The Neural Correlates of Allocentric Spatial Memory in Schizotypy

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The Neural Correlates of Allocentric Spatial Memory in Schizotypy

Thesis submitted to Kings College London for the degree of Doctor of Philosophy.

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Abstract

In this thesis, allocentric spatial memory was investigated in healthy volunteers with average and high levels of schizotypal traits assessed using the Schizotypal Personality Questionnaire. Functional and structural MRI was used to investigate the neural correlates of allocentric spatial memory in schizotypal personality.

Allocentric spatial memory is reported to be impaired in schizophrenia and this is thought to be related to alterations in hippocampal function and structure. Previous literature suggests individuals with schizotypal personality traits have a similar cognitive and neural profile to schizophrenia spectrum disorders for example reduced hippocampal volumes and compromised cognition. It was therefore hypothesised that high schizotypy would be associated with worse performance on these tasks and a different pattern of functional activation in the hippocampus and parahippocampal gyrus compared to controls.

No behavioural differences were observed on the cognitive measures in this thesis. Investigation of brain function revealed decreased volume of the right hippocampus and bilateral medial frontal gyrus and increased volume of the posterior cingulate, superior temporal gyrus and anterior prefrontal cortex, in line with previous literature. Functional MRI revealed decreased activation of the right hippocampus during memory encoding and increased activation of the hippocampus bilaterally during memory retrieval in high schizotypy compared to controls. Memory retrieval was also associated with increased activation of the anterior cingulate gyrus, inferior frontal gyrus and insular cortex in this group. Further, activation of the right hippocampus is related to better performance across allocentric spatial memory tasks in controls but this relationship is absent in high schizotypy.

The results suggest that high schizotypy is associated with structural and functional alterations of the right hippocampus compared to controls. Increased activation of frontal-limbic regions and comparative behavioural performance may reflect a use of compensatory mechanisms in healthy volunteers with schizotypal traits, in line with existing models of schizotypal personality.

Declaration

I declare that all the work in this thesis is original and my own except where otherwise specified.

Katrina McMullen

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Acknowledgements

Abbreviations

Abbreviation	Full Term
AC-PC	Anterior Commissure – Posterior Commissure
ACC	Anterior Cingulate Cortex
ANCOVA	Analysis of Co-Variance
ARMS	At Risk Mental States
BA	Brodmann Area
BOLD	Blood Oxygenated Level Dependent
CA	Cornu Ammonis
CNS	Central Nervous System
COMT	Catechol-O-Methyltransferase
CPT	Continuous Performance Task
CSF	Cerebrospinal Fluid
CVLT	California Verbal Learning Test
DAAO	D-Aminoacid Oxidase
DARTEL	Diffeomorphic Anatomical Registration Through Exponential Lie Algebra
DISC1	Disrupted In Schizophrenia 1 (DISC1)
DLPFC	Dorsolateral Prefrontal Cortex
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders Third Edition Revised.
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DTNBMP1	Dysbindin
DZ	Dizygotic Twins
EC	Entorhinal Cortex
FD	Fascia Dentata
fMRI	Functional Magnetic Resonance Imaging
GM	Grey Matter
GMV	Grey Matter Volume
GLM	General Linear Model
HATA	Hippocampal Amygdaloid Transition Area
IQ	Intelligence Quotient
ICA	Independents Component Analysis
LH	Left Hemisphere
LI	Latent Inhibition
Lirr	Learned Irrelevance
LNS	Letter Number Sequencing
MRI	Magnetic Resonance Imaging
MWM	Morris Water Maze
MZ	Monozygotic Twins
NRG1	Neuregulin 1
PHG	Parahippocampal Gyrus

PPI	Prepulse Inhibition
RAM	Radial Arm Maze
RFT	Random Field Theory
RGS-4	Regulator of G protein Signaling 4 (RGS-4
RH	Right Hemisphere
ROI	Region of Interest
SPD	Schizotypal Personality Disorder
SPM	Statistical Parametric Mapping
SPQ	Schizotypal Personality Questionnaire
SPQ-B	Schizotypal Personality Questionnaire Brief
SPSS	Statistical Package for Social Sciences
SUB	Subiculum
VBM	Voxel Based Morphometry
WAIS-R	Wechsler Adult Intelligence Scale Revised
WCST	Wisconsin Card Sorting Task
WFU	Wake Forest University
WM	White Matter

Chapter 1: Introduction to schizotypy

1.1 Concept of Schizotypy

1.1.1 Continuum of Psychosis

It has been suggested that the psychosis phenotype can be expressed at sub-clinical levels commonly referred to as psychosis proneness, psychotic experiences or schizotypy(Crow, 1998; Johns & van Os, 2001; P. E. Meehl, 1962; Siever, Kalus, & Keefe, 1993; Stefanis et al., 2002; van Os, Hanssen, Bijl, & Ravelli, 2000; Vollema, Sitskoorn, Appels, & Kahn, 2002). A psychosis continuum implies that symptoms reported in psychotic disorders can be measured in non-clinical populations (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009).

Epidemiology studies have provided support for the continuity of psychotic experiences in the general population (Johns & van Os, 2001; van Os, et al., 2000; van Os, Hanssen, Bijl, & Vollebergh, 2001). These psychotic experiences typically manifest as unusual beliefs, perceptual abnormalities, a lack of interpersonal skills and disorganised/odd speech and behaviour (Raine, 2006; Siever, et al., 1993). Empirical evidence for the continuity of psychosis comes from research into genetics, psychophysiology and neuropsychology of schizophrenia(van Os, et al., 2009), supporting the idea that multiple genes contribute to the inheritance of personality traits that define an individual's disposition for psychosis (Claridge, 1985).

This chapter will provide an outline of the historical origin of the schizotypy construct, the three main theoretical models of schizotypy and the related issues of measurement and factor

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structure. The relationship between schizotypy and schizophrenia will be discussed in light of the genetic and non-genetic (environmental) literature.

1.1.2   Historical Background

The origin of sub-clinical psychosis expression can be traced back to observations of personality types in relatives of schizophrenia patients in the early twentieth century. Eugen Bleuler (1911)[1] introduced the phrase *latent schizophrenia* to describe a less severe, non-psychotic presentation of schizophrenia.   Bleuler characterised latent schizophrenia as possessing all the symptoms of schizophrenia but within normal limits. He also proposed that latent schizophrenia was more frequent than clinical schizophrenic illness and that they shared a common etiology based on his observations of a familial link between the two forms.   Contemporaries of Bleuler's also reported a familial non-psychotic presentation of schizophrenia in relatives of patients with schizophrenia (Kallman, 1938; Kretschmer, 1970; Rosanoff, 1911)

At the same time investigators also noted a non-psychotic variant of schizophrenia in individuals without a familial link to the disorder. Zilboorg(1941) coined the term "ambulatory schizophrenia" to describe patients characterised by schizophrenia like autism and absence of intimate relationships. Deutsch (1942) described the "as if personality" characterised by lack of affective connection to work or others and by a lack of personal identity. Hoch and Polatin (1949) coined the term "pseudoneurotic schizophrenia" to describe patients who possessed schizophrenia-like symptoms particularly brief psychotic episodes.

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[1] Emil Kraepelin also proposed that a non-psychotic form of schizophrenia existed but this was during a later revision of his seminal book on dementia praecox.

The term schizotype was first proposed by Rado in 1953 as an abbreviation of "schizophrenic genotype" and was intended to reflect the genetic predisposition to schizophrenia. The key feature in schizotypal psychopathology was the inability to experience pleasurable emotions, what Rado called an "integrative pleasure deficiency". Rado saw the course of the schizotypal personality as moving backward and forward among a compensated state, a decompensated state, a disintegrated state and a deteriorating state. Compensated schizotypes on the one hand would go through life without ever experiencing a psychotic break whilst decompensated schizotypes are those that have become overtly schizophrenic but may return to a compensated state with the right treatment (Rado, 1953).

1.1.3 Theoretical models of schizotypy

There have been three major theoretical models of schizotypal personality: the *quasi-dimensional* model (P. E. Meehl, 1962; Rado, 1953) which places the psychosis continuum within the realm of illness; the *totally dimensional* model (H. J. Eysenck, 1947; H. J. Eysenck & S. B. Eysenck, 1975; H. J. Eysenck & Eysenck, 1977), based in personality theory and which makes no distinction between enduring personality traits and signs of abnormality; and the *fully dimensional* model (Claridge, 1997), which is an extension of the quasi dimensional model to include personality traits but also proposes that there is a discontinuity of function which demarcates the line between healthy psychosis and disease.

Extending the work of Rado, Meehl (1962) sought to specify the nature of the genetic contribution to schizophrenia concluding that only an "integrated neural deficit" (termed "hypokrisia") could be thought of as inherited. The effect of hypokrisia on the brain is characterised by an "insufficiency of separation, differentiation, or discrimination" in neural transmission that amounts to "ubiquitous anomaly of synaptic control with the central nervous system", termed "schizotaxia" (P. E. Meehl, 1990). Meehl contended that the expression of

schizotypy depends on interaction of environmental factors and presence of other personality traits (termed "polygenic potentiators") so that all individuals with schizotaxia will demonstrate schizotypal traits but only a small group of these persons will develop schizophrenia (Vollema & van den Bosch, 1995). Like Rado, Meehl's model proposes that schizotypy (as a personality organisation reflective of a latent liability for schizophrenia) can manifest itself behaviourally and psychologically in various degrees of clinical compensation. Schizotypes therefore can range from apparent normality through psychosis, yet they will all share the "schizogene" and resultant schizotypic personality organisation(Lenzenweger & Korfine, 1992).

Meehl's model is quasi-dimensional as it places the continuity of function within the schizophrenia spectrum completely in the abnormal/illness domain by making the distinction between signs of health and signs of disease. Within this model, schizotypic expression is a sign of abnormality.

In contrast to Meehl's quasi-dimensional model of schizotypy, the totally dimensional model places schizotypal personality within the normal personality domain. In personality psychology the concept of dimensionality refers to continua that describe smoothly varying individual differences in healthy functioning that may have no reference point in abnormality (Claridge, 1997). Eysenck (1960) proposed that psychotic illness was the extreme end of a continuous personality dimension arising from naturally occurring variation in CNS functioning. However, Eysenck's theory has been criticised for its failure to account for the discontinuities between traits and symptoms implied in the transition from normal personality to illness (Claridge, 1997). As Graham Foulds (1965) pointed out there is a logical distinction to be made between personality traits and the symptoms of illness.

This has led to the development of the *fully* dimensional model proposed by Claridge (1985). Historically the notion of "schizoid personality" has been seen as both personality deviation and

as an incipient sign of disease (Claridge, 1997). Kretschmer (1970) considered schizoid qualities to be both clinical manifestations and traits of normal temperament. Schizophrenia was the end point of a dimension of normal temperament called schizothymia which had an intermediary form termed "schizoid." Figure 1 demonstrates how the fully dimensional model can be conceptualised.
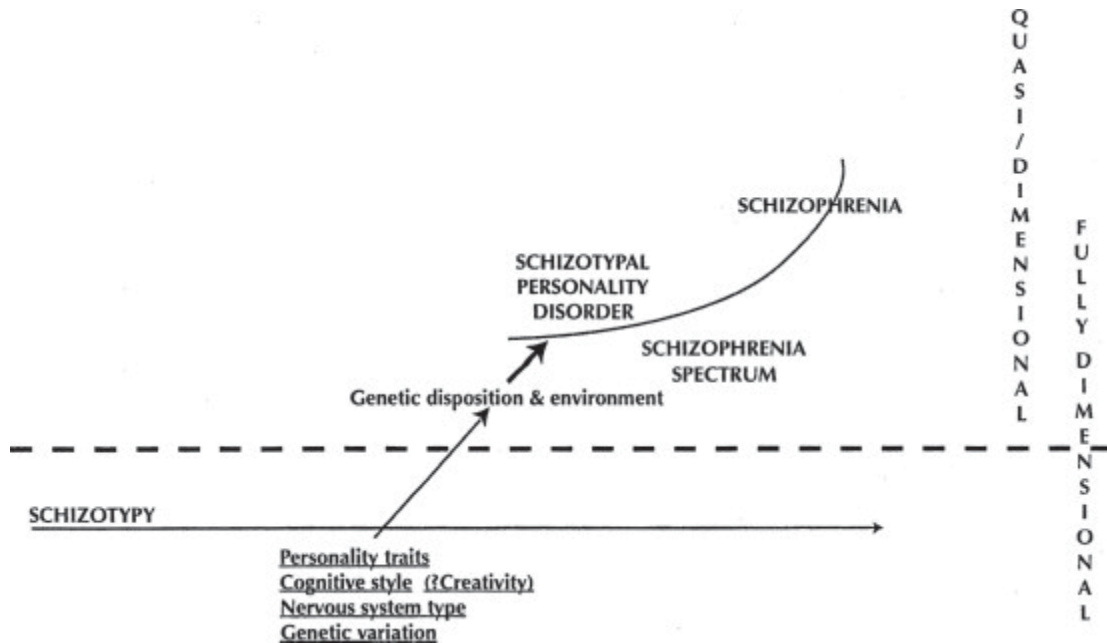
Figure 1 Comparison between quasi-dimensional and fully dimensional continuity models of psychosis (Claridge, 1997).

According to Claridge, schizophrenia is an exaggeration of the cognitive and personality characteristics found in the general population (Claridge, 1972). What connects the illness and personality domain is that the latter describes predisposition to the former whilst remaining part of normal variation (Claridge, 1987). Claridge argued that parallels can be drawn between mental illness and systemic diseases such as hypertension which could both be seen as arising from a breakdown in the otherwise normal functioning of a biological system. Just as normal individual variations in blood pressure may predispose a person to hypertension-related diseases, normal individual variations in schizotypy may predispose a person to schizophrenia(Claridge,

1987). Thus, continuity exists both in the normal individual variation but also in expression of disease once a threshold had been passed between adaptive and maladaptive functioning. Consistent with Meehl (1990) Claridge argued that the outcome of an individual's genetic predisposition to disorder will be determined by an interaction between the underlying disposition and environmental and developmental factors.

1.2 Clinical significance of schizotypy

Individuals with schizophrenia who receive treatment early in the course of the disorder are reported to have better outcomes than those who receive treatment later in the course of the illness. This is evidenced by fewer cognitive deficits, less severe negative symptoms, greater treatment compliance, better social functioning and decreased risk of relapse (Edwards, Maude, McGorry, Harrigan, & Cocks, 1998; Haas, Garratt, & Sweeney, 1998; Johnstone, Crow, Johnson, & MacMillan, 1986). Accurate identification of at-risk individuals provides means with which to study the development of psychotic disorders like schizophrenia and to examine the factors that serve to potentiate this risk or conversely serve as protective factors. The ultimate goal of this research is to facilitate early treatment and preventative measures.

Several ways of studying "at risk" groups have been proposed. The genetic high risk approach involves identifying individuals with a first degree relative with schizophrenia whereas the clinical approach is to either identify people with schizotypal personality disorder (SPD) or those experiencing brief, intermittent psychotic episodes. Ultra high risk paradigms involve recruiting individuals currently in the prodromal state with or without additional genetic liability (sometimes termed At Risk Mental States [ARMS]) and it has been suggested that a combination of genetic liability and schizotypal trait expression also constitutes a ultra high risk group(Diwadkar, Montrose, Dworakowski, Sweeney, & Keshavan, 2006). Other high risk

strategies have focused on individuals at risk of schizophrenia due to intellectual impairments (Moorhead et al., 2009).

Of interest to this thesis is the psychometric high risk paradigm, which involves recruitment of individuals who express high levels of schizotypal traits. Individuals who report high levels of schizotypal traits have shown similar patterns of performance as schizophrenia patients on several cognitive, psychophysiological and neuropsychological domains and these findings are reviewed in Chapter 2. Additionally, it has been suggested that high scores on measures of schizotypy have high predictive validity for development of a psychotic disorder and these finding are reviewed later in this chapter. Research therefore has focussed much attention on the development of accurate psychometric measures aimed at capturing the observable psychological traits of schizotypy and in development of endophenotypes that capture the behavioural correlates of schizotypy.

1.3   Measurement of schizotypal traits

1.3.1   Questionnaire measurement of schizotypy

A vast range of self-report questionnaires have been developed to measure schizotypy and similar constructs like psychosis proneness or psychoticism. These scales have all been developed from different perspectives; some are symptom or syndrome based whilst others lie solely in the personality domain. However, all three approaches are based on the assumption that schizotypal traits and schizophrenia psychosis are points on a continuum (Bentall, Claridge, & Slade, 1989). Table 1 lists the most common schizotypy/schizotypal trait questionnaires.

