 25 4	52 26 6	45	3.8	0.14/ 0.006 (unc)
HR- > C	Inferior frontal gyrus	R	22	52 26 2	51 25 0	45	3.4	*0.99/ 0.22 (unc)*
HR + > C	Inferior frontal gyrus	R	154	51 25 4	52 26 6	45	4.0	0.095
	Inferior parietal lobule	L	111	-45 –46 39	-46 –50 40	40	4.0	0.22/ 0.013 (unc)
HR- > HR+	Cingulate gyrus	R	91	1 –57 10	2 –60 8	31/23	4.2	0.39/0.022 (unc)
HR + > HR-	Inferior parietal lobe	L	168	-45 –57 48	-46 –62 50	40/7	3.9	0.069

[1] Results presented at height threshold p<0.001, spatial extent 20, z scores > 3, z statistic significant at p corrected for multiple comparisons, unless otherwise stated (i.e. unc = p uncorrected for multiple comparisons.

Table 6F: Maxima of significant between group differences in brain fMRI response which are greater during correct recognition (old) responses relative to baseline experimental activation

Group comparison: Correct Old P<0.001	Anatomy	Hemisphere	Cluster size (K_E)	Talairach Tournoux x y z	MNI x y z	BA	Z	Cluster –level Significance (p corrected)[1]
C > HR	NSA							
C > HR-	Frontal lobe, precentral gyrus	R	131	58 –1 30	62 –2 30	6	4.2	0.16/ 0.012 (unc)
C > HR+	NSA							
HR > C	Middle occipital gyrus	R	124	23 –98 4	24 –102 -2	18	4.1	0.19/ 0.014 (unc)
	Superior temporal gyrus (WM)	L	61	-64 –34 2	-63 –32 3	22	3.7	0.65/0.069 (unc)
HR- > C	Middle occipital gyrus	R	119	23 –98 4	24 –102 -2	18	4.5	0.21/ 0.015 (unc)
HR+ > C	NSA							
HR- > HR+	NSA							
HR+ > HR-	NSA							

[1] Results presented at height threshold p<0.001, spatial extent 20, z scores > 3, z statistic significant at p corrected for multiple comparisons, unless otherwise stated (i.e. unc = p uncorrected for multiple comparisons, NSA = No significant activations

Table 6G: Maxima of significant within group differences in brain fMRI response which are greater during correct rejection (new) responses relative to baseline experimental activation

Group comparison:	Anatomy	Hemisphere	Cluster size (K_E)	Talairach Tournoux x y z	MNI x y z		BA	Z	Cluster –level Significance (p corrected)[1]
C (+)	Inferior frontal gyrus	R	665	37 19 -6	38 20 -6		47	5.3	<0.001
	Inferior frontal gyrus (WM)	L	632	-33 19 -7	-34 20 -8		47	5.4	<0.001
	Medial frontal gyrus	L	752	-3 17 45	-4 16 50		6	4.6	<0.001
	Frontal lobe, precentral gyrus	R	249	61 3 25	62 2 28		6	5.4	0.003
	Parietal lobe, post central gyrus (WM)	L	1713	-57 -20 17	-58 -22 18		2/42	5.1	<0.001
	Temporal lobe, fusiform gyrus	L	1734	-47 -61 –17	-48 -62 -24		37	5.0	<0.001
	Cerebellum, culmen	R	1836	33 -49 -24	34 -50 -32			5.4	<0.001
C (-)	Medial frontal gyrus (WM)	R	30274	7 61 -4	8 64 -2		10	5.7	<0.001
	Middle temporal gyrus (WM)	L	617	-53 -3 -21	-54 -2 –26		21	4.3	<0.001
	Inferior temporal gyrus	R	348	57 -11 -28	58 -10 -34		20	4.3	<0.001
	Occipital lobe, cuneus	R	309	13 -86 24	14 -90 22		19/18	4.2	<0.001
HR- (+)	Orbito frontal lobe (WM)	R	1112	21 57 -18	22 60 –18		11	5.3	<0.001
	Middle frontal gyrus	R	264	45 43 16	46 44 20		46	3.9	0.009
	Inferior frontal gyrus (WM)	L	1011	-51 9 32	-52 8 36		9/44	5.0	<0.001
	Inferior frontal gyrus	L	324	-43 54 0	-44 56 2		10	4.1	0.003
	Inferior frontal gyrus (WM)	R	570	35 19 –7	36 20 –8		47	5.3	<0.001
	Inferior parietal lobule	L	6362	-39 -47 50	-40 -52 52		40	6.3	<0.001