Table 1 Scale for the measurement of schizotypal and psychosis proneness traits

Scale	References	Measurement
Perceptual Aberration Scale (PAS)	Chapman et al. (1978)	Perceptual Aberration
Magical Ideation Scale (MIS)	Eckblad and Chapman (1983)	Magical Ideation
Physical Anhedonia Scale (PhA)	Chapman et al. (1976)	Physical Anhedonia
Social Anhedonia Scale (SA) Social Anhedonia Scale (revised)	Chapman et al (1976) Eckblad et al (1982)	Social Anhedonia
Impulsive Non-conformity Scale (IN)	Chapman et al. (1984)	Impulsive and non-conformist behaviour
Psychotism Subscale (P) (revised)	Eysenck and Eysenck (1975) Eysenck et al (1985)	Predisposition to psychosis
Schizoidia Scale	Golden and Meehl (1979)	Schizotypy
Schizotypal Personality Scale (STA)	Claridge and Broks (1984)	Schizotypal personality
Schizophrenism	Nielson and Peterson (1976)	Hypersensitivity and cognitive dysfunctions
Hallucination Scale (LSHS)	Launay and Slade (1981)	Predisposition to hallucinations
Schizotypy Scale (SS)	Venables et al. (1990)	Positive and negative schizotypy
Rust Inventory of Social Cognitions (RISC)	Rust (1988)	Positive symptoms of schizotypy
Schizotypal Personality Questionnaire (SPQ) (brief version SPQ-B)	Raine (1991) Raine and Benishay (1995)	Schizotypal personality disorder Brief version of the SPQ
2-7-8 Minnesota Multiphasic Personality Inventory (MMPI)	Lachar (1974)	The 2-7-8 refers to the scales of the MMPI relevant to schizotypy (2 depression, 7 psychasthenia and 8 schizophrenia)
Cognitive Slippage Scale	Miers and Rawlin (1985)	Cognitive Slippage
Community Assessment of Psychic Experiences (CAPE)	Stefanis et al (2002)	Positive schizotypal traits (unusual beliefs and experiences)
Oxford Liverpool Inventory of Feelings and Experiences (OLIFE)	Mason & Claridge (2006)	Schizotypy
Peters Delusion Inventory (PDI)	Peters et al (1999)	Delusion proneness
Paranoia/Suspiciousness Questionnaire (PSQ)	Rawlings & Freeman (1996)	Paranoia

The earliest schizotypy scales focused on the measurement of vulnerability for specific symptoms of schizophrenia, including perceptual aberration (Chapman, Chapman, & Raulin, 1978), magical ideation (Eckblad & Chapman, 1983) physical and social anhedonia (Chapman, Chapman, & Raulin, 1976), hypomania personality traits (Eckblad & Chapman, 1986), hallucination proneness (Launay & Slade, 1981) and more recently delusion proneness (E. R. Peters, Joseph, & Garety, 1999) and paranoia (D. Rawlings & Freeman, 1996). Personality measures such as the P scale of the EPQ and the revised EPQ-R (H. J. Eysenck & S. B. Eysenck, 1975) were designed to measure psychosis-proneness but were found to be more adept at measuring antisocial, impulsive and nonconformity traits. Other psychometric scales have been developed based on the psychiatric classification systems for schizotypal personality disorders (Raine, 1991) and/or borderline personality disorder (Claridge & Broks, 1984). The recent development of psychometric scales has been based upon the observed factor structure of schizotypal traits for example the Oxford Liverpool Inventory of Feelings and Experiences (Burch, Steel, & Hemsley, 1998).

The use of self-report measures is not without its limitations. People may not wish to admit to having certain personality traits or experiences. As David Funder (2007) has pointed out, some people are not able to tell you everything about themselves either due to memory problems, repression and/or lack of insight. This may be relevant to schizotypy research as some aspects of the schizotypal personality for example odd speech, aloofness and poor non-verbal communication is not easy to assess by self-report.

1.3.2 Multidimensionality of schizotypy

Exploratory (Andreasen, Arndt, Alliger, Miller, & Flaum, 1995) and confirmatory (Lenzenweger & Dworkin, 1996) factor analytic studies have suggested that schizophrenia is best organized

into three factors: positive symptoms or reality distortion (hallucinations, delusions), negative symptoms (blunted affect) and cognitive disorganization (thought disorder).

Factor analytic studies of schizotypal traits in the general population have provided evidence for up to four psychometrically distinct schizotypal dimensions depending upon the range and content of the scales included (Vollema & van den Bosch, 1995).

The most comprehensive measure of schizotypal personality is the Combined Schizotypal Traits Questionnaire (Claridge et al., 1996) which comprises 18 self-report scales with a total of 420 items. Scales included in the CSTQ were as follows:

- Schizotypy Questionnaire (STQ) - STA and STB scales (Claridge & Broks, 1984)

- Physical & Social Anhedonia scales (Chapman, et al., 1976)

- Perceptual Aberration Scale (Chapman, et al., 1978)

- Magical Ideation Scale (Eckblad & Chapman, 1983)

- Launay Slade Hallucinations Scale (Launay & Slade, 1981)

- Schizophrenism scale (Nielsen & Petersen, 1976)

- MMPI Schizoidia scale (Golden & Meehl, 1979)

- Delusions Symptoms (Grandeur; Disintegration; Persecution; Contrition) (Foulds & Bedford, 1975)

- E, N, P, L (EPQ) scales (H. J. Eysenck & S. B. Eysenck, 1975)

Exploratory factor analysis of the CSTQ scales, using an iterative maximum likelihood method with oblique simple structure rotation, produced four schizotypal factors reflecting 'perceptual

aberration', 'cognitive disorganisation', 'introverted anhedonia' and 'impulsive non-conformity' (Claridge, et al., 1996). This four factor solution attained a ±.10 hyperplane count of 35.7%. Boyle (1998) re-analysed the CSTQ data using a different sample but the same methods extracting five factors relating to 'positive schizotypy', 'extraverted personality', neurotic personality', and 'psychopathic personality'. This five factor model attained a ±.10 hyperplane count of 48.9% suggesting a better approximation to simple structure criteria that that obtained by Claridge et al (1996). These findings extended those of Claridge et al (1996) and highlighted the distinction between positive and negative schizotypal traits which were shown to be distinct from Eysenckian personality dimensions. The inclusion of the EPQ scales in the CSTQ may explain why factors emerged relating to antisocial and psychopathic personality disorders such as 'impulsive non-conformity' and 'psychopathic personality'. These factors are not specific to schizotypal personality (P. H. Venables & Rector, 2000) and are not a feature of schizophrenia either (Cochrane, Petch, & Pickering, 2010; Vollema & van den Bosch, 1995).

In contrast to the CSTQ which attempted to measure all aspects of schizotypy as well as related personality dimensions, the schizotypal personality questionnaire (Raine, 1991) was designed to specifically measure the nine schizotypal personality traits as listed in the Diagnostic and Statistical Manual of Mental Disorders Third Edition-Revised (DSM-III-R) diagnostic criteria for SPD. Raine (1994) reported that the three factor solution which consisted of what he termed cognitive perceptual, interpersonal and disorganised components provided a good fit of the data. Evidence for a three factor structure has been reported using multiple paradigms and populations including the biological relatives of schizophrenics(e.g. Calkins, Curtis, Grove, & Iacono, 2004), psychiatric outpatients (e.g. Battaglia, Cavallini, Macciardi, & Bellodi, 1997) personality-disordered patients (e.g.Bergman et al., 1996), inpatient adolescents (e.g. Axelrod, Grilo, Sanislow, & McGlashan, 2001), community adults (e.g.Reynolds, Raine, Mellingen, Venables, & Mednick, 2000), community adolescents (e.g. W. J. Chen, Hsiao, & Lin, 1997), high school

students (e.g. Fossati, Raine, Borroni, & Maffei, 2007), undergraduates (e.g. Raine, et al., 1994) and military conscripts (Stefanis et al., 2004). This three factor structure appears to be invariant to sex, gender, ethnicity, religion or social background (Reynolds, et al., 2000). In an assessment of two and three factor models using Generalised Multidimensional Rasch Models (GMRMs) of SPQ responses Vollema and Hoijink (2000) reported that the three factor model of 'positive schizotypy', 'negative schizotypy' and 'disorganised' provides the best fit to the data.

Therefore, across factor analytic studies positive and negative schizotypal traits consistently emerge. The third factor to emerge is contentious but generally reflects some form of cognitive disorganisation and/or social anxiety. Bentall et al (1989) have argued that this factor "appears to refer to the social anxiety aspects of schizotypy" and "it might also be argued that this factor reflects a degree of cognitive disorganisation as the scales loading on this factor also tend to include items pertaining to attentional difficulties and distractibility".

Consideration must also be given to the relationship between schizotypy dimensions and the five factor model (FFM), which suggests all personality can be explained by five general traits of extraversion, neuroticism, agreeability, openness to experience and conscientiousness (B. P. O'Connor, 2002). Studies that have sought to explain personality disorders using the five factor model have found that individuals with schizotypal personality disorder demonstrate high levels of neuroticism and low levels of agreeability and extraversion whilst no relationship is observed between schizotypal traits and openness to experience or conscientiousness (Samuel & Widiger, 2008; Saulsman & Page, 2004). It is interesting that openness to experience, which includes traits of fantasy, is not related to SPD; it would be anticipated that these traits should be related to the cognitive perceptual features of SPD. A general criticism of the five factor model of personality disorders is that the five domains are simply to broad to have any real diagnostic utility.(Clark, 1993). Of interest, the same personality traits that are related to SPD (high

neuroticism, low extraversion and low agreeability) are also found to be related to schizophrenia (Camisa et al., 2005).

Thus at a phenotypic level, schizotypic signs and symptoms bear some resemblance, in an attenuated form, to schizophrenia manifestations and they are also organized in a similar fashion at the latent level (Lenzenweger, 2010).

1.3.3 The Schizotypal Personality Questionnaire

The SPQ is used extensively as a measure of schizotypal traits and is one of the most reliable and validated measures of schizotypy used today. As mentioned above the SPQ was developed based on the nine features of schizotypal personality disorder as defined in the DSM-III-R (APA, 1994) ideas of reference, odd beliefs or magical thinking, unusual perceptual experiences, odd thinking and speech, suspiciousness or paranoid ideation, inappropriate or constricted affect, odd behaviour, lack of close friends and excessive social anxiety.

1.3.3.1 Development of the SPQ

A sample of 302 undergraduates, divided into two groups of 151 per group was used in the construction of the SPQ. A second sample of 195 undergraduates was used as a replication sample to test reliability. A pool of 110 items was generated from four sources. Firstly, existing interview schedules for schizophrenia and schizotypal personality including the Present State Examination (Wing, Cooper, & Sartorius, 1974) the Scale for the Assessment of Negative Symptoms (Andreasen, 1982), the Structured Clinical Interview for DSM-III-R Personality Disorders (Spitzer, Williams, & Gibbon, 1987) and the Schedule for Affective Disorders (Endicott & Spitzer, 1978) were used. Second, new items were modelled on examples of schizotypal traits outlined in DSM-III-R(APA, 1994). Third, items were included from other questionnaire measures including the STA scale (Claridge & Broks, 1984) , Schizotypy Scale (P.

Venables, Wilkins, Mitchell, Raine, & Bailes, 1990) Perceptual Aberration Scale (Chapman, et al., 1978)and Magical Ideation Scale (Eckblad & Chapman, 1983). Fourth, the author included items of his own to fill gaps in the item pool. Percentage of contributions were as follows: interviews (34%), DSM-II-R (8%), questionnaires (18%), author generated (40%). Items were deleted if they were not endorsed by at least 10% in each of the samples, if the corrected total item correlation was below 0.15 and additional items were removed if they did not appreciably reduce the coefficient alpha for that subscale. To increase the reliability of nine of the subscales, items were added when the questionnaire was given to the second sample and 8 of these items added to the final questionnaire. This made a total of 74 items in the final questionnaire.

1.3.3.2 Reliability and Validity of the SPQ

Two scales, the STA (Claridge & Broks, 1984) and the Schizophrenism scale of the Schizotypy Questionnaire (P. Venables, et al., 1990) were administered to sample 1 to test for convergent validity. As these questionnaires were also used to generate items in the SPQ, items were corrected for this overlap. Convergent validity between the SPQ and the STA was 0.81 (sample 1) and 0.81 (sample 2) and for Schizophrenism 0.59 (sample 1) and 0.65 (sample 2). Divergent validity was tested by administering questionnaires that should not tap schizotypal traits. These included the anhedonia scale of the Schizotypy Questionnaire (P. Venables, et al., 1990) and the Psychoticism scale of the Eysenck Personality Questionnaire (H. J. Eysenck & S. B. Eysenck, 1975). Divergent validity between the SPQ and Anhedonia was 0.19 (sample 1) and 0.37 (sample 2). Two month test-retest reliability was 0.82. Internal reliability and normative means are reported in Table 2.

Table 2 Internal reliability, means and standard deviations for the SPQ in two independent samples

SPQ items	Sample 1				Sample 2			
	Alpha	Mean	SD	Range	Alpha	Mean	SD	Range
Ideas of Reference	0.71	5.19	2.4	0-9	0.71	4.33	2.4	0-9
Social Anxiety	0.72	3.67	1.9	0-7	0.68	3.06	2.0	0-7
Odd beliefs/magical thinking	0.81	2.23	2.0	0-7	0.75	1.99	2.1	0-7
Unusual perceptual experiences	0.71	2.82	2.2	0-9	0.73	2.83	2.2	0-9
Eccentric odd behaviour and appearance	0.76	2.03	1.5	0.4	0.74	1.92	1.4	0-4
No close friends	0.67	2.24	2.1	0-9	0.74	2.36	2.0	0-9
Odd speech	0.70	3.99	1.8	0-7	0.63	3.86	2.0	0-7
Constricted affect	0.66	1.47	1.5	0-6	0.65	1.69	1.5	0-6
Suspiciousness/paranoid ideation	0.78	3.31	2.2	0-8	0.73	3.39	2.4	0-9
Total SPQ score	0.90	26.9	11.0	0-58	0.91	26.3	11.4	1-57

1.3.3.3 Advantages and limitations of the SPQ

The advantage to using the SPQ is that it is designed to provide a total syndrome score as well as the nine subscales and three composite scores. This is in contrast to measures that focus on individual symptoms for example the Chapman et al scales. Furthermore by modelling the SPQ on the diagnostic criteria for SPD, comparisons can be made between psychometric schizotypy identified using the SPQ and clinical SPD. Fifty-five percent of people who scored in the top 10% on the SPQ were found to also meet the criteria for SPD. The SPQ therefore also has the advantage of being able to identify extreme scores who would meet the criteria for SPD as well as identifying varying levels of schizotypal expression in the general population. This opens up avenues for research into schizotypal research for researchers without clinical access to patients or for those with large samples of university students. Additionally, the avoidant nature of schizotypal personality means many individuals who would meet the criteria for SPD do not seek help and psychometric questionnaires can identify these individuals in the general population. Raine and Allbutt (1989) highlight the significant benefit of being able to use this questionnaire to screen control samples to exclude individuals with schizotypal personality.

However, modelling a questionnaire based on DSM criteria for SPD is not without its limitations. Although the relevance between psychotic traits and SPD is undeniable, the co-morbidity between diagnostic features amongst the various personality disorders is high (Widiger, Trull, Hurt, Clarkin, & Frances, 1987). Also, modelling questionnaires on SPD neglects some aspects of schizoid personality, a personality disorder linked historically to schizophrenia. Although overlap between the two means that social and interpersonal features are included in the SPQ, anhedonia, a central feature in schizophrenia and in some constructions of schizotypy, is not included (Claridge, 1997). Anhedonia, the inability to feel pleasurable emotions, is the core component of Rado's and Meehl's (P. E. Meehl, 1962; Rado, 1953) theory of schizotypy.

Despite these limitations, the SPQ is a well-established instrument for schizotypy research and has good reliability and validity. Furthermore, as previously discussed, the three factor structure of the SPQ (cognitive perceptual, interpersonal and disorganised) mirrors that reported in schizophrenia making comparisons between schizotypal traits, SPD and schizophrenia plausible (Siever & Davis, 2004).

1.4   Genetic research in schizotypy

1.4.1   Family-genetic studies

As previously mentioned, the idea of a subclinical form of psychosis was driven by early observations of a familial non-psychotic presentation of schizophrenia. The observational basis of this work, whilst interesting, lacked empirical evidence until the Danish-American adoption studies which began in 1963. Kety and Colleagues (Kety, Rosenthal, Wender, & Schulsinger, 1968, 1975) conducted a series of experiments to elucidate whether a latent schizophrenia existed in the relatives of schizophrenic adoptees. All Danish adoptions from 1924-1947 were

screened to identify schizophrenic adoptees and comparisons were made as to the illness prevalence between biological relatives of schizophrenic adoptees and the biological relatives of well adoptees. The results demonstrated both chronic and latent schizophrenia amongst the biological relatives of schizophrenia adoptees. As the adoptees had not shared an environmental upbringing with their biological relatives, the presence of the latent schizophrenia was attributed to shared genes. However they did not report an increase in schizoid personality in the biological relatives of schizophrenic adoptees compared to well adoptees. Kety et al originally defined the schizophrenia spectrum as ranging from inadequate personality through to chronic schizophrenia however this was not borne out in the empirical findings. These results were based on hospital records and later interviews found a significant excess of schizoid personality in the biological relatives of schizophrenic adoptees (Kety, et al., 1975)

As well as providing empirical support for the concept of latent schizophrenia, the Danish-American adoption studies formed the basis of the DSM-III criteria for SPD when a subsample of the data was analysed by Spitzer, Endicott and Gibbon(1979). Working within the DSM-III definition of schizotypal personality Kendler & Colleagues (Kendler & Gruenberg, 1984; Kendler, Gruenberg, & Strauss, 1981) reported a clustering of SPD among the biological relatives of schizophrenic adoptees.

More recent studies of the familial genetic link between schizophrenia and schizotypal personality have also reported elevated SPD in the relatives of those with SPD and in adoptees of mothers with schizophrenia spectrum disorders (Battaglia, Bernardeschi, Franchini, Bellodi, & Smeraldi, 1995; Tienari et al., 2003). Of particular interest to this thesis, support has been found for psychosis proneness scales (Kendler, Thacker, & Walsh, 1996) although results are mixed. Stronger evidence has been found for elevated self-report schizotypy in relatives of

schizophrenics using DSM-defined schizotypy self-report measures (Appels, Sitskoorn, Vollema, & Kahn, 2004; Calkins, et al., 2004; Yaralian et al., 2000).

1.4.2 Twin Studies

Studies of monozygotic (MZ) and dizygotic (DZ) twins are traditional methods of conducting genetic research. Livesley, Jang, Jackson and Vernon (1993) recruited MZ and DZ twins from the general population and gave them pen and paper questionnaires measuring suspiciousness, paranoia and cognitive distortion. They found that suspiciousness and cognitive distortion showed a high degree of heritability. Torgersen et al (2000) recruited twin pairs drawn from a twin register and interviewed them for personality disorders. The results demonstrated Cluster A personality disorders (schizotypal personality, paranoid personality and schizoid personality) were found in both MZ and DZ with MZ twins being more concordant than DZ twins. A recent study by Kendler and colleagues (Kendler, Myers, Torgersen, Neale, & Reichborn-Kjennerud, 2007) demonstrated a high degree of heritability for schizotypal, paranoid and schizoid personality. These results demonstrate that schizotypal features are subject to notable genetic influence.

1.4.3 Identifying candidate genes for schizotypy

There has been a paucity of research into the molecular genetics involved in schizotypal features. Several candidate genes have been investigated in schizophrenia, the most widely reported of which are: catechol-O-methyltransferase (COMT), dysbindin (DTNBP1), neuregulin1 (NRG1), d-aminoacid oxidase (DAAO) Disrupted in Schizophrenia 1(DISC1) and regulator of G protein signalling-4 (RGS-4). Are these same genes implicated in schizotypal expression?

COMT has received much attention due to its involvement in dopamine degradation and neurocognitive performance. Specifically, the val-met genotype is particularly related to poorer cognition and increased risk for schizophrenia (Egan et al., 2001). Avramopoulos et al (2002) reported high activity val-val COMT genotype was significantly associated with high levels of perceptual aberration scores (positive schizotypy) as well as higher levels of schizotypal features as measured using the SPQ. A study by Smyrnis et al (2007) found higher levels of disorganised and negative schizotypal traits were associated with the val-val COMT genotype. This same group also report an association between RGS-4 and negative schizotypal traits. Research is beginning to emerge concerning NRG1 and schizotypy. Lin et al (2005) found there was a allele-dose trend for the NRG1 polymorphism and perceptual aberration scores. Hall (2006) report that the NRG1 risk allele SNP8NRG243177 is related to the development of psychotic symptoms, lower premorbid IQ and impaired activation of the frontal and temporal lobe regions in a sample of genetically high risk for schizophrenia subjects. However not all researchers have found this association. Schmechtig et al (2010) found no association between NRG1 rs3924999 and self-report schizotypy. These results demonstrate that genes implicated in schizophrenia are also beginning to be found in schizotypal individuals further cementing the genetic relationship between the two. Several meta-analyses have been conducted on genes involved in schizophrenia but no meta-analyses have been conducted on genes in schizotypy, which likely reflects the paucity of research in this field to date. Although in its infancy, exciting research is emerging within this field.

1.5 Non-genetic factors in schizotypy

As well as the well documented research on the genetics of schizotypy and schizophrenia, considerable attention has been given to environmental factors. Environmental factors are important because it is these stressors that could be influential in determining whether an

individual has an unexpressed liability, or varying degrees of expressed schizotypic psychopathology from the compensated schizotype through to the clinically diagnosed schizophrenic (Lenzenweger, 2010)2.

Several key environmental factors have been identified that impact upon schizotypal trait expression. Environmental inputs that have garnered evidence to date include: exposure to urban environments (Spauwen, Krabbendam, Lieb, Wittchen, & van Os, 2006; Spauwen & Van Os, 2006), cannabis use (Arseneault, Cannon, Witton, & Murray, 2004; Barkus & Lewis, 2008; Henquet et al., 2005; Henquet, Murray, Linszen, & van Os, 2005), birth/obstetric complications (especially perinatal hypoxia, prenatal complications; Byrne, Agerbo, Bennedsen, Eaton, & Mortensen, 2007; M. Cannon, Jones, & Murray, 2002; Clarke, Harley, & Cannon, 2006) and viral exposure to influenza (Brown, 2006). Additionally, in a comprehensive review of schizotypal personality, Raine (2006) highlighted several studies that have observed a link between schizotypal personality and child abuse (Berenbaum, 1999; Berenbaum, Valera, & Kerns, 2003; Irwin, 2001; Startup, 1999), childhood trauma (Yen et al., 2002) and parental neglect (Torgersen & Alnaes, 1992).

Although none of these environmental factors are *causes* of psychosis, they are *stressors* that interact with an already compromised system thereby increasing the risk for psychosis. How might these factors interact in the development of psychosis? One view is that stress adversely affects the dopaminergic system (Deutch, Clark, & Roth, 1990; Thompson, Pogue-Geile, & Grace, 2004) and may serve to augment the dysfunctional phasic dopaminergic response hypothesised to be important in the development of both schizophrenia and schizotypal

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2 An interesting analogy used by Lenzenweger (2010) is that "if you have one foot on a banana peel, you are more likely to slip and fall if someone bumps into you. If we think of schizotypy as the banana peel then the environment can be thought of as delivering some of the bumps" (p. 377)

personality disorder(Grace, 1991). A recent review of genetic and environmental factors by van Os et al (2009) has suggested a proneness-persistence-impairment model whereby genetic and/or environmental factors cause transient subclinical psychotic experiences to become persistent, perhaps due to biological or psychological sensitisation, which leads to impairment and a clinical need for treatment.

From the data available on genetic and non-genetic risk factors in schizotypal personality Raine (2006) has proposed a biosocial neurodevelopmental model of schizotypal personality in which two different forms of schizotypal personality emerge based on different etiological paths. The "neuro-schizotypy" form of schizotypal personality is thought to have its origins predominantly in the genetic, neurodevelopmental and neurobiological processes that are shared with schizophrenia and gives rise to interpersonal and disorganised schizotypal features. "Pseudo-schizotypy" on the other hand arises from environmental influences and gives rise to cognitive-perceptual features. However, Raine was clear to emphasize that the different etiological pathways were relative rather than absolute and that both forms will have contributions from genes and environment; the difference lies in which of these contributions is predominant and that schizophrenia or SPD will only be an outcome for neuro-schizotypy. In this model, neuro-schizotypy is viewed predominantly as a brain disorder (Raine, 2006). Genetic factors and prenatal environmental insults are proposed to precipitate structural and functional brain changes (reviewed in chapter 2) in frontal, temporal and limbic regions which in turn give rise to psychological abnormalities in cognition and affect. Post-natal environmental influences both contribute to further brain changes and also directly result in cognitive and affective disturbances. At a personality level, cognitive disturbances give rise to cognitive perceptual and disorganised features and affective disturbances give rise to interpersonal impairments. This model is similar to that proposed by Venables (1995)and Torgersen et al (2002) who suggest that individuals with predominantly negative and disorganised schizotypal traits are within the

schizophrenia spectrum whereas those individuals with predominantly positive schizotypal traits fall outside the schizophrenia spectrum, sharing more overlap with other personality disorders.

This model encapsulates all the research thus far into schizotypy but evidence is required to support whether schizotypal personality can be delineated into these two forms and to ascertain the features that characterise them. Specifically, does neuro-schizotypy have a stronger genetic and neurodevelopmental basis, greater symptom severity, greater psychopharmacological treatment response and does it present a greater risk for schizophrenia than pseudo-schizotypy? Conversely, does pseudo-schizotypy have a stronger environmental and psychosocial influence, higher degree of cognitive perceptual features, fluctuating symptomatology and greater response to psychological interventions?

1.6 Conversion rates from early psychotic experiences to later development of a psychotic disorder

Arguably, if a continuum of psychosis is valid, individuals who express high levels of subclinical psychotic traits are vulnerable to break down for psychotic disorder. In other words, do schizotypy measures have high predictive validity? Several studies have addressed this issue.

Chapman et al (1994) were the first group to report high rates of psychotic outcomes in individuals who had high scores on magical ideation and perceptual aberration 10 years previously. Impulsive non-conformity and physical anhedonia were not predictive of later psychosis. This suggests that "positive trait schizotypy" is predictive of psychosis. However, a follow up of this study failed to find any rate of breakdown to psychotic disorder in a high magical ideation/perceptual aberration group but did find a higher rate of schizophrenia

spectrum disorders in those with high social anhedonia scores (Gooding, Tallent, & Matts, 2005).

The longest prospective investigation was the Dunedin Multidisciplinary Health and Development Study. Children who had reported psychotic experiences at age 11 years were followed up at 26 years. The 16 year risk of developing schizophreniform[3] disorder associated with psychotic experiences at age 11 was increased 16 fold compared to children without reported psychotic experiences. To quantify it a different way 25% of children with psychotic experiences at age 11 developed schizophreniform disorder at age 26 over the follow up period (Poulton et al., 2000).

In a study designed to investigate new incident cases of psychotic experiences, (Hanssen, Bak, Bijl, Vollebergh, & van Os, 2005) followed up 7076 individuals after 1 year. Of those individuals 79 (2%) were identified as a new case and followed up again after 2 years. The 2 year transition rate to clinical psychotic disorder was 8% representing a greater than 60 fold increase in risk compared to those without incident psychotic experiences (van Os, et al., 2009).

Researchers have also investigated the rate of breakdown between SPD and schizophrenia reporting break down rates of 40% over a 15 year follow up (Fenton & McGlashan, 1989) and 25% over 2 years (Schulz & Soloff, 1987). Others have estimated the rates of breakdown from adolescent schizotypy to schizophrenia to be in the order of 20%–40% (E. Walker, Kestler, Bollini, & Hochman, 2004). Johnstone et al (2005) investigated the impact of premorbid variables on development of schizophrenia in individuals at high risk of schizophrenia for genetic reasons. Out of a sample of 163 young adults with two or more relatives with

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3 Schizophreniform disorder is diagnosed when the symptoms of schizophrenia are present for the majority of a period of one month but not for the full 6 months required for a diagnosis of schizophrenia.

schizophrenia, 20 went on to develop schizophrenia within 2.5 years. Further those who developed schizophrenia differed from those who did not on levels of social anxiety, withdrawal and other schizotypal features.

1.7 Base rate, demographics and taxometrics

Prevalence wise, DSM-IV lists a base rate of 3% but rates vary from 0.6% (Torgersen, Kringlen, & Cramer, 2001) to 4.6% (J. G. Johnson, Smailes, Cohen, Brown, & Bernstein, 2000) for SPD. Raine (2006) argues that 2% would be a conservative estimate of clinically defined schizotypal personality disorder but that it could be as high as 10% when psychometrically defined schizotypy is included. Taxometric analysis of psychosis proneness scales (Lenzenweger & Korfine, 1992)and samples of undergraduate students completing the SPQ (Fossati et al., 2005) support this 10% figure.

Similar to the pattern found in schizophrenia there is an over-representation of males with schizotypal personality disorder (Kotsaftis & Neale, 1993) and whilst males have higher levels of negative schizotypy, the reverse is true for positive schizotypy (Fossati, Raine, Caretta, Leonardi, & Maffei, 2003). However, Miller and Burns (1995) found that whilst males have higher levels of negative schizotypy there was no difference between genders on positive schizotypal traits. Individual psychosis proneness traits have also been explored. Goulding, McClure-Tone & Compton (2009) report higher scores for males on social anhedonia scales but no other gender differences. Fonseca-Pedrero et al (Fonseca-Pedrero, Lemos-Giraldez, Muniz, Garcia-Cueto, & Campillo-Alvarez, 2008) report higher levels of impulsive non conformity, social and physical anhedonia in males whereas females score higher on positive schizotypy, social paranoia and negative evaluation.

Associations between age and schizotypal trait expression have been mixed. Generally studies across multiple age groups suggest that younger individuals tend to score higher in schizotypy especially positive schizotypy (Fossati, et al., 2003). However, Fonseca-Pedrero et al (Fonseca-Pedrero, et al., 2008) demonstrated higher schizotypy scores with increasing age in a sample of 321 Spanish adolescents. Goulding et al (2009) found no effect of age (Battaglia et al., 1999) on any of the schizotypy measures.

Little research has been done investigating ethnicity in schizotypy. One study of four personality disorders revealed significantly increased rates of SPD in African-Americans compared to Hispanics and Caucasians (Chavira et al., 2003). Similar findings were obtained for self-reported schizotypy with higher scores reported in African-Americans and Asian-Americans (Chmielewski, Fernandes, Yee, & Miller, 1995). Kwapil et al (2008) report higher scores on both perceptual aberration and social anhedonia in African-Americans however Goulding et al (2009) report lower scores in this ethnicity group on perceptual aberration and disorganised schizotypy.

1.8   Summary

To summarise, schizotypy may be expressed at a subclinical level through the expression of high levels of schizotypal traits or at a clinical level through a diagnosis of SPD or schizophrenia. Schizotypy is a multidimensional construct that can be identified in the general population using psychometric self-report questionnaires specifically designed to tap either the schizotypy syndrome or individual traits associated with schizotypy. The factor structure of schizotypy is similar to that reported in schizophrenia, demonstrating the phenotypic similarities between traits of schizotypal personality and symptoms of schizophrenia.

Evidence suggests that schizotypal personality is genetically related to schizophrenia; shares several key environmental risk factors and similar demographic characteristics. Additionally, there is some evidence that schizotypal status or early psychotic experiences are a risk factor for development of a psychotic disorder. Schizotypal personality is also thought to share similarities with schizophrenia at the cognitive, psychophysiological and neural level and these will now be discussed in chapters 2 and 3.

Chapter 2:   Experimental correlates of schizotypy

As well as the genetic and phenomenological relationship between schizotypy and schizophrenia, experimental findings on measures of psychophysiology and cognition have been investigated in schizotypal personality. These have provided overwhelming evidence of replicable impairments common to individuals with clinical schizophrenia, schizotypal personality disorder and healthy individuals exhibiting schizotypal personality traits. These findings will now be reviewed. Brief reference will be made to the underlying neural correlates associated with the areas of cognition presented, where relevant, but structural and functional neuroimaging data will be reviewed in Chapter 3.

2.1   Psychophysiology Research

One of the psychophysiological measures most commonly employed in schizotypy and schizophrenia is Prepulse Inhibition (PPI). Sensorimotor gating is thought to be a process which regulates sensory input by filtering out irrelevant or distracting stimuli, preventing sensory information overflow, and allowing for selective and efficient processing of relevant information (H. Takahashi et al., 2010). Prepulse inhibition is the automatic suppression of startle magnitude that occurs when the startling stimulus is preceded by a weak stimulus (Swerdlow et al., 2006). PPI is the most common psychophysiological measure of sensorimotor gating ability. Reductions in PPI are consistently reported in schizophrenia (Braff, 2010), in relatives of schizophrenia patients (Cadenhead, Swerdlow, Shafer, Diaz, & Braff, 2000) and in those at ultra high risk for psychosis (Ziermans, Schothorst, Magnee, van Engeland, & Kemner, 2011). Deficient PPI has also been reported in schizotypal personality disorder (Cadenhead, Geyer, &

Braff, 1993; Cadenhead, et al., 2000) and in healthy volunteers with schizotypal traits (H. Takahashi, et al., 2010).

Other psychophysiological abnormalities in schizotypal personality are electrodermal correlates of the human orienting response (Gruzelier & Raine, 1994; Mason, Claridge, & Clark, 1997; Raine, Venables, Mednick, & Mellingen, 2002), dysfunctions in eye movement parameters for example smooth pursuit (Kelley & Bakan, 1999; Lenzenweger & O'Driscoll, 2006; O'Driscoll, Lenzenweger, & Holzman, 1998) and antisaccades (U. Ettinger et al., 2005; Holahan & O'Driscoll, 2005; O'Driscoll, et al., 1998) reduced P50 suppression (Evans, Gray, & Snowden, 2007; Wan, Crawford, & Boutros, 2006) and altered gamma and beta neural oscillations (Pizzagalli et al., 2000; Vernon, Haenschel, Dwivedi, & Gruzelier, 2005).

A general failure in inhibitory processes could be a common factor underlying excessive orienting, reduced P50 suppression and reduced prepulse inhibition of the startle reflex. Reduced inhibition, hyper arousal and lack of filtering of environmental stimuli that should be ignored "could account for the positive schizotypal features with a possible basis in prefrontal, hippocampal and thalamic brain structures" (Raine, 2006).

2.2   Neuropsychological Research

The neurodevelopmental model of schizophrenia purports that schizophrenia is the result of changes in the brain that occur long before the expression of illness (Weinberger, 1986, 1987) . One of these brain changes is alterations in the normal asymmetry of the brain. It has been argued that schizophrenia results from genetically determined failure in normal cerebral lateralisation (Crow, 1997).   Reduced left planum temporale volume has been reported in schizophrenia (Oertel et al., 2010; Shenton, Dickey, Frumin, & McCarley, 2001) as well as

functional differences in cerebral lateralisation especially for left sided language functions (Li et al., 2007). Additionally hand preference, a proxy measure of cerebral asymmetry, has demonstrated a higher prevalence of non-right handedness in patients with schizophrenia (Sommer, Ramsey, Kahn, Aleman, & Bouma, 2001). This is attributed to a "failure to establish cerebral asymmetry" (Dragovic & Hammond, 2005). Using verbal dichotic listening tasks, reduction in the normal right ear advantage (left hemisphere) has also been found in schizophrenia (Wexler, Giller, & Southwick, 1991).

Cerebral asymmetry has been investigated in schizotypal personality using divided visual field and dichotic listening tasks. Generally, in the divided visual field and dichotic listening paradigms, stimuli are presented separately to each visual field or ear that have predominantly contralateral connections to the cerebral hemispheres (Lencz et al, 1995). The relative functioning of the hemispheres is compared by examining the reaction time or accuracy in reporting the stimuli for that hemisphere. In normal controls, relative left versus right performance on these tasks reflects normal asymmetries in the brain; left hemisphere (LH) dominance for verbal stimuli and right hemisphere (RH) dominance for non-verbal stimuli (Lencz, Raine, Benishay, Mills, & Bird, 1995). Using the visual field paradigm both reductions in normal cerebral asymmetry (Broks, 1984) and enhanced cerebral asymmetry (D. Rawlings & Claridge, 1984) have been reported in schizotypal individuals. Increased asymmetry has also been reported for dichotic listening tasks (Raine & Manders, 1988; D. Rawlings & Borge, 1987) Raine and Manders (1988) report a significantly enhanced right ear (LH) advantage in subjects with high levels of schizotypal traits, which they attribute to LH overactivation.