[1] Results presented at height threshold p<0.001, spatial extent 20, z scores > 3, z statistic significant at p corrected for multiple comparisons, unless otherwise stated (i.e. unc = p uncorrected for multiple comparisons.

Group comparison:	Anatomy	Hemisphere	Cluster size (K_E)	Talairach Tournoux x y z	MNI x y z		BA	Z	Cluster –level Significance (p corrected)[1]
	Superior temporal gyrus	L	1451	-55 11 –3	-56 12 –4		22	5.9	<0.001
	Cerebellum, culmen	R	11747	35 -51 -27	36 -52 -36			7.2	<0.001
HR- (-)	Parietal lobe, precuneus (WM)	R	67459	7 –36 46	8 –40 48		7	Inf.	<0.001
HR + (+)	Orbito frontal gyrus	R	213	23 49 –19	24 52 –20		11	4.2	0.01
	Middle frontal gyrus	R	285	49 32 20	50 32 24		46	4.4	0.003
	Middle frontal gyrus (WM)	L	258	-43 45 10	-44 46 14		10	4.0	0.005
	Inferior frontal gyrus (WM)	R	516	37 19 –6	38 20 -6		46/10	4.1	<0.001
	Frontal, precentral gyrus	R	171	59 –12 30	60 –14 32		4	4.3	0.04
	Frontal precentral gyrus	L	271	-37 –6 62	-38 –10 68		4	3.9	0.004
	Inferior parietal lobule	L	2039	-47 38 55	-48 –42 58		40	4.7	<0.001
	Superior temporal gyrus	L	1050	-53 11 –3	-54 12 –4		22	4.3	<0.001
	lentiform nucleus, putamen	L	418	21 11 -7	22 12 -8			4.6	<0.001
	lentiform nucleus, putamen	R	497	-21 7 –3	-22 8 –4			5.4	<0.001
	Cerebellum, declive, posterior	L	3965	-39 –65 –20	-40 –66 –28			6.8	<0.001
	Cerebellum, culmen, posterior	R	4260	35 –65 –23	36 –66 –32			6.0	<0.001
HR + (-)	Medial frontal gyrus	L	31501	-3 50 –5	-4 52 –4		10	7.2	<0.001
	Middle temporal gyrus (WM)	R	1350	55 –8 –14	56 –8 –18		21	5.4	<0.001
	Limbic lobe, anterior cingulate	L	371	0 11 –7	0 12 –8			4.9	<0.001
	Limbic lobe, uncus	R	579	27 –1 –21	28 0 –26			4.6	<0.001
	Parahippocampal gyrus	L	274	-23 –20 –22	-24 –20 –28		35/36	4.8	0.004

Table 6H: Maxima of significant between group differences in brain fMRI response which are greater during correct rejection (new) responses relative to baseline experimental activation

Group comparison:	Anatomy	Hemisphere	Cluster size (K_E)	Talairach Tournoux x y z	MNI x y z	BA	Z	Cluster –level Significance (p corrected)[1]
C > HR	NSA							
C > HR-	NSA							
C > HR+	NSA							
HR > C	Middle occipital gyrus	R	59	23 –98 4	24 –102 0	18	3.7	0.68/0.076 (unc)
HR- > C	Middle occipital gyrus	L	143	-29 –96 4	-30 –100 0	18	3.6	0.013/0.01 (unc)
HR+ > C	NSA							
HR- > HR+	NSA							
C < HR-	NSA							

[1] Results presented at height threshold p<0.001, spatial extent 20, z scores > 3, z statistic significant at p corrected for multiple comparisons, unless otherwise stated (i.e. unc = p uncorrected for multiple comparisons.