The varying syndromes of schizotypy and their relationship with cerebral asymmetry has been investigated by Gruzelier, Burgess, Stygall, Irving & Raine (1995) who reported that "active" schizotypal traits (odd speech and behaviour) are associated with a LH > RH imbalance whereas

"withdrawn" traits (no close friends and blunted affect) are associated with a RH > LH capacity. Gruzelier argues that cognitive perceptual features are non-lateralising although this is in contrast to the findings presented above. A study by Nunn & Peters (2001) investigated positive and negative schizotypal traits using tasks selected from the Wechsler Adult Intelligence Scale Revised (WAIS-R; Wechsler, 1981) that tap LH functioning (vocabulary, similarities and logical semantic tests) and RH functioning (proverbs, logical grammatical and humour tests). They demonstrated that low scores on RH tasks predicted high scores in positive schizotypal traits. Low scores on both LH and RH tasks predicted high scores on cognitive disorganisation. Neither LH nor RH tasks predicted scores on negative schizotypy subscales. This implies that a right hemisphere dysfunction may be central to schizotypy.

2.3 Cognitive Research

A general definition of cognition is that it can be thought of as encompassing all aspects of learning about, understanding and knowing the world around oneself. It includes all of one's mental abilities, such as attention, perception, memory, language processing, visuo-spatial ability, executive functions and others used to interact with and to make sense of the environment (Harvey & Sharma, 2002).

2.3.1 Cognition in patients with schizophrenia

Cognitive deficits are a core feature of schizophrenia (Gold, 2004). They are a primary deficit and not secondary to other features of the illness (clinical symptoms) or treatment related factors (medication) (Harvey & Sharma, 2002). They are common to most persons with schizophrenia. Cognitive deficits are lifelong, stable in adulthood and persist into later life where there may be further decline; they are unrelated to psychotic or remitted states (Nuechterlein et al., 1998). Deficits also occur in prodromal samples and meta analyses of family studies of at risk children

and adolescents (Cornblatt, Lenzenweger, Dworkin, & Erlenmeyer-Kimling, 1992). Generally schizophrenia patients show deficits across a large number of cognitive domains including working memory, speed of processing, verbal learning and memory, attention and vigilance, reasoning and problem solving and visual learning and memory (Nuechterlein et al., 2004). Performance has been reported to be as high as 1.5 to 2.5 standard deviations below population norms on standardised tests, consistent with mild to moderate cognitive impairment (Palmer et al., 1997). Reviews of the literature highlight cross sectional and prospective ties between selected areas of cognitive functioning and areas of functional outcome including community functioning (e.g. work and social functioning), ability to perform instrumental role skills and psychosocial rehabilitation success (Green, 1996; Green, Kern, Braff, & Mintz, 2000; Green, Kern, & Heaton, 2004).

Clearly elucidating the core cognitive deficits in schizophrenia spectrum disorders is critical to understanding the disorder. However studying cognition in schizophrenia is plagued by confounding variables such as medication use and hospitalisation. The widespread cognitive impairments across all areas of cognition raises the question about whether there is a generalised cognitive deficit in schizophrenia rather than impairments in specific functioning (Chapman & Chapman, 1978). Lower premorbid IQ and lower education status also make interpretation of cognitive results difficult. Many studies compare patients with normal controls on a specific cognitive measure but normal controls do not have similar reductions in general intelligence and cognitive functioning making comparisons unrealistic. Alternatively, schizophrenia groups can be matched on intelligence with controls, but this has the problem that the matching process might obscure cognitive impairments. Patients with schizophrenia who have comparable IQ to controls are not representative of the general patient population and thus might not have similar levels of cognitive impairment; likewise controls that have comparable IQ to patients with schizophrenia i.e. lower IQ may have similar cognitive impairments but this may be attributable

to the lower IQ levels rather than any specific deficit. Schizophrenia is also associated with lower motivation which may affect performance on tasks.

These factors can be addressed in part by studying cognitive function in healthy volunteers with schizotypal traits who are thought to share a cognitive vulnerability to patients with schizophrenia. High schizotypal individuals evince similar, but attenuated, cognitive deficits to patients with schizophrenia in the absence of the above confounds (Trestman et al., 1995). Thus, if a specific cognitive component is identified in schizotypal persons, it may represent a core feature of the schizophrenia spectrum and be less related to illness and illness related factors.

2.3.2   Cognition in schizotypy

By far the largest body of experimental research in schizotypy is in the field of cognition. I will first present the general findings in cognitive research in schizotypy and then discuss the cognitive areas that have produced the most consistent findings: executive function, attention and inhibition, and importantly for this thesis, memory[4].

2.3.2.1 General cognitive functioning in schizotypy

Extensive evidence implicates impairments in executive functioning (Lenzenweger & Korfine, 1994), sustained attention (Gooding, Matts, & Rollmann, 2006), working memory (Matheson & Langdon, 2008), spatial working memory (Park & McTigue, 1997) verbal learning and memory (Vollema & Postma, 2002), latent inhibition (Braunstein-Bercovitz & Lubow, 1998) and negative priming (Claridge & Beech, 1996). In general, performance of high schizotypes tends to be intermediate between individuals with no or low expression of schizotypal traits, and

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4 Although I discuss each area of cognition separately, I am aware that these cognitive domains are not truly independent and that each task taps a variety of cognitive processes. For simplicity however, each cognitive area is discussed individually.

patients with schizophrenia (Trestman, et al., 1995) with worse performance seen in clinically defined SPD than in self-report schizotypal trait expression (Raine, 2006).

Social-emotional cognitive tasks for example perspective taking (Langdon & Coltheart, 2001) and self-related information processing (Platek, Myers, Critton, & Gallup, 2003) has also been reported in high schizotypal individuals. Investigations into social cognition are only just emerging and as such social cognition will not be reviewed in this chapter.

Some cognitive functions appear to be spared or even enhanced in schizotypy. IQ, is widely reported as spared in schizotypic individuals although studies have occasionally reported verbal IQ decrements (Noguchi, Hori, & Kunugi, 2008) and lower matrix reasoning scores (Matheson & Langdon, 2008). Several studies have reported enhanced creativity in schizotypy in association with increased verbal fluency and increased right hemisphere functioning (Duchene, Graves, & Brugger, 1998; S. Weinstein & Graves, 2002). A plausible explanation is that impairments in inhibition often reported in schizotypal individuals may paradoxically enhance ability to form broad, unusual associations that favour cognitive flexibility and creativity. At a clinical level this may be expressed in odd speech, magical thinking, eccentric behaviour and unusual perceptual experiences (Raine, 2006).

Within the scope of this thesis it is impossible to discuss all the cognitive findings within this group so this review will be limited to cognition rather than social cognition and will focus on domains relevant to providing a cognitive background in schizotypy.

2.3.2.2 Executive functioning

The executive system is thought to control and manage other cognitive processes often referred to as executive functioning. The executive system is particularly important in situations that involve planning and decision making, error correction and troubleshooting, novel sequences of

actions, dangerous or technically difficult situations and finally situations that require overcoming strong habitual response (D. A. Norman & Shallice, 1986). For the most part this section will review studies on executive function using the WCST as this is by far the most frequently used test of executive function in schizotypy.

The Wisconsin Card Sorting Task (WCST; Heaton, 1981) has been extensively used for assessing executive functioning. In this task subjects are required to match response cards to four stimulus cards along one of three dimensions: colour, form or number. In the extended version of the task subjects are neither informed of the sorting principle nor are they told when the principle changes during the task. The fundamental challenge for subjects is to discern the sorting principle in use in the task and to apply that principle to the cards that are placed in front of them. Thus if the sorting principle is colour, then the subject needs to sort the target cards according to colour; if the sorting principle is shape then the target cards should be sorted according to shape. Importantly, the task requires a subject to keep in mind the current sorting principle and apply it until the sorting principle changes. Performance indexes typically measured are: categories (overall success), percentage perseverative errors (perseverative tendencies), failures to maintain set (non-perseverative errors), trials to complete first category (conceptual ability) and "learning to learn" (learning). The WCST requires concept formation and cognitive flexibility thought to be related to selective activation of the DLPFC (Weinberger, 1986).

Using this task Lenzenweger & Korfine (1994) demonstrated that individuals with higher scores on the perceptual aberration scale (Chapman, et al., 1978) failed to maintain set, tended towards completing fewer categories and required more trials to complete their first category than controls. This is consistent with a study by Lyons, Merla, Young, & Kremen (1991)who found that schizotypic subjects completed fewer categories and had more failures to maintain set than

did normal control subjects. Failure to maintain set is the tendency to acquire a correct sorting principle on the WCST and then to lose that principle during its application. It's particularly interesting because it is a deficit not reported in patients with schizophrenia who tend to be impaired on categories completed and perseverative errors (Lenzenweger, 2010). The authors suggest perseverative errors may be more associated with schizophrenia once it begins to unfold rather than a feature of trait vulnerability (Lenzenweger & Korfine, 1994). A later study by Park, Holzman & Lenzenweger (1995) reported similar findings of failure to maintain set in high scorers on the perceptual aberration scale but not on any other WCST measure. Extending the schizotypy profile to include high scorers on magical ideation (Eckblad & Chapman, 1983) and social anhedonia (Chapman, et al., 1976) as well as perceptual aberration, Gooding, Kwapil and Tallent (1999) report increased perseverative errors and fewer categories achieved in high schizotypes compared to controls.

Broadly consistent findings have been reported for high scores on alternate measures of schizotypy. Daneluzzo, Bustini, Stratta, Casacchia, & Rossi (1998) found that high SPQ (Raine, 1991) scores are associated with worse performance on the WCST as indexed by fewer categories achieved and increased perseverative errors. Raine et al (1992) report increased WCST perseverative errors associated with high SPQ scores and reduced volume of the prefrontal cortex. Kim, Oh, Hong and Choi (2010) found that impaired WCST performance (fewer categories achieved and more total and perseverative errors) was related to negative schizotypy as measured using the SPQ. However, this is in contrast to the above studies who have found impaired performance on the WCST in high scorers on perceptual aberrations, a positive schizotypal trait measure.

However, not all studies have demonstrated lower performance on the WCST in schizotypy. Vollema and Postma (2002) report no association between WCST performance and schizotypy

in first degree relatives with schizotypal traits. However, the authors limited their analysis to categories completed and perseverative errors only and did not look at other indices of the WCST such as failure to maintain set. As previously discussed, worse performance on the failure to maintain set index of the WCST is consistently reported in those with high scores on various schizotypy measures, sometimes in the absence of performance differences on other measures. One explanation for this would be that failure to maintain set may reflect an inability to control inhibitory processes and inhibition impairments are a core feature of the schizotypal cognitive make up (see below). In support of this interpretation, Vollema and Postma (Vollema & Postma, 2002) report that the high schizotypes in their sample were impaired on the continuous performance test, a measure of sustained attention.

In respect to schizotypy, most studies have used the WCST to investigate executive functioning. Other studies have employed verbal fluency tasks or trail making A and B tasks to assess executive function and frontal lobe functioning reporting impairments in executive functioning related to high levels of negative schizotypal traits (Dinn, Harris, Aycicegi, Greene, & Andover, 2002) and high levels of positive and negative schizotypy (Koychev et al., 2011). However, executive function measured using tasks other than the WCST have provided inconsistent results. Several studies report no differences in verbal fluency in relation to schizotypal traits (Laurent et al., 2000) and others increased verbal fluency (Duchene, et al., 1998). Executive function measured using random generation and memory updating tasks have also shown largely no differences between low and high schizotypy scorers (e.g. Avons et al, 2002). Executive function has also been assessed using the Stroop task, which is also a measure of selective attention, and this is reviewed in the next section.

2.3.2.3 Attention

Human beings need efficiently functioning attention to do almost anything that matters whether in the technical, social/interpersonal, emotional, educational or other psychological domain. There is a broad array of attentional processes but the two I will focus on here are selective and sustained attention.

2.3.2.3.1 Sustained attention

Sustained attention is consistently reported to be impaired in schizophrenia (Cornblatt & Keilp, 1994; Cornblatt & Malhotra, 2001; Cornblatt, Risch, Faris, Friedman, & Erlenmeyer-Kimling, 1988). Sustained attention deficits are also found in biological relatives with high perceptual aberration scores (Grove et al., 1991) and clinically defined SPD (Condray & Steinhauer, 1992).

Studies of psychometrically defined schizotypal individuals have also demonstrated impaired sustained attention using the Continuous Performance Test (CPT). The CPT is a task that requires subjects to focus on a succession of targets, often infrequently presented to increase attentional demands, over a period of time. Many versions of this task exist, one of which is the CPT- Identical Pairs (CPT-IP). In this task subjects view a succession of target objects and then following a delay must respond whether the current stimuli they are viewing are identical to the one before the delay. Lenzenweger, Cornblatt & Putnick (1991) reported that deficits in sustained attention measured using this task were associated with extreme scores on the Perceptual Aberration Scale. Additionally, the authors using data from the New York High Risk Project, found that early deficits in attentional processing were predictive of non-psychotic schizotypic psychopathology (Cornblatt, et al., 1992). The laboratory findings of Lenzenweger et al 1991 have been consistently replicated using the same task (Gooding, et al., 2006; Lenzenweger, 2001). Interestingly, a study investigating attentional deficits in a group at risk for affective disorders found that attentional deficits were only observed for subjects who were also

co-morbid for schizotypal traits (Meyer & Blechert, 2005) indicating the potential specificity of attentional deficits to the risk for psychotic disorders. All of these investigations have used carefully selected populations but Bergida & Lenzenweger (2006) found that deficits in sustained attention are predictive of schizotypic features in a quasi-random, unselected population as well. In terms of factor structure, Vollema and Postma (2002) have argued that sustained attention deficits as measured using the CPT are related to disorganised schizotypy which may be related to orbitofrontal dysfunction.

2.3.2.3.2 Selective Attention

Many researchers regard a difficulty in selective attention as a core cognitive component of schizophrenia (e.g. J. A. Gray, 1998). Selective attention has been studied using latent inhibition, learned irrelevance and Stroop paradigms.

Latent inhibition (LI) is observed when a repeatedly presented irrelevant stimulus is pre-exposed before becoming relevant in a subsequent learning task. Under those conditions it becomes difficult for that stimulus to enter into new associations as compared to learning with a novel stimulus (Kaplan & Lubow, 2011). Since normal LI is assumed to be the result of a stimulus specific decline in attention to a repeatedly presented task-irrelevant stimulus, attenuated LI has been attributed to a failure to reduce the attentional response to that stimulus i.e. an inability to ignore irrelevant stimuli. The absence or reduction of the LI effect has been reported for acute schizophrenics (Baruch, Hemsley, & Gray, 1988; N. S. Gray & Snowden, 2005; Sitskoorn, Salden, & Kahn, 2001) and has also been found in high compared to low schizotypes (Braunstein-Bercovitz & Lubow, 1998; N. S. Gray, Fernandez, Williams, Ruddle, & Snowden, 2002). Williams et al (1998) however have suggested that the reduced LI effect observed in patients with schizophrenia may actual reflect exposure to antipsychotic medication rather than a feature of the illness itself. In this study, patients who were antipsychotic naïve displayed latent

inhibition compared to patients who had recently started treatment with antipsychotics. Also, control subjects who received haloperidol demonstrated a reduction in latent inhibition compared to controls that were infused with saline.

Related to LI is a paradigm of learned irrelevance (LIrr) which is the retardation of learning that one stimulus predicts the occurrence of another due to pre-exposure of both stimuli but in an unrelated manner. Disruption in LIrr is observed in acute schizophrenic patients but not in chronic patients (Gal et al., 2005), in ultra high risk for psychosis groups (Orosz et al., 2010) and high scorers on schizotypy measures (Schmidt-Hansen, Killcross, & Honey, 2009) consistent with the LI literature.

The Stroop effect is observed when time to name the ink colour of an incompatible coloured word is longer than the time to name the colour of a non-colour word or group of letters. The participant is required to name the ink colour and thus the interference effect will be increased if the participant is unable to ignore the task irrelevant written words. Evidence suggests that Stroop interference is increased in patients with schizophrenia (Abramczyk, Jordan, & Hegel, 1983) and in healthy subjects with high scores on measures of psychosis proneness (N. J. Gray, Klein, Noyce, Sesselberg, & Cantrill, 2005; N. S. Gray, Brown, MacCulloch, Smith, & Snowden, 2005). A study conducted by Cimino & Haywood (2008) demonstrated that high schizotypal individuals as measured using the OLIFE (Burch, et al., 1998) did not display disproportionately increased Stroop facilitation or inhibition. However, high schizotypes were slower to switch between congruent and incongruent conditions indicating a problem with switching rather than selective attention, per se.

2.3.3.4 Memory

Memory has been extensively studied in schizophrenia, SPD and schizotypal personality and represents the largest body of cognitive research in schizotypy. Additionally, verbal learning and memory has been found to explain the most variance in predicting functional outcome on the basis of cognition in schizophrenia (Green, et al., 2000). Elucidating the mechanisms underlying memory, its dysfunction in psychosis and its validity as a treatment target have become key areas of investigations in schizophrenia spectrum research.

2.3.3.4.1 Working Memory

Memory is a broad and elaborate set of cognitive processes that has many facets and sub processes (Tulving & Craik, 2000). Working memory is thought of as a specific type of memory, separate and apart from short term memory, as well as episodic and procedural long-term memory.   The original definition of working memory and its related system is attributed to Baddeley (1986) who defined it as an *active* short term memory system consisting of a central executive and modality specific slave systems (the phonological loop for auditory stimuli and the visuospatial sketch pad for visual stimuli). Working memory has also commonly become defined as a system that helps to keep information needed for task completion *online* for a short period of time (Goldman-Rakic, 1991). Working memory has been identified as a core component of both schizophrenia (Forbes, Carrick, McIntosh, & Lawrie, 2009) and SPD (Conklin, Curtis, Katsanis, & Iacono, 2000; Mitropoulou et al., 2005)and in relatives of schizophrenia patients (Conklin, et al., 2000).

Working memory impairments have also been reported in healthy volunteers with schizotypal traits. Matheson and Langdon (2008) demonstrated increased positive and negative schizotypy scores were associated with poorer performance on a letter-number-sequencing test (LNS), a measure of executive working memory derived from the working memory index of the WAIS-

III(Wechsler, 1997). However, they also found compromised matrix reasoning scores in high schizotypal subjects which is contrary to the intact intellectual functioning that is usually reported in non-clinical schizotypic populations. Kerns & Becker (2008) have demonstrated that performance on the N-Back, a task of verbal working memory, is impaired in schizotypes with elevated disorganised traits whilst verbal intelligence is intact. SPD patients with elevated disorganised symptoms also show impairments on the N-back task especially at the two-back level (McClure, Barch, Flory, Harvey, & Siever, 2008).

A recent study by Schmidt-Hansen & Honey (2009) demonstrated that positive schizotypal traits, as measured using the OLIFE, were associated with worse performance accuracy and slower response times on the N-back. They also report that low levels of negative schizotypy were associated with a more conservative response bias, longer response times and increased response variability. Unlike the Kerns & Becker (2008) study, they found no association between disorganised schizotypy and worse N-back performance.

Smynis et al (2007) also used the 2 back condition of a verbal and spatial N-back task to investigate working memory in military conscripts with schizotypal traits as measured using the SPQ. The *verbal* N-back consisted of 12 Greek letters presented for 500 ms, one every 3 seconds. Subjects responded "yes" when the current letter matched the one that was presented two letters ago and "no" if it did not match. In the *spatial* version of the task, the subjects were instructed not to remember the letters themselves by their locations. Each letter appeared randomly in 1 of 12 locations again for 500ms, at a rate of one every 3 seconds. Subjects were instructed to press yes when the currently presented letter appeared in the same location as the letter presented two trials previously. A negative relationship was revealed between negative schizotypy and performance accuracy such that accuracy decreased as negative schizotypy scores increased. This study demonstrates that verbal and spatial working memory is impaired

in schizotypy, a result that supports previous literature on spatial working memory deficits in healthy volunteers with schizotypal traits (see below).

Working memory is a high g loading task (it requires a high degree of general mental ability as well as specific task related skills) and thus lower working memory performance should also indicate lower general intelligence scores (IQ scores) but IQ is reportedly spared in schizotypy. One suggestion for why this should be the case is that WM tasks tap a wide range of cognitive functions aside from WM functions including attentional resources, inhibitory processes and executive functioning and thus lower WM performance may reflect alterations in processes other than working memory.

2.3.3.4.2 Spatial working memory

Spatial working memory has been shown to be impaired in patients with schizophrenia (Park & Holzman, 1992) schizotypal personality disorder (Mitropoulou, et al., 2005), in familial relatives of schizophrenic patients (T. D. Cannon et al., 1994; Park, Holzman, & Goldman-Rakic, 1995) and in those classified as high risk for development of psychotic disorders (M. O'Connor et al., 2009; C. W. Smith, Park, & Cornblatt, 2006; Wood et al., 2003). It has also been reported as impaired in healthy volunteers with schizotypal traits (Park, Holzman, & Lenzenweger, 1995; Park & McTigue, 1997).

Park et al (1995) used an oculomotor delayed response task to determine spatial working memory performance between schizotypes and controls. Subjects were identified as high and low schizotypy based on the Perceptual Aberration Scale (Chapman, et al., 1978). The task involved subjects being presented with a circle on the screen for 200ms at one of eight locations. After a delay of 10s they were presented with eight reference circles and asked to move their eyes to the reference circle where the target has been located prior to the delay. To control

rehearsal in the 10s delay subjects were presented with words and asked to decide which semantic category they belonged to. They found that subjects with high perceptual aberration scores performed less accurately than did the group with low scores. However, the authors acknowledge the limitations of using the perceptual aberration scale. The perceptual aberration scale primarily measures only one aspect of schizotypy and is also used to measure features of other disorders (Chapman, et al., 1994). Therefore as well as identifying schizotypic individuals the sample may have been a diverse collection of others who as a group displayed subtle cognitive deficits. This criticism applies across the schizotypy literature and highlights the methodological issues with the way researchers identify schizotypes.

In a follow up study Park & McTigue (1997) investigated spatial working memory using the same paradigm but using the schizotypal personality questionnaire as the schizotypy measure. The spatial working memory task used was the same as for Park et al (1995) but without the oculomotor response component; subjects touched a screen rather than moved their eyes to the target location. A weak association was found between total SPQ score and spatial working memory performance but this was not significant. The authors then divided subjects into a high schizotypy group and a control group. To do this they classified those who scored above the 90th percentile as high and those below the 90th percentile as the control group. Using this method a significant difference in spatial working memory performance was found, with high schizotypal subjects making more errors than controls. However it should be noted that out of 89 subjects recruited, only 14 of these fell into the 90th percentile. The finding of only a weak association of SPQ score and spatial working memory performance may have been the result of a sample that contained very few high schizotypal individuals. They also found that the SPQ subscale most strongly correlated with spatial working memory score was that of "no close friends". This suggests that poorer working memory performance may be mediated by being socially isolated. Gooding & Tallent (2003) also demonstrated impaired spatial working memory in social

anhedonia, a negative schizotypal trait, using a delayed match to sample task. In this task a target stimulus is displayed for 200ms in one of five squares presented at different spatial locations. After a delay period (which included a distractor task), the participant was instructed to press the key matching the prior spatial location of the target. Individuals with social anhedonia had significantly lower accuracy than controls.

Other studies have also provided evidence of a relationship between negative symptoms and spatial working memory using similar tasks in patients with schizophrenia (C. Carter et al., 1996). This study also highlighted that spatial working memory performance is likely to be the result of deficits in spatial attention and encoding as well as working memory maintenance since patients were significantly impaired even at a delay of 0 seconds. The authors suggest that research into memory should be broken down into its subcomponents of encoding, recall and recognition (C. Carter, et al., 1996) a statement that echoes other authors who have suggested using these fine-grained distinctions developed in non-clinical neuropsychology research (Serper & Harvey, 1994).

2.3.3.4.3 Learning and Memory

Verbal learning and memory have received some attention in schizotypy typically using the California Verbal Learning Test (CVLT). The CVLT is a verbal learning and memory test which involves subjects reading and learning lists of words that they need to then recall over short or long delay periods. Vollema & Postma (2002) used the Verbal Learning and Memory Test (VLGT) which is the Dutch version of the CVLT (Mulder, Dekker, & Dekker, 1996). Subjects were presented with a list of 16 words once and after 30 minutes were asked to recall the words previously learnt. Variables were total number of correct words and total number of incorrect words. Positive schizotypy scores were negatively correlated with performance on the

CVLT as measured by number of correctly retrieved words. Thus high positive schizotypy scorers remember fewer words indicating impairment in verbal learning and memory.

Lenzenweger & Gold (2000) failed to find any differences in verbal memory between low and high scorers on the perceptual aberration scale. In this task, each subject received three trials of a 38 word list for immediate recall and a delayed recall trial that followed approximately 20 minutes after the immediate recall trials. The authors suggest that perhaps verbal recall that does not rely on manipulation of retained information is not impaired in schizotypy. However, an auditory working memory test, the letter-number span task, was also administered to the same subjects and no differences were found on this task either. This latter finding is interesting because the study used the same subjects as those by Park et al (1995) who did find differences in spatial working memory using the delayed response task. The authors attribute this difference to the use of a distracter task in Park et al's study which provides a greater opportunity for distraction and interference.

A possible explanation for the negative verbal recall results is that verbal memory may be influenced by emotion and social functioning. A study by Aguirre, Sergi & Levy (2008) also found no differences between low and high schizotypes in verbal learning and memory using the CVLT however high schizotypes demonstrated impaired emotional intelligence and social functioning and these were related to verbal learning and memory.

Working memory has been covered extensively in the schizotypy literature using a variety of paradigms to tap verbal, auditory and spatial working memory. However, there is a paucity of cognitive research investigating long term memory processes. Verbal learning and memory have received some attention but other areas have gone relatively unexplored. One such area that has received little attention is spatial learning and memory. Traditionally the domain of animal research, human analogues of spatial memory tasks used in animals such as the Morris Water

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Test (1984) have been developed and are beginning to be employed in psychiatric disorders. These tasks mimic the demands of real life spatial cognition, allow different spatial frames of reference to be explored and may be a more sensitive marker of spatial ability. This field of cognition and its application in schizophrenia will be discussed in Chapter 4.

2.4   Summary

Schizotypy is associated with changes in psychophysiology, cerebral asymmetry and cognition. The latter is by far the most extensively studied and provides broadly consistent results of cognitive impairments across domains in schizotypal personality. Inconsistencies within the literature tend to reflect methodological issues with selecting schizotypes particularly whether a symptom based scale (e.g. perceptual aberration) or a syndrome based scale (e.g. SPQ) is used. With regards to the latter, findings also differ between studies which use the total score and those who use the underlying dimensions as their measure of interest.

Whilst this chapter is not an exhaustive coverage of cognition and schizotypy, it aims to summarise the main findings in the field and present a backdrop of the cognitive profile of schizotypal personality. The cognitive and psychophysiological research suggests involvement of the prefrontal cortex and temporal-limbic regions in schizotypal personality. Although in its infancy the use of structural and functional imaging within schizotypal individuals is also beginning to provide evidence of abnormal neural structure and function within this group. This research will now be reviewed in Chapter 3 along with the neurochemical and physiological basis of the structural and functional abnormalities reported in schizotypal personality.

Chapter 3:   Neuroimaging in schizotypal personality

Neuroimaging has become an important tool in psychiatric and personality research. Several techniques have been developed in order to understand the biological determinants of illness, effects of treatment and the influence of genetic and environmental risk factors. The two techniques most commonly used are structural and functional magnetic resonance imaging (MRI). Interested readers are directed to Suckling & Bullmore (2000) and Bullmore & Suckling (2000) for a comprehensive explanation of structural and functional MRI, respectively. Specific details of image acquisition and analysis relevant to the techniques used in this thesis will be provided in the relevant experimental chapters.

In this chapter I will discuss the structural and functional MRI findings to date in schizotypal personality. Although this thesis is concerned with determining the structural and functional correlates of schizotypal personality I will briefly introduce the structural and functional findings in schizophrenia for three reasons: 1) the schizophrenia results have informed many of the hypotheses concerning schizotypal personality; 2) In some areas, little research has been done in schizotypal personality; and 3) impetus for schizotypal research has partly been in search of clues to the etiology of schizophrenia. Also, as structural and functional MRI are used in this thesis findings using these imaging modalities will be the main focus but Diffusion Tensor Imaging (DTI) and neurochemistry will also be discussed. Finally, I will present a model by Siever & Davis (2004) that has sought to integrate the findings in schizophrenia and schizotypal personality.

3.1 Brain structure in schizophrenia and schizotypal personality

Both Kraepelin and Bleuler (1911) believed that brain abnormalities would ultimately be linked to the etiology of schizophrenia. It is only recently that the tools have become available to test this hypothesis, firstly with Computerised Tomography (CT) and then later using MRI, the latter providing an unprecedented and exquisitely detailed view of neuroanatomical differences, in vivo.

3.1.1 Structural MRI in schizophrenia

A meta-analysis by Wright et al (2000) reported reduced cerebral volume (2% reduction) but enlarged ventricular volume (26% increase) in patients with schizophrenia compared to controls. Enlargement of the lateral ventricles is one of the most robust MRI findings in schizophrenia with 80% of studies reporting this abnormality (Shenton, et al., 2001).

A review by Shenton et al also reported that the temporal lobes were preferentially involved in schizophrenia with 74% of studies reporting this (Shenton, et al., 2001)[5]. The temporal lobes have received widespread attention for their involvement in the pathogenesis of schizophrenia. Volume reductions of the amygdala (e.g. Barta, Pearlson, Powers, Richards, & Tune, 1990; L. Marsh, Suddath, Higgins, & Weinberger, 1994), hippocampus (Becker et al., 1990; Becker et al., 1996; Gur et al., 2000), and parahippocampal gyrus (Becker, et al., 1990) are reported in chronic schizophrenia. First episode patients also evince volume reductions in these regions (Copolov et al., 2000; Lawrie et al., 1999) as do first degree relatives (Seidman et al., 1999). Those at high risk for developing psychosis have also demonstrated volume reductions in the medial temporal lobes (Lawrie, et al., 1999) suggesting that medial temporal lobe abnormalities represent a

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[5] Although this review was conducted in 2001, a recent review by the lead author in 2010 reports that these figures have not changed appreciably in the last decade (Shenton, Whitford, & Kubicki, 2010).

marker for vulnerability to the disorder. Weinberger (Weinberger, 1987, 1999) suggests that "genes involved in the development and maintenance of hippocampal circuitry or in the expression of molecules that mediate certain aspects of neural plasticity" in the hippocampus may play a critical role in the genetic predisposition to schizophrenia. A recent meta-analysis of VBM studies also revealed the most consistent reductions are found in the left medial temporal and left superior temporal gyrus in patients with schizophrenia (R. Honea, Crow, Passingham, & Mackay, 2005). This review highlighted the left hemisphere as displaying the most prominent abnormalities in schizophrenia, a finding that has been extensively reported in the literature.

The prefrontal cortex is one of the most highly complex and evolved neocortical regions of the human brain with both efferent and afferent connections to all other areas of the cortex, as well as to limbic and basal ganglia structures (Goldman-Rakic, Selemon, & Schwartz, 1984). It has been implicated in the pathophysiology of schizophrenia because of its involvement in executive functioning, working memory, language production, attention and motivation and emotional processing (Barch, 2005). Structural MRI suggests a moderate involvement of the prefrontal cortex, specifically the inferior and middle frontal gyrus (Buchanan et al., 2004; J. M. Goldstein et al., 1999; R. Honea, et al., 2005; Suzuki et al., 2005; Zhou et al., 2005). Investigations into the prefrontal cortex in at risk groups has demonstrated reduced prefrontal volumes (Pantelis et al., 2005) and increased right prefrontal cortical folding (Johnstone, Ebmeier, Miller, Owens, & Lawrie, 2005) in those at risk for developing schizophrenia. A review by Pantelis et al (2005) of longitudinal MRI studies in first episode patients, prodromal patients and high risk individuals has suggested that an acceleration of gray matter reduction in prefrontal regions early in the course of the illness leads to further progressive changes in the medial temporal and orbitofrontal regions. These investigators interpret findings to date as indicative of an early neurodevelopmental insult that "renders the brain vulnerable to later brain maturational processes" which take place during adolescence and early adulthood (Shenton, et al., 2010).

Other brain regions implicated in schizophrenia are the parietal lobe (60% of studies), cavum septum pellucidum (92% of studies), basal ganglia (68% of studies), corpus callosum (63% of studies), thalamus (42% of studies) and cerebellum (31% of studies) (Shenton, et al., 2001; Shenton, et al., 2010).

The pattern and number of abnormalities is consistent with disturbed connectivity within and between brain regions. Several theories have been proposed to explain the abnormalities observed in schizophrenia, many of which are likely functionally related. Andreasen et al (1999) proposed a theory of "cognitive dysmetria" whereby abnormalities in the thalamus and its cortical and subcortical connections underpin a central information processing deficit. Buchsbaum et al (1990) have focused on abnormalities of the frontal lobes, basal ganglia and temporal lobe connections. In contrast, Weinberger et al (1987) have proposed that schizophrenia arises from alterations in temporal lobe structures that interrupt connections between temporo-limbic and prefrontal regions and vice versa. Feinberg (1982) proposed that neurodevelopmental abnormalities arise from errors in synaptic pruning that occur during adolescence and early adulthood. Crow (1990) has suggested a neurodevelopmental theory that focuses on temporal lobe regions that are highly lateralised and essential for language production. Shenton and colleagues (McCarley, Hsiao, Freedman, Pfefferbaum, & Donchin, 1996; McCarley et al., 1999; Shenton et al., 1992) have also placed emphasis on the temporal lobe structures and highlight damage to an "interconnected neural network that is functionally important for language and associative links in memory" as being the fundamental deficit in schizophrenia. Pearlson et al (1996) have highlighted heteromodal association areas of the brain as being fundamental to the neuropathology of schizophrenia. Gray et al (1998) has proposed a neuropsychological model which suggests that structural abnormalities of the limbic forebrain affecting the hippocampal formation, amygdala and frontal neocortex leads to functional neurochemical abnormalities in ascending mesolimbic dopaminergic pathways. This in turn

disrupts cognitive processes and so produces the positive symptoms of psychosis. Many other theories exist and so far a unifying theory remains elusive.

These models can also be applied to schizotypal personality and Shenton et al (2001) suggest that evidence acquired from the study of structural and functional imaging in this group would forward our understanding of the pathogenesis of schizophrenia spectrum disorders.

3.1.2 Structural MRI in schizotypal personality

The findings from structural MRI of schizotypal personality disorder mirror those reported in schizophrenia to a large extent. Volume reductions are reported in the temporal lobes including medial temporal lobe structures such as the hippocampus (Dickey et al., 2007; Kawasaki et al., 2004; Suzuki et al., 2002) and left entorhinal cortex (Yoneyama et al., 2003), and neocortical regions such as the superior temporal gyrus (K. E. Goldstein et al., 2009; Wolf, Strenziok, & Kyriakopoulos, 2009). It has been suggested that structural abnormalities of the temporal lobe regions are common to all schizophrenia spectrum disorders (Siever et al., 2002). In relation to these altered temporal regions, a large cavum septum pellucidum is also reported in schizotypal personality disorder (Dickey, et al., 2007; Hoppe et al., 2008)). The Cavum Septi Pellucidum (CSP) is caused by an incomplete fusion of the septum pellucidi and is a normal anatomical variant however an unusually large CSP may reflect abnormal development of the corpus callosum, amygdala and hippocampus (Kyriakopoulos, Bargiotas, Barker, & Frangou, 2008). One study demonstrated no differences in the size of the cavum septum pellucidi in schizotypal or schizophrenic subjects. However, a large CSP in schizotypal patients was related to smaller bilateral amygdalae and left posterior parahippocampal gyrus whereas a large CSP in normal controls did not affect medial temporal lobe structures (T. Takahashi et al., 2007). Other areas where volume alterations have also been observed in schizotypal personality disorder are the parietal lobes (Zhou et al., 2007), insula (Yoneyama, et al., 2003), thalamic nuclei (Byne et al.,

2001) and the caudate nucleus (Levitt et al., 2002). Given the inconsistent findings in schizophrenia of volume alterations in thalamic and basal ganglia regions due to medication effects, findings of volume alterations in schizotypal personality suggests these are altered in the absence of significant illness confounds.