Table 6I: Maxima of significant within group differences (random effects) in brain fMRI response between correct recognition (old) responses relative to correct rejection (new) responses.

Group comparison: C old > Cnew	Anatomy	Hemisphere	Cluster size (K_E)	Talairach Tournoux x y z	MNI x y z	BA	Z	Cluster –level Significance (p corrected)[1]
C	Parietal lobe, post central gyrus	L	100	-63 -19 43	-64 –18 48	2	4.0	0.1/ 0.005(unc)
HR-	Limbic lobe, parahippocampus	L	959	-15 –4 -13	-16 –4 16	34	5.1	<0.001
	Inferior parietal lobule	R	48	37 –59 43	38 –64 44	7	4.0	0.76/ 0.08 (unc)
HR+	Middle frontal gyrus	L	646	-43 38 -8	-44 40 -8	47	5.2	<0.001
	Superior frontal gyrus (WM)	L	111	-25 56 -6	-26 58 –4	10	4.1	0.14/ 0.005(unc)
	Superior frontal gyrus (WM)	R	86	-25 57 -6	26 60 -4	10	4.1	0.30/ 0.009(unc)
	Cerebellum, anterior lobe	R	66	35 –53 -29	36 –54 –38		4.0	0.52/ 0.02 (unc)
	Cerebellum, pyramis, posterior	L	78	7 –77 -29	8 –78 -40		3.7	0.38/ 0.016 (unc)
Cnew > C old								
C	Medial frontal gyrus	L	79	-7 45 16	-8 46 20		4.5	0.31/0.01 (unc)
	Occipital lobe, lingual gyrus	R	196	15 –46 –2	16 –48 -6	19	4.1	0.009
	Cerebellum, culmen	L	132	-19 –52 -9	-20 –54 -14		4.1	0.057
HR-	Occipital lobe, cuneus (WM)	R	349	21 –84 28	22 –88 26		5	<0.001
	Occipital lobe, cuneus	L	282	-17 –86 22	-18 –90 20	18	4.8	0.005
	Middle temporal gyrus (WM)	R	134	43 –78 18	44 –82 16	19	3.9	0.13/ 0.006 (unc)
HR+	Orbito-frontal gyrus	L	51	-8 50 -30	-7 47 -27	11	4.0	0.73/0.04 (unc)
	Superior temporal gyrus	L	54	-45 –57 15	-46 –60 14	22	4.6	0.69/ 0.04 (unc)
	Cerebellum, tonsil, posterior	L	56	-27 –38 -35	-28 –38 -44		4.6	0.66/ 0.04 (unc)

[1] Results presented at height threshold p<0.001, spatial extent 20, z scores > 3, z statistic significant at p corrected for multiple comparisons, unless otherwise stated (i.e. unc = p uncorrected for multiple comparisons.

Table 6J: Maxima of significant between group differences in brain fMRI response between correct recognition (old) responses relative to correct rejection (new) responses

Group comparison: Correct Old > Correct New	Anatomy	Hemisphere	Cluster size (K_E)	Talairach Tournoux x y z	MNI x y z	BA	Z	Cluster –level Significance (p corrected)[1]
C > HR	NSA							
C > HR-	NSA							
C > HR+	NSA							
HR > C	Inferior frontal gyrus (WM)	L	63	-45 23 4	-46 24 6	45	3.6	0.69/ 0.052 (unc)
	Middle temporal gyrus	R	77	55 –5 –24	56 –4 30	20/21	4.0	0.53/ 0.034 (unc)
	Cerebellum, culmen, anterior	L	61	-9 –56 -2	-10 –58 -6		3.5	0.71/0.05 (unc)
	Cerebellum, pyramis, posterior	L	58	-77 –77 -26	-8 –78 -36		3.9	0.74/0.061 (unc)
	Cerebellum, tuber, posterior	R	388	9 –59 –27	40 –60 -36		4.4	<0.001
HR- > C	Cerebellum, culmen, anterior	L	183	-1 –46 –6	-2 –48 –10		3.9	0.05
	Cerebellum, culmen, anterior	R	202	27 –53 -17	28 –54 -24		3.9	0.03
HR+ > C	Middle temporal gyrus	R	106	55 –5 -24	56 –4 -30	20/21	4.6	0.29/ 0.01 (unc)
	Cerebellum, tuber, posterior	R	300	39 –59 -28	40 –60 -38		4.4	0.005
	Cerebellum, culmen, anterior	L	162	-29 –53 -17	-30 –54 -24		3.9	0.084
HR- > HR+	Thalamus, ventral anterior nuc.	R	190	13 –5 11	14 –6 16		4.1	0.04
HR+ > HR-	Middle frontal gyrus (WM)	L	96	-43 36 -3	-44 38 -2	11/47	3.6	0.36/ 0.02 (unc)

Table 6K: Levene's test of homogeneity of variance of groups for encoding and retrieval response measures

Test Measures	Levene Statistic	df1	df2	Sig.
EncIncorrect	.311	2	86	.734
Enccorrect	.247	2	86	.782
EncNoresp	1.989	2	86	.143
RetIncorrect responses made	2.175	2	86	.120
RetCorrect responses made	.155	2	86	.857
RetNo resp	2.550	2	86	.084
False positives	.657	2	86	.521
False negatives	.097	2	86	.908
True Positives	.320	2	86	.727
True negative	.106	2	86	.900
Old	.076	2	86	.927
New	.401	2	86	.671
Enc RT	.077	2	86	.926
Ret RT	.308	2	86	.736
RTincorrect	.407	2	86	.667
RTcorrect	.062	2	86	.939
RTcorrectNew	.195	2	86	.823
RTcorrectOld	.020	2	86	.980

Table 6L: Tests of normality at each level of the independent variable (C, HR- & HR+) for each encoding and retrieval response measure

Test measure	Symptom status	Kolmogorov-Smirnov		
		Statistic	df	Sig.*
EncIncorrect	CONTROL	.444	21	**.000**
	HR-	.296	41	**.000**
	HR+	.267	27	**.000**
Enccorrect	CONTROL	.444	21	**.000**
	HR-	.284	41	**.000**
	HR+	.267	27	**.000**
Enc RT	CONTROL	.323	21	**.000**
	HR-	.227	41	**.000**
	HR+	.303	27	**.000**
RetIncorrect	CONTROL	.138	21	.200
	HR-	.124	41	.112
	HR+	.134	27	.200
RetCorrect	CONTROL	.251	21	**.001**
	HR-	.169	41	.005
	HR+	.143	27	.163
False negatives	CONTROL	.113	21	.200
	HR-	.118	41	.166
	HR+	.225	27	**.001**
True Positives	CONTROL	.180	21	.073
	HR-	.110	41	.200
	HR+	.117	27	.200
True negative	CONTROL	.143	21	.200
	HR-	.152	41	.018
	HR+	.187	27	.017
Old	CONTROL	.191	21	.045
	HR-	.087	41	.200
	HR+	.146	27	.148
New	CONTROL	.179	21	.078
	HR-	.114	41	.200
	HR+	.127	27	.200
Ret RT	CONTROL	.234	21	.004
	HR-	.190	41	**.001**
	HR+	.186	27	.018
RTincorrect	CONTROL	.195	21	.037
	HR-	.240	41	**.000**
	HR+	.201	27	.007
RTcorrect	CONTROL	.290	21	**.000**
	HR-	.209	41	**.000**
	HR+	.217	27	.002
RTcorrectNew	CONTROL	.213	21	.014
	HR-	.188	41	**.001**
	HR+	.214	27	.003
RTcorrectOld	CONTROL	.241	21	.002
	HR-	.193	41	**.001**
	HR+	.198	27	.008