Unlike the widespread structural alterations observed in the prefrontal cortex in schizophrenia, findings for prefrontal alterations in schizotypal personality disorder have been remarkably inconsistent. Both Kawasaki et al (2004) and Hazlett et al (2008) have reported reduced volume of the prefrontal cortex in SPD but several studies have not found any differences between controls and patients in this region (Raine et al., 2002; Siever, et al., 2002). Additionally, although the inferior frontal gyrus was reduced in schizotypal personality there was a sparing of key regions such as BA10 which was larger in schizotypal personality (Hazlett, et al., 2008). This study therefore questioned a simple spectrum model where attenuated differences are seen in schizotypal personality; instead some regions demonstrate volume reductions to the same magnitude as schizophrenia whereas other regions show attenuated volume reductions. In addition, volume increases of some regions are observed in schizotypal personality. Taken together this pattern is consistent with a multiple gene model in which several deficits produce schizophrenia, fewer deficits produce schizotypal personality and protective factors modulate the full development of schizophrenia in schizotypal personality. Several authors have suggested that prefrontal regions, or at least some regions of the prefrontal cortex, may act as these protective factors in schizotypal personality reducing the impact of genetically determined temporal lobe abnormalities (Siever & Davis, 2004; Suzuki, et al., 2005).

However, studies in patients with schizotypal personality disorder are often subject to the same considerations as research into schizophrenia patients in that some patients have received medication, and have received a diagnosis indicating the disorder was severe enough to seek

help. Also, some studies recruit patients with schizotypal personality disorder from the community and others use subjects who are psychiatric outpatients which suggest stage of illness may be a factor in interpretation of these studies. Thus, researchers have also assessed brain structure in healthy volunteers with schizotypal traits.

Interestingly, the pattern of volume loss observed above has also been reported in this group. An early study by Raine et al (2002) reported negative correlations between several of the schizotypal scale scores and morphometric measures, most notably in the prefrontal areas bilaterally. That is the smaller the frontal lobes the higher the schizotypal scores and the poorer the neuropsychological functioning. Flaum & Andreasen (1995) also obtained MRI scans and scores on several schizotypy scales in a sample of 85 healthy volunteers demonstrating a trend towards larger ventricular sizes and smaller brain volumes with higher schizotypy scores. However, the only statistically significant correlation was that between hippocampal volume and the perceptual aberration score indicating that reduced hippocampal volume in those subjects with higher positive schizotypy scores. This is particularly meaningful in light of the wealth of neuroimaging data implicating the hippocampus in schizophrenia and provides further support for the commonality of medial temporal lobe impairments along the schizophrenia spectrum.

Two recent studies have examined volumetric differences in schizotypal individuals with a focus on the positive features of schizotypy using the CAPE (Modinos et al., 2010) or the RISC (U. Ettinger et al., In press). Modinos et al (2010) reported increased volume of the precuneus and medial posterior cingulate cortex in high positive schizotypy scorers compared to low positive schizotypy scorers. In contrast, Ettinger et al (In press) report that high schizotypy scores on the RISC are associated with reduced brain volume in the superior and orbital medial frontal gyrus, gyrus rectus, anterior cingulate cortex, insula, middle and superior temporal cortex and the rolandic operculum. Unlike Modinos et al (2010) who found that high positive schizotypes had

larger global volumes compared to subjects with low positive schizotypy scores, Ettinger et al (In press) found no association between positive schizotypy scores and global volume. The discrepancy between the two studies is likely due to methodological differences including different schizotypal measures and different statistical treatment of schizotypal traits. Modinos et al (2010) compared regional and global brain volume between two groups, high and low scorers on the CAPE whereas Ettinger et al (in press) performed correlational analysis between RISC scores and regional and global brain volumes. Notably, the findings are surprising from the Ettinger et al (in press) study since the sample did not include particularly high scores on the RISC and included areas commonly reported in schizophrenia including prefrontal regions. However, correlation between regional brain volume and schizotypy scores does not indicate that brain volumes are reduced significantly in schizotypal personality merely that they vary according to schizotypal traits. Both studies interpret their findings as indicative of the neurobiological relationship between schizotypal traits and schizophrenia but clearly more research needs to be done in schizotypal research before firm conclusions of this nature can be drawn. Using a questionnaire with negative symptoms dimensions for example the SPQ (Raine, 1991) or OLIFE (Burch, et al., 1998) would further our knowledge about brain structure in healthy volunteers with schizotypal traits.

The multifocal nature of gray matter volume deficits in schizophrenia and schizotypy is consistent with theories of schizophrenia as a disturbance in the connections between brain regions. Brain connectivity is dependent upon the integrity of the myelinated axon sheaths that form the infrastructure for the transmission of signals between proximal and distant populations of neurons (Davis et al., 2003). These interconnecting fibres form neural circuits which subserve cognitive functions, for example. Interest in the integrity of these white matter connections has grown exponentially since the introduction of diffusion tensor MR imaging, a method for quantifying and visualising white matter structure.

3.1.3　DTI studies in schizophrenia and schizotypal personality

DTI is based on modification of conventional MRI in a way that allows quantification of the diffusion characteristics of water molecules (Le Bihan et al., 2001). Diffusion is isotropic when the motion is the same in all directions but in the brain water molecules are restricted by tissue components (i.e. myelin sheaths, cell membranes) so that they diffuse more freely along neural fibre tracts than across them.

The most commonly reported measure of diffusion is fractional anisotropy (FA), which is an estimate of the diffusion attributed to anisotropy with values ranging from 0 (no anisotropy) to 1 (diffusion hypothetically allowed only in a single direction). To provide a concise overview of the literature on white matter microstructure, studies will be reviewed here that utilise FA as the primary measure of interest. FA is thought to be a marker of the structural integrity of fibres, the degree of myelination, coherence of fibre tracts and fibre diameter and packing density (Koychev, et al., 2011). Change in this index could indicate changes in any one of these characteristics or indeed in any combination of them.

DTI findings in schizophrenia have largely shown that FA is reduced in patients compared to controls (Kyriakopoulos, et al., 2008). White matter tracts that are reported to be affected include the corpus callosum (Agartz, Andersson, & Skare, 2001; Ardekani, Nierenberg, Hoptman, Javitt, & Lim, 2003; Buchsbaum et al., 2006; Caan et al., 2006; Foong et al., 2000), the arcuate fasciculus (Burns et al., 2003; Kubicki et al., 2005; Kubicki, Westin, McCarley, & Shenton, 2005), the cingulum bundle (Kubicki et al., 2003; Sun et al., 2003; Wang et al., 2004) and internal capsule (Federspiel et al., 2006; Kubicki, Park, et al., 2005; Szeszko et al., 2005). Similar to findings reported using conventional MRI, compromised white matter integrity is most commonly reported to affect the frontal and temporal lobes (Kyriakopoulos, et al., 2008) especially in the left hemisphere (Ellison-Wright & Bullmore, 2009).

A small number of studies have also reported no differences between groups on measures of diffusion (Begre et al., 2003; Kanaan et al., 2005; Kubicki, Westin, Maier, Frumin, et al., 2002; Kubicki, Westin, Maier, Mamata, et al., 2002; Mendelsohn, Strous, Bleich, Assaf, & Hendler, 2006; Price, Bagary, Cercignani, Altmann, & Ron, 2005; Wang et al., 2003). This may be due to methodological issues as is the case with studies that have used a single slice of a region of interest (Kubicki, Westin, Maier, Frumin, et al., 2002) or choice of patient group (Mendelsohn, et al., 2006; Price, et al., 2005). These last two studies used first episode patients and this patient group has so far demonstrated equivocal results in terms of white matter imaging with as many negative as positive findings (for review see B. D. Peters, Blaas, et al., 2010). Evidence has also emerged suggesting that FA values are altered in high risk groups although again results are inconsistent (Hoptman et al., 2008; B. D. Peters et al., 2010).

Alterations in white matter integrity have also been reported in schizotypal personality using diffusion tensor imaging (Hazlett et al., 2011; Nakamura et al., 2005). In the Hazlett et al (2011) study lower FA was revealed in left temporal lobe and posterior cingulum but no differences in FA were found in prefrontal regions. This is in line with the conventional MRI results that suggest relative sparing of the prefrontal regions in SPD (Siever & Davis, 2004). A study by Nakamura et al (2005) did not find alterations in the cingulum bundle in SPD patients; however they did not segment the cingulate into its anterior and posterior regions. They did however demonstrate reduced anisotropy in the uncinate fasciculus, suggesting that the connections between temporal and frontal regions may be compromised in SPD.

Alterations of FA have also been demonstrated in healthy volunteers with schizotypal traits, as measured using the SPQ (M. T. Nelson et al., 2011). Regression analysis revealed relationships between reduced FA of seven white matter tracts and increased scores on the cognitive perceptual dimension of the SPQ. This subscale reflects positive schizotypal traits and is in line

with research in schizophrenia that has linked altered brain connectivity to positive symptoms. The authors suggest that the neurobiological basis of schizotypy may be the same as the neurobiological basis of schizophrenia spectrum disorders.

3.2 Brain function in schizophrenia and schizotypy

Functional imaging studies are numerous and diverse in psychosis and thus I shall focus mainly on fMRI results that are related to this thesis and which best summarise the functional imaging literature in schizophrenia and schizotypal personality. Spatial learning and memory will be discussed in the next chapter and results obtained, where available, for the tasks used in this thesis will be introduced in the relevant experimental chapters.

3.2.1 Functional studies in schizophrenia

It has long been proposed that schizophrenia is associated with abnormal neuronal activity. The first reports of abnormal brain function in schizophrenia using functional neuroimaging techniques were of hypofrontality at rest as measured by regional CBF (Ingvar & Franzen, 1974). However, in studies of patients at rest hypofrontality has been an inconsistent finding since resting is physiological and psychologically variable (Weinberger & Berman, 1996).

The alternative is to study neuronal activity during cognitive task completion and functional imaging has provided the means to study the neural basis of cognition directly and to assess the abnormal neural circuitry underlying cognitive dysfunction (Mitchell, Elliott, & Woodruff, 2001). During "activation paradigms" neural response is compared to response during a period of rest or a neutral control condition (usually matched for visual and/or motor components). Careful experimental design ensures that the subsequent difference between the active and control condition "reflects" the brain's response to the cognitive process of interest. Cognitive

activation paradigms have also demonstrated prefrontal hypofunction in schizophrenia patients during working memory (e.g. Callicott et al., 1998; Perlstein, Dixit, Carter, Noll, & Cohen, 2003; Weinberger et al., 1996) executive functioning (e.g.Volz et al., 1997) and verbal recall and word generation (Yurgelun-Todd et al., 1996). However some studies have failed to find evidence of hypofrontality (Honey, Bullmore, & Sharma, 2002) and some have observed hyperfrontality (Callicott et al., 2003; Manoach et al., 2000; Ramsey et al., 2002). Inconsistency within the literature may to some extent reflect the choice of task. Firstly, hypofrontality has been demonstrated in schizophrenia only when placed under increasing cognitive demands (C. S. Carter, Perlstein, et al., 1998). Secondly attenuated prefrontal activation has been reported on a verbal fluency task but not a semantic decision making task in the same group of patients (Curtis et al., 1999). The complex pattern of hypo- and hyper-activation may also suggest alterations in the underlying circuitry for example fronto-parietal connectivity (Honey, et al., 2002) or frontal-striatal connectivity (Manoach, et al., 2000) that subserve working memory and executive function.

The temporal lobes have received much attention in the structural neuroimaging domain demonstrating widespread reductions within this region (for review, see Shenton et al, 2001). There is evidence to suggest this region is also susceptible to significant functional differences in patients. Functional neuroimaging studies have confirmed decreased recruitment of the hippocampus in subjects with schizophrenia particularly pronounced in memory tasks (Achim & Lepage, 2005; Heckers, 2001; Heckers et al., 1998; Ongur et al., 2006). A recent study by Hall et al (2010) compared schizophrenia patients to healthy controls and bipolar patients on a face-name pair memory task during fMRI and found decreased activation of the anterior hippocampus during memory encoding and increased activation of the prefrontal cortex during retrieval. As increased activation of the dorsal-lateral and dorsal-medial prefrontal cortex is imperative for the adoption and maintenance of retrieval strategies, the authors interpret this

finding as indicative of the higher demand placed on schizophrenia subjects to maintain task performance. This increase in demand could reflect either the relatively inefficient prefrontal activation in schizophrenia or a compensation for impaired hippocampal functioning (Heckers, et al., 1998). Hippocampal dysfunction is often concomitant with alterations in prefrontal functioning suggesting that fronto-temporal connectivity is disrupted in schizophrenia (Gur & Gur, 2010).

Functional neuroimaging studies have also identified the anterior cingulate cortex (ACC) as a region of interest in schizophrenia. It has been suggested that the ACC has a modulatory effect on the prefrontal-temporal relationship and that schizophrenia is associated with a disruption of the normal anterior cingulate modulation of prefrontal-temporal integration (Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004). Several tasks have yielded reduced activation in the cingulate gyrus in patients with schizophrenia including the continuous performance task, a measure of sustained attention and a virtual water maze task (Carter et al, 1999), a measure of spatial learning and memory (Sava & Yurgelun-Todd, 2008). Carter et al (1998) suggests that the ACC is sensitive to increasing difficulty and erroneous responses in the continuous performance task suggesting its role in maintaining attention and monitoring performance. However, like other frontal regions, the anterior cingulate has also been shown to be hyperactive in patients (Glahn et al., 2005) possibly suggesting a greater monitoring of cognitive operations in the patient group, or a partial failure to avoid superfluous processing of information non-specific to the task being completed (Nosarti & Shergill, 2008).

Interpretation of functional neuroimaging results in schizophrenia is difficult. For the majority of studies impaired performance in the patient group is reported and generalised cognitive deficits and lower IQ make determining the specificity of functional and cognitive impairments near impossible. Some studies have found functional abnormalities in the absence of

performance differences suggesting some sort of functional reorganisation may take place during development (Mitchell, et al., 2001). Additionally even where no activation differences are found in patients decoupling of performance and neural activity has sometimes been reported suggesting a fundamental abnormality which may present in performance difficulties at higher cognitive loads (Honey, et al., 2002). It has been proposed (Manoach et al, 2000) and demonstrated empirically (Callicott et al, 2003) that some patients (those that do not evince behavioural impairments) are able to recruit alternative brain regions or utilise alternative strategies to accomplish cognitive tasks. However, the underlying mechanism by which this subset of schizophrenia patients can compensate is poorly understood for example do patients who can functionally compensate have less structural alterations than other patients or more successful regulation of neurotransmitter systems or less severity of symptoms or a different profile of symptoms to those who cannot?

3.2.2 Functional studies in schizotypal personality

Several studies have evaluated brain function in schizotypal personality using a wide range of paradigms. In line with the neurocognitive literature executive function and working memory have received most attention. Using SPECT to measure regional CBF schizotypal patients performing the Wisconsin Card Sorting Task revealed lower activation in the left medial frontal gyrus and increased activation in the right prefrontal cortex compared to control subjects (Hoptman, et al., 2008). Reversal of normal lateralisation for performance on the WCST in schizotypal subjects may reflect a compensation for reduced efficiency in the left prefrontal cortex (Hoptman, et al., 2008; Siever & Davis, 2004). Decreased activation of the lateral temporal lobe was also observed in schizotypal subjects in this study but this observation did not reach significance. In a [18F] fluorodeoxyglucose (FDG) PET paradigm measuring brain glucose metabolism demonstrated reduced metabolic rates in lateral temporal regions but not

medial frontal or medial temporal regions in schizotypal subjects whilst performing a verbal learning task. Additionally, SPD patients showed increased metabolic rates in BA10 and occipital regions BA17, 18 and 19 (Buchsbaum et al., 2002).

Koenigsberg et al (2005) investigated visuospatial working memory during fMRI in schizotypal subjects and revealed decreased activation in schizotypal patients in the left ventral prefrontal cortex, superior frontal gyrus, intraparietal cortex and posterior inferior gyrus during memory retention. Increased activation of the right prefrontal cortex and prestriate cortex was observed in schizotypal subjects compared to controls at a trend level. As task performance did not differ between groups the authors interpret increased activation of these regions as indicative of a compensatory mechanism for diminished activation in left prefrontal regions necessary for task performance, similar to what was observed in early SPECT studies of WCST performance. Haznedar et al (2004) investigated cingulate gyrus functioning during a verbal learning test (a modified CVLT) and found increased metabolic rates in the posterior cingulate gyrus in schizotypal personality. However, other studies have reported normal anterior cingulate functioning in schizotypal personality (Mohanty et al., 2005).

Functioning of the prefrontal cortex has also been tested using an emotional version of the Stroop task with decreased activation of the dorsolateral prefrontal cortex observed in schizotypal subjects along with increased activation in the amygdala, hippocampus, basal ganglia and nucleus accumbens (Mohanty et al., 2005). Additionally reduced dorsal and ventro-medial prefrontal functioning has been demonstrated in high schizotypy scorers on a self-other processing task (Platek et al., 2005). Increased activity of the dorsolateral prefrontal cortex (BA9/46) and frontopolar region (BA10) has been observed in positive schizotypy during a theory of mind mentalising task. This suggests that increased activation of task related areas is required to efficiently perform this task in high schizotypy. This study was performed in healthy

volunteers who scored highly on the CAPE and demonstrates a similar pattern of functional activation to that reported in clinically diagnosed schizotypal personality disorder. It should be noted however that not all studies have demonstrated an increase in BA10 in schizotypal subjects; Lagioia et al (2011) reports a decrease in BA10 with increasing schizotypal trait expression in adolescents when deciding whether a word or word-pair was spoken by themselves or an experimenter.

Across tasks and subject groups the functional imaging results suggest that schizotypal personality is associated with decreased activation of task related regions but recruitment or hyperactivation of alternative regions as a compensatory strategy. The findings from the healthy volunteer studies suggest that where task related regions are recruited successfully by schizotypes, increased activation may be necessary to perform efficiently. This complex pattern of decreased/increased activation in prefrontal regions warrants further investigation in schizotypal personality as currently there are a very limited number of functional imaging studies in this group. Further, no studies have specifically investigated brain function of the medial temporal lobes in schizotypal personality using paradigms sensitive to functioning of this region. This is remarkable given the wealth of functional imaging studies implicating that dysfunctional hippocampal activation is observed in schizophrenia and at risk mental states (see above). Also, the structural imaging results suggest that the medial temporal lobes are altered in schizotypal personality which may underlie functional and cognitive differences observed on tasks thought to tap medial temporal lobe abnormalities.

3.3   Neurochemistry in schizophrenia and schizotypy

Here, I will focus on findings from the dopamine literature in schizophrenia and schizotypal personality; research into the latter is still its infancy but is beginning to show similarities with

findings from schizophrenia. I will not discuss other neurotransmitters e.g. glutamate and serotonin, as these have not yet been explored in schizotypy. Some studies have also looked at the relationship between stress and cortisol in schizotypal personality and this will also be mentioned.

According to the dopamine theory, schizophrenia, or more precisely its psychotic symptoms, is the result of subcortical dopaminergic hyperfunction (A. Carlsson, Waters, & Carlsson, 1999). The dopamine hypothesis arose from two observations: 1) the correlation between the antipsychotic potency of neuroleptics and their potency to block D2 receptors (Seeman & Lee, 1975); and 2) That DA enhancing drugs such as amphetamine has psychogenic effects (Lieberman, Kane, & Alvir, 1987). Empirical evidence has converged from two main sources: the density of D2 receptors in the striatum and increased responsiveness to d-amphetamine in schizophrenia patients. Firstly, there is a small increase in the density of D2 receptors in schizophrenia although there is considerable overlap between controls and patients (Zakzanis & Hansen, 1998). Secondly, enhanced dopamine release is evident in patients after acute administration of amphetamine and exacerbates positive symptoms (Laruelle, Abi-Dargham, Gil, Kegeles, & Innis, 1999; Laruelle et al., 1996). The clinical relevance of increased dopamine is explained by the salience attribution theory of schizophrenia which proposes that enhanced dopamine release in schizophrenia could underlie hallucinations and delusions through the attribution of abnormal salience to neutral (not especially salient) internal and external stimuli(Kapur, 2003)

It has been suggested that negative symptoms are associated with decreased dopaminergic function in the cortex and positive symptoms with increased dopaminergic transmission in subcortical/mesolimbic pathways (Weinberger, 1987). The relationship between cortical and subcortical dopamine functioning has been explored by Bertolini et al (1998) who measured

striatal dopamine release and N-acetyl aspartate (NAA) levels in the frontal cortex in the same schizophrenic patients. Lower NAA measures in dorsolateral PFC were correlated with higher striatal dopamine release after amphetamine administration in patients but not in controls suggesting that dopamine release is related to prefrontal integrity.

The dopamine hypothesis has dominated the literature but researchers are also paying attention to other neurotransmitter functioning including serotonin (Wooley & Shaw, 1984), glutamate (J. S. Kim, Kornhuber, Schmid-Burgk, & Holzmuller, 1980), GABA (Goldberg, Berman, Randolph, Gold, & Weinberger, 1996) and noradrenaline (Brodaty et al., 2002). Furthermore, dopamine is modulated by other neurotransmitter activity and greater emphasis has been placed on understanding the systems modulating or acting on dopamine neurons and their mutual interactions, cortically and subcortically, for example glutamatergic and monoaminergic interactions (M. Carlsson & Carlsson, 1990)dopaminergic, serotonergic and noradrenergic limbic interactions (Joyce, 1993)and dopaminergic, glutamatergic, GABAminergic, noradrenergic, serotonergic and acetylcholine interactions (A. Carlsson, 1995).

Patients with schizotypal personality disorder also demonstrate exaggerated dopamine release in the striatum following d-amphetamine challenge (Abi-Dargham et al., 2004). A study by Woodward et al (2011) has demonstrated that dopamine release in striatal and extrastriatal regions (left middle frontal gyrus and left supramarginal gyrus) is increased in healthy volunteers with schizotypal trait expression. The magnitude of this dopamine increase is greater than normal controls but less than schizophrenia patients. This suggests that altered dopamine functioning may be a trait marker for schizophrenia. Elevated dopamine response in prefrontal regions in this study seems to contradict the frontal hypodopaminergic hypothesis. However, the authors question the validity of the hypodopaminergic hypothesis as results have been largely inconsistent (Woodward et al., 2011). Using [11C] Raclopride positron emission tomography

Soliman et al (2008)measured changes in synaptic dopamine concentrations in controls and psychometric schizotypes, 9 with perceptual aberrations (positive schizotypy) and 7 with physical anhedonia (negative schizotypy) whilst doing a psychological stress test and sensory-motor control task. Both controls, positive and negative schizotypes displayed increased self-report stress and cortisol levels in the stress condition. Only negative schizotypy was associated with stress induced dopamine release.

Disturbances in hypothalamic-pituary-adrenal axis (HPA) functioning as indicated by cortisol have been reported in schizotypal personality. Increased cortisol has been reported in patients with SPD and interpreted as a function of hypersensitivity to test novelty (D. D. Weinstein, Diforio, Schiffman, Walker, & Bonsall, 1999). Increases in cortisol at baseline have also been associated with increased severity of SPD symptoms two years later (E. F. Walker, Walder, & Reynolds, 2001). A change in cortisol levels suggests increased vulnerability to stress in schizotypes and mirrors findings reported in schizophrenia. However, introduction of a metabolic stressor (2-deoxy-glucose), which produces an increase in plasma homovanillic acid (HVA) in patients with schizophrenia, does not have this effect in schizotypal individuals. In schizotypal individuals, this same stressor produces equivalent HVA levels between schizotypes and controls and a blunted cortisol response which has been interpreted as a buffering mechanism against hypothalamic-pituary-adrenal axis stress activation in schizotypal personality (Mitropoulou et al., 2004).

Clearly more research is needed into the neurochemical and endocrinological basis of schizotypal personality both in terms of expansion of the literature on dopamine and cortisol and also initiating research into other neurotransmitters particularly glutamate, GABA and serotonin.

3.4   A pathophysiological model of schizotypal personality

Schizotypal personality evinces many of the same structural and functional disturbances as schizophrenia, but schizotypal personality has one clear difference in that structural and functional disturbances are attenuated and the prefrontal cortex is to some extent spared compared to schizophrenia (see sections above).

This has important implications for the understanding of schizophrenia and schizotypal personality and Siever & Davis (2004) propose a model that suggests that a frontal buffer system in schizotypal personality protects schizotypal individuals from developing a more severe psychotic disorder. They hypothesise that both disorders share a "common genetic anomaly that renders the temporal lobe particularly vulnerable to environmental insults such as hypoxia." (Siever & Davis, 2004, p. 406). However, other genetic factors or more favourable environmental influences leave the schizotypal individual better 'buffered with regard to frontal lobe volume and function as well as stabilisation of subcortical dopaminergic activity." (Siever & Davis, 2004, p. 406). In schizotypal personality, mitigating factors may be increased frontal reserve capacity or preservation of general intelligence.

Based on the broadly consistent findings of normal or increased prefrontal volumes in schizotypal personality, this model suggests that greater prefrontal reserves in schizotypal personality disorder are protective against cognitive and social deterioration associated with the more severe schizophrenic expression. These frontal reserves may be used to compensate for dysfunction in other regions of the cortex or even other dysfunctional frontal regions. For example, the dorsolateral prefrontal cortex is preferentially recruited by healthy volunteers to accomplish working memory tasks but hypoactivation is reported in schizophrenia and schizotypal personality disorder. However, individuals with schizotypal personality recruit

alternative frontal regions such as BA10, to a greater extent than controls. Additionally schizotypal subjects have increased volume in BA10 (Hazlett, et al., 2008) and increased glucose metabolism in this region (Buchsbaum, et al., 2002). This model purports that schizophrenia patients however would not be able to similarly compensate substantially by activating supplementary brain regions because of the widespread volume reduction evinced by patients with schizophrenia. See Figure 2 which demonstrates a cascade of pathology in schizophrenia.
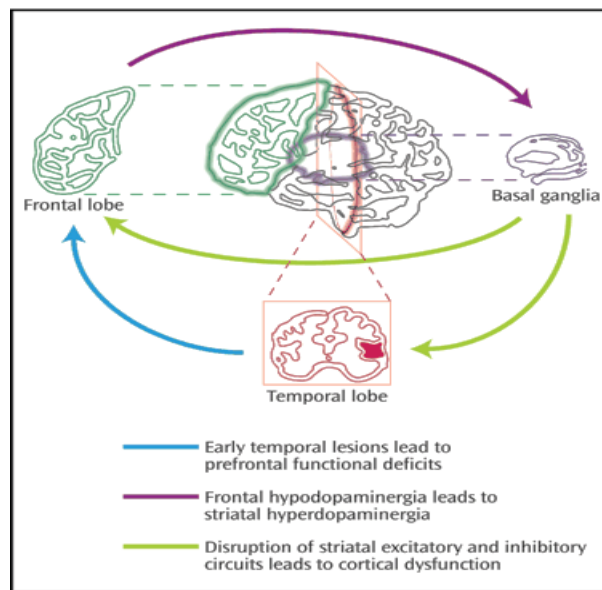
Figure 2 Cascade of pathology in schizophrenia (Siever & Davis, 2004)

Previous findings of reduced dopamine release in schizotypal personality compared to schizophrenia following amphetamine administration or stressors that perturb dopaminergic activity has led to the suggestion that intrinsic dopamine activity in the striatum may be more effectively regulated in schizotypal personality.

Animal models of schizophrenia have demonstrated that lesions in the prefrontal cortical dopamine circuits results in up-regulation of subcortical dopamine release and dopamine receptor sensitivity (Pycock, Kerwin, & Carter, 1980). Thus, frontal cortical hypodopaminergia

could lead to subcortical dopaminergic overactivation in schizophrenia (see Figure 2). Schizotypal individuals may therefore "be constrained in their capacity for up regulation of subcortical dopaminergic activity, receptor regulation or other key modulator systems such as the glutamate system" (Siever & Davis, 2004. p. 409). Individuals with schizotypal personality may be less likely to up-regulate subcortical dopaminergic systems than patients with schizophrenia in response to frontal hyodopaminergia, which is protective against the overt psychosis. (Figure 3).
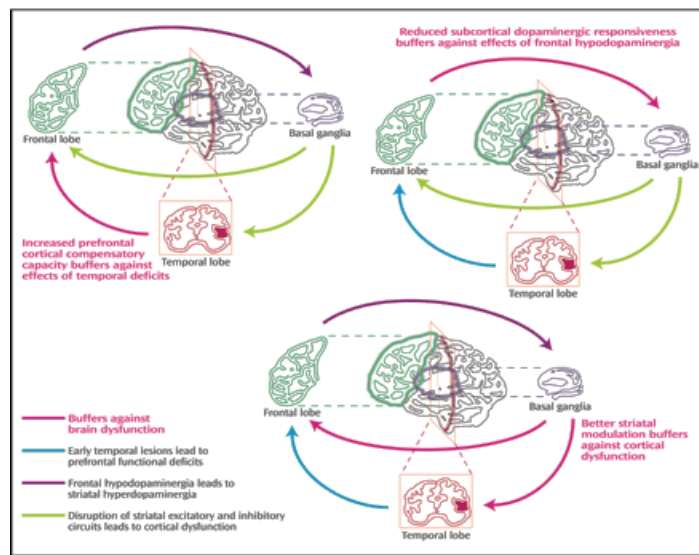
Figure 3 Buffers against deficits and dysfunctions in schizotypal personality (Siever & Davis, 2004)

Although Siever & Davis (2004) base this model on patients with schizotypal personality disorder, the evidence from healthy volunteers with schizotypal traits suggests that they too have demonstrable structural and functional impairments involving the temporal lobes and some areas of the prefrontal cortex with less evidence for significant widespread frontal deficits. The authors suggest that this model provides the means of testing phenotypic trait expression particularly traits that are common to all schizophrenia disorders and which "might reflect genetically

determined impairment prominently expressed in temporal or hippocampal regions" (Siever & Davis, 2004).

However, one caveat to the model presented by Siever and Davis is findings from studies of relatives of patients with schizophrenia. Evidence suggests that relatives of patients with schizophrenia have higher levels of schizotypal traits (Grove, et al., 1991; Kremen, Faraone, Toomey, Seidman, & Tsuang, 1998; P. M. Miller, Lawrie, Byrne, Cosway, & Johnstone, 2002; Yaralian, et al., 2000) as well as alterations in executive function (Sitskoorn, et al., 2004) and reduced prefrontal cortical volumes (Harms et al., 2010; Rosso et al., 2010). Several suggestions can be made as to why this may be the case including additional genetic factors in the families of those with schizophrenia, more obstetric complications that may be associated with the medical history of families with schizophrenia, a more favourable environment in individuals with schizotypal personality disorder or lower IQ and educational status in families with schizophrenia.

This model encapsulates the findings from diverse imaging modalities and attempts to explain how schizotypal personality can be both similar and yet distinct from schizophrenia. Although this model is based on empirical findings, the number of imaging studies in schizotypal personality are neither numerous nor overwhelmingly consistent. As research into schizotypy continues evidence will illuminate the neural correlates associated with schizotypal personality. If sufficient research accumulates to support the idea of temporal lobe impairment alongside relative sparing of the frontal lobes in schizotypal personality, this represents a potential target for treatments and early intervention.

3.5   Summary

To summarise, brain structure and function is altered in schizophrenia, schizotypal personality disorder and in healthy volunteers with schizotypal traits. The latter evinces subtle structural and functional changes that are beginning to emerge with the advancements in imaging technology and analysis and with renewed interest in schizotypal personality. The findings in schizotypal personality are similar to those reported in schizophrenia but with a clear difference; the degree to which the brain is affected is attenuated and specifically there appears to be a relative sparing of some regions of the prefrontal cortex reported in most of the studies. The results overall indicate that medial temporal lobe impairments are indicative of the vulnerability to schizophrenia being demonstrable in schizophrenia, clinical schizotypal personality and healthy volunteers with schizotypal traits. Lastly a model has been suggested in which individuals with schizotypal personality possess prefrontal reserves that act as a "buffer" to lessen the effects of shared susceptibility genes. It remains to be seen if this model will hold out in the face of expanding research into the neurobiology of schizotypal traits.

Chapters 1 to 3 of this thesis have introduced the concept of schizotypy and presented the cognitive and neural findings in schizotypal personality research to date. In chapter 4, I will discuss the area of cognition addressed in this thesis, allocentric spatial memory, and the study rationale for exploring this cognitive domain in schizotypy.

Chapter 4: Spatial Cognition

This chapter will introduce the area of cognition investigated in this thesis. To begin, I will present the types of spatial navigation used to describe how humans navigate through space with specific attention paid to the distinction between allocentric and egocentric frames of reference. I will then discuss the two most common tasks used to assess spatial memory in animals, namely the Morris Water Maze (MWM) and the Radial Arm Maze (RAM) before introducing the human analogues of these tasks. The neural correlates of allocentric spatial memory in healthy volunteers will be discussed and then the application of these tasks in schizophrenia. No studies to date have assessed spatial cognition in schizotypal personality and this forms the rationale for this thesis.

4.1   Frames of reference

Spatial information can be organised using two frames of references: egocentric and allocentric. The framework in which spatial information is organised is integral to understanding how an individual represents and responds to the environment (Dolins & Mitchell, 2010).   How information is organised affects how it will be used in spatial strategies, in updating navigational decisions and in creating an organisational basis for future spatial behaviour (Wickens, Vincow, & Yeh, 2005).

An egocentric frame of reference is based on the perspective of the perceiver and can focus on the entire body or on body parts such as a shoulder or hand or on objects relative to the body (Gurfinkel & Levick, 1991). Navigational strategies based on egocentric frameworks are those that use self-movement related or idiothetic cues or static external reference points as a beacon. Similarly multiple sequential discrete points can be integrated within an egocentric framework in

route following/path integration (Collett & Graham, 2010). Therefore, an egocentric framework changes as the body moves through space constantly updating egocentric spatial maps by incorporating new information derived from new bodily positions. However, spatial updating of egocentric representations fall prey to cumulative errors after relatively short paths (Etienne, Maurer, & Seguinot, 1996). Thus, when attempting to return to a remembered location from a new direction after a short period of self-motion, representation of the location relative to the environment will often be of more use than egocentric representations.

An allocentric frame of reference represents external objects and locations as defined by the relationships amongst them and is independent of the observer's viewpoint (Klatzky, 1998). Allocentric spatial frameworks provide the potential for computing novel routes during navigation as it is not dependent on the self to provide details of distance, angle or direction to an object or multiple objects within space. Thus, an individual can move freely about in familiar space from any starting place to any destination. Generation of novel routes as defined by Klatzky (1998) uses primitive parameters derived from exploration of the environment to compute derived parameters. For example an individual may have knowledge of the route between X and Y and the route between X and Z. If they want to get to point Y without an internal allocentric representation they would need to travel back to point X as the common point between the two routes and then travel to point Y. However, with an internal allocentric representation, they have the ability to compute a novel route between Z and Y.

For the most part, the rest of this chapter will be dedicated to discussions about allocentric spatial learning and memory.

4.2 An outline of spatial strategies

Several strategies can be employed to navigate around an environment. The main four are: 1) dead reckoning; 2) use of a single cue or beacon; 3) use of sequential cues/route following and 4) place learning.

It is fundamental to animal orientation to be able to start at a fixed point, visit several locations and return to the original point(Gallistel, 1990). Dead reckoning (also termed path integration) is the ability to compute on an on-going basis the direction, speed and physical effort of moving from each of these points, using the self as a cue to map spatial information, movement can be monitored using a mixture of proprioceptive and otolithic input, optic flow and corollary discharge (Waller, Lippa, & Richardson, 2008). As path integration involves computing the current position based on previous positions, there is a margin for error and as such usually involves incorporating at least one distal cue or landmark as a beacon to enable the animal to orient its position in space, in the case of some species using the sun as the main directional marker (Dolins & Mitchell, 2010). Both dead reckoning and use of a single cue/beacon are thought to be based on egocentric frameworks however cue guidance is essentially allocentric as the directional information is not necessarily in relation to the body.

Route following can be both egocentric and allocentric depending on how spatial information is encoded and utilised. In egocentric route navigation, each consecutive cue within a sequence provides directional information and elicits an individual spatial response (e.g. at the tree stump turn right); however, this is not fully egocentric in that directional cues provide orientation in space irrespective of bodily orientation. In order to successfully navigate using this strategy, the animal needs to rigidly use these cues to respond appropriately to each individual cue in the sequence(Dolins & Mitchell, 2010). For a more flexible means of navigation, a more allocentric type of route navigation can be employed. This type of navigation (referred to as a topological

map) relies on knowledge of pre-set routes but with opportunity to compute novel routes or transfer from one route to another as long as there is landmark information common to one or more routes. The animal cannot stray from the pre-set routes but has greater flexibility in terms of generating novel routes(Garber & Dolins, 1996).

Lastly, there is an allocentric framework also referred to as a "cognitive map"(Tolman, 1932, 1948). Within this type of navigation an individual navigates by relying on the spatial relationships between several landmarks/cues simultaneously(Nadel, 1991). Using two or more cues in the environment, additional points in space can be localised and this internal representation of the environmental layout can be used to generate novel spatial information(O'Keefe & Nadel, 1979). The spatial configuration of these landmarks can be as multiple individual landmarks or perceived geometric shapes and how these are perceived will affect the way this spatial information is encoded and exhibited behaviourally. Cognitive mapping provides the most flexible type of navigational strategy provided the relevant, distal cues can be seen in order to compute position within a spatial domain, hence for humans in a city environment it is not always an effective strategy.

Finally it is worth noting that these procedures, although labelled 'strategies' may not necessarily be under strategic control, but deployed 'automatically' or as implicit processes to guide orientation for example, a "sense of direction' in humans may reflect implicit cognitive mapping . In humans, the flexible use of different strategies, also supplemented by prosthetic procedures such as physical maps, deployed also using aerial perspectives is characteristic of navigational behaviour.

4.3   Animal studies of spatial cognition

Many different paradigms have been developed to investigate spatial cognition across many different species of animals.   Two of the most informative are the Morris Water Maze (MWM; R. Morris, 1984) and Radial Arm Maze (Olton & Samuelson, 1976) which have been used to assess spatial learning and memory in rats. The tasks used in this study are human analogues of these two animal tasks and as such these tasks are directly relevant to this thesis. However, the animal literature is vast and as such I will only give a brief introduction to these tasks before discussing their application in humans and ultimately in psychiatric conditions.

4.3.1   Morris Water Maze

The MWM has been employed as a measure of spatial learning and memory in rats for over 25 years. It is a challenging task that requires acquisition and spatial localization of relevant visual cues that are subsequently processed, consolidated, retained and then retrieved in order to successfully navigate and thereby locate a hidden platform to escape the water(D'Hooge & De Deyn, 2001). The standard procedure involves a large circular pool of room temperature water and a fixed platform hidden from view under the surface of the water. In order to hide the location of the platform several techniques can be employed: 1) adding an agent to colour the water opaque; 2) having a clear Plexiglas platform in clear water; or 3) painting the platform the same colour as the pool wall and floor (e.g. black on black). For example, in the original experiment the water was rendered opaque using the addition of powdered or pure milk. Thus, the platform offered no local cues to guide escape behaviour. Four points around the pool are arbitrarily labelled North (N), South (S), East (E), and West (W) and divided on this basis into 4 quadrants.

During training the animals are repeatedly placed in the pool and must learn to escape by locating a platform hidden beneath the surface of the water. An animal can use three different

strategies to reach the escape platform during a trial: 1) it can use a learned sequence of movements, which brings it to the platform (praxis strategy); 2) it can approach the platform using proximal cues (taxis strategy); or it can navigate to the platform using information about the platform's location within the spatial configuration of distal cues (mapping or spatial strategy) (D'Hooge & De Deyn, 2001). Visible platform conditions are sometimes included to control for motivational/emotional and sensori-motor factors and also as a non-spatial control task. Basic training protocols include hidden platform acquisition training, probe trial testing and working memory testing. Standard hidden platform training usually consists of blocks of four swimming trials starting randomly from four positions. After each successful trial, which takes a maximum of 60-120seconds, the animal will have to remain on the platform for a short amount of time. Data from the four starting positions are usually pooled to provide summed or averaged data per trial block. After a series of acquisition trial blocks, probe or transfer trial (s) are usually performed, during which the platform is removed from the pool and the trained animal is allowed to swim freely for a fixed amount of time after being placed in the pool from a different starting location. The spatial accuracy of the rat during such a probe trial is determined by the length of time spent looking for the platform in the quadrant of the pool in which it was previously located and/or by the number of times it crosses the former platform area. Performance measures are usually escape latency (time taken to locate the platform), length of the swimming path and path directionality (correct heading direction).

One of the reasons for the popularity of the MWM lies in its simplicity and it has provided the means to study the neurobiology and neuropharmacology of spatial learning and memory(D'Hooge & De Deyn, 2001). However several characteristics of the experimental animals need to be controlled for when planning and analysing MWM experiments including the effects of age, gender and the physical and psychological health of the animals. For example, males perform better than females (Brandeis, Brandys, & Yehuda, 1989) and physical

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differences aside this has been related to different expressions of sex hormones (Daniel, Roberts, & Dohanich, 1999; Roof, 1993). Age also has a significant effect on MWM performance with increasing age being associated with decline in MWM performance (Brandeis, et al., 1989). This is likely related to age related decline in swimming abilities, locomotion and exploration as well as coinciding with structural and physiological changes in brain regions involved with these functions (Gallagher & Nicolle, 1993). Additionally, spatial learning can be severely impaired in stressed (Holscher, 1999), sick (Gibertini, Newton, Friedman, & Klein, 1995) and undernourished animals (Bedi, 1992).

Spatial learning and memory deficits have been observed in animals with damage to the hippocampus (R. G. Morris, Garrud, Rawlins, & O'Keefe, 1982; Moser, Moser, & Andersen, 1993; Pearce, Roberts, & Good, 1998). Typically animals with hippocampal lesions are impaired on the hidden but not visible platform trials (D'Hooge & De Deyn, 2001) and performance on the MWM has been directly related to the size of the damaged hippocampal tissue (Moser, et al., 1993). Related regions such as the parahippocampal gyrus, entorhinal (Roof, Zhang, Glasier, & Stein, 1993) and perirhinal (Liu & Bilkey, 1998) cortices are also essential for MWM performance. Additional regions involved in MWM performance are the thalamus (Savage, Sweet, Castillo, & Langlais, 1997), striatum (Whishaw, Mittleman, Bunch, & Dunnett, 1987), basal forebrain (Brandner & Schenk, 1998; Waite, Chen, Wardlow, & Thal, 1994) and cerebellum (Lalonde, 1994). Several neocortical regions are also involved in MWM performance including the prefrontal cortex, anterior cingulate cortex and insula and damage to these regions impairs spatial learning and memory (Bermudez-Rattoni, Introini-Collison, & McGaugh, 1991; Mogensen, Pedersen, Holm, & Bang, 1995; Warburton, Aggleton, & Muir, 1998). The involvement of brain regions in spatial cognition is complex and comprises a large number of co-ordinated brain regions constituting a functionally integrated network. Not only does destroying these brain regions impair performance but so does disconnecting the regions

within the spatial neural network (D'Hooge & De Deyn, 2001). For example, lesions to the fimbria-fornix impair spatial learning and memory on the MWM (Nilsson, Shapiro, Gage, Olton, & Bjorklund, 1987); the fimbria-fornix is densely connected with the hippocampus and damage to the fimbria-fornix pathways deprives the hippocampus of many of its cholinergic, noradrenergic and serotonergic afferents rendering the hippocampus dysfunctional and causing lasting impairments to spatial learning and memory capacities (Whishaw & Jarrard, 1995).

4.3.2   Radial Arm Maze

A second task that is routinely employed to assess spatial memory in rodents is the Radial Arm Maze (Olton & Samuelson, 1976). In a typical RAM a number of identical arms radiate out from a central area. At the distal end of each arm a well is situated that may be baited with food. In a standard 8 arm maze, 4 out of the 8 arms would be baited with food. During a trial an animal must retrieve all four rewards, after which the animal is removed from the maze. In subsequent trials, the same 4 arms are rewarded and with training rodents learn to retrieve all 4 rewards without venturing into the never rewarded arms. Also, rodents learn that after retrieving a reward from one arm not to re-enter the same arm again during the same trial. Typically performance is measured as whether the animal remembers which arms are always or never baited (reference memory) and the extent to which the animal remembers previously visited arms during a single trial (working memory), the latter a concept distinct from the notion of working memory in humans.

As with the MWM, age (Barnes & McNaughton, 1980) and sex (LaBuda, Mellgren, & Hale, 2002) have both been shown to significantly affect performance. Stress also appears to impair performance on the radial arm maze (Conrad, 2010) as does malnutrition (Ranade et al., 2008)and infection (Beers, Henkel, Kesner, & Stroop, 1995).

These tasks have been used extensively in neuropharmacological studies and hence this provokes an interest in developing human analogues that can subsequently be used for translational research in humans. The robust nature of these tasks for assessing spatial learning and memory and the flexibility with which these tasks can be used to assess different types of navigation has also encouraged development of human analogues of these tasks, also by taking advantage of advancements in virtual reality (VR) for the study of human cognition. The next section introduces the concept of using virtual environments to study spatial cognition in humans.

4.4   Development of human analogues of animal tasks of spatial cognition

4.4.1   Introduction to virtual environments and their use in cognitive neuroscience.

Over the last decade the study of the neuroscience of human navigation has moved from "table top tests of spatial memory" to real world virtual environments (VE) (Maguire, Burgess, & O'Keefe, 1999). However, real world navigation is not the same as traditional table top tests of spatial memory as they differ in both observer perspective (i.e. viewer centred during navigation compared to an aerial perspective in geographical knowledge tasks) and in terms of their frame of reference (i.e. allocentric in navigation but egocentric in table top tasks). The recent development of computer simulated and virtual environments (VE) have allowed for the capture of the "true dynamism of human navigation" whilst allowing for a degree of experimental control (Maguire, et al., 1999). Further, they reduce the methodological limitations of uncontrolled naturalistic navigation and the financial costs of constructing real life analogues of tasks such as the MWM or the RAM.

Several studies have utilised virtual environments in the study of spatial learning and memory. For example, a study by Maguire et al (1998) used PET to scan subjects whilst they navigated to

locations in a virtual town using their internal representation of the town acquired during a period of training immediately before scanning. Two types of navigation were possible: 1. Subjects could head straight for the goal, and 2. Subjects had to take detours as direct routes were closed or blocked off. Navigation was compared to a task where subjects followed a route, defined by arrows, around the virtual town which required no internal representation. Successful navigation across conditions was associated with bilateral activation of the hippocampus as well as activation in the left lateral temporal cortex, left frontal cortex and thalamus. Interestingly, recruitment of the right hippocampus and inferior parietal cortex were associated with more accurate navigation. The authors interpret this finding as indicative of cooperation between the right hippocampal and right inferior parietal cortex to navigate to an unseen goal. Specifically, the hippocampus provides an allocentric representation of space that allows computation of direction from any start location to any goal location and the parietal cortex uses this information to compute the correct body turns to enable movement toward the goal given the relative location of obstacles in the way and the current heading direction (Maguire, et al., 1998). Thus, the parietal cortex would be involved regardless of the type of navigation employed and is related to an ability to represent or act upon objects located with respect to the egocentric left-right body axis, a fact that has been consistently reported in the literature. Activity in the left hippocampus was interpreted as involved in the active maintenance of the appropriate destination or recollecting specific paths taken during learning; either explanation is consistent with involvement of the left hippocampus in episodic memory for personally experienced events. Navigation involving detours was associated with increased left frontal activation resulting from the demands of switching strategy and its involvement in decision making.

An essentially similar task was used by Spiers et al (2001) to assess spatial learning and memory impairments in subjects with bilateral or unilateral damage to the medial temporal lobes. Subjects were tested on their ability to navigate to ten locations in the town (shown to them as

pictures), their ability to recognise scenes from the town and their ability to construct an accurate map of the town. The right temporal lobectomy patients were impaired on all 3 tests compared to controls taking longer routes, making worse maps and recognising fewer scenes; left lobectomy patients meanwhile performed at an level intermediary between controls and right temporal lobectomy patients.

A key question regarding the development of these tasks has been the degree to which they can simulate the real world environment. In the virtual representation of space the field of view is typically smaller and the detail resolution may be reduced or contain fewer landmark type cues than the real world. Navigation based on cues is also limited to visual cues in the absence of olfactory or auditory cues which are usually present in real world navigation and navigation is based purely on visual information in the absence of vestibular or proprioceptive information. In particular, vestibular and proprioceptive information provides key information in navigational processes such as dead reckoning. Despite this, for allocentric memory and cue guidance these types of cues are not so important and may even provide conflicting information. An important limitation is that the ability to navigate within a VE is via an abstract interface (e.g. mouse, joystick or keypad) which requires a participant to be familiar with such hardware and is not ideal for the perception of the amplitude of turning movements (Chance, Gaunet, Beall, & Loomis, 1998), which tend to be overestimated (Klatsky, Loomis, Beall, Chance, & Colledge, 1998) or underestimated(Witmer & Klein, 1998). The lack of physical locomotion and navigational experience of moving around a real world environment may mean that spatial knowledge is acquired in a VE is qualitatively different to that obtained in the real world.

Despite these limitations, several studies have indicated good correspondence between the acquisition of spatial knowledge in a real environment and a model of that environment in a VE (Ruddle, Payne, & Jones, 1997). This study demonstrated that subjects extensively trained in a

VE had similar accuracy to that of subjects who had worked in the equivalent real building for 1-2 months. Navigation within the VE was aided with structural landmarks created by the building layout but had a limited range of object cues (e.g. plants, pictures) that are present in the real building. Further, subjects were observed to use the landmarks in two ways: 1) by forming associations between landmarks and the position of target rooms and 2) by using landmarks to trigger changes in direction of the routes between two locations. Studies have also demonstrated that spatial information acquired during VE navigation is transferred when subjects subsequently navigate in the real place (Arthur, Hancock, & Chrysler, 1997; Waller, Hunt, & Knapp, 1998). Another important consideration for VE studies is the issue of "presence" which has been defined as the subjective experience of being in one place when one is physically in another. Presence and performance in virtual environments is significantly correlated (Witmer & Singer, 1994).

4.4.3   Virtual Morris Water Maze Studies

Several explicit versions of a virtual Morris Water MWM (vMWM) have been developed. These virtual navigation tasks consist of either a computer generated display of a pool filled with water (Astur, Ortiz, & Sutherland, 1998; Astur, Taylor, Mamelak, Philpott, & Sutherland, 2002; Chamizo, Asznar-Casanova, & Artigas, 2003; Hamilton, Driscoll, & Sutherland, 2002; Moffat & Resnick, 2002; Sandstrom, Kaufman, & Huettel, 1998) or a computer generated circular Arena (W. J. Jacobs, Laurance, & Thomas, 1997; W. J. Jacobs, Thomas, Laurance, & Nadel, 1998; Thomas, Hsu, Laurance, Nadel, & Jacobs, 2001).

For example a common vMWM consists of a circular pool located in the centre of a square room. Surrounding the pool are distal cues but no local cues are available. Subjects are required to virtually swim in the pool using a joystick to navigate and the goal is to locate the hidden platform submerged beneath the surface of the water and thus escape from the pool. The most

efficient method for locating the hidden platform is to encode the location of the hidden platform using the distal cues surrounding the pool. Subjects start from four different locations (N, S, E and W) five times for a total of 20 trials. If a participant swims over the hidden platform a tone sounds and the platform rises out of the water and a message says "congratulations you have escaped the water". Subjects then swim freely or hold still for 10 seconds and then the trial is terminated. After these training trials a probe trial is initiated in which the platform is removed entirely from the water and subjects search for the missing platform. Following this phase of testing the platform is moved to a different location and raised out of the water so that it was visible to subjects. Subjects start from four different locations, two times each, for a total of eight trials. This phase is referred to as "visible platform" training. Measurement is generally how long subjects spend in the correct quadrant of the pool during the probe trials; this measures the success of the subjects encoding of the hidden platform is relation to the distal cues (Astur, et al., 1998; Astur, et al., 2002). Using this task, patients with unilateral temporal lobectomy (5 left sided, 5 right sided), patients with tumours removed outside of the medial temporal lobe and healthy controls were tested. Results revealed that the temporal lobectomy patients performed worse of the virtual MWM and this was not accounted for by global memory differences. Interestingly, the results were not lateralised; patients with left as well as right temporal lobectomies had spatial memory impairments. This in line with the functional imaging studies that have observed left and right sided activation during virtual navigation (Maguire, et al., 1998)

In order to assess the neural correlates associated with this task Shipman & Astur (2008) conducted an fMRI study. Similarly to the Astur et al (2002) study, there was a visible and a hidden platform condition and in order to make comparisons of functional activation, a fixation period. Three important findings were revealed: 1) spatial memory during the hidden condition is associated with activation of the parahippocampal gyrus, precuneus and fusiform gyrus; 2)

activity in the hippocampus proper is greater during the fixation period than during spatial navigation, owing both to an increase in activity during fixation and a decrease in hippocampal activity over hidden trial blocks. Finally an increase in right hippocampal activity is evident during the beginning of hidden platform trials as compared to visible trials. The recruitment of the parahippocampal gyrus is in line with previous studies that have linked parahippocampal activity to the processing of scenes (N. Burgess, Maguire, & O'Keefe, 2002). The precuneus activation is surprising given its strong association with egocentric processing (Committeri et al., 2004; Galati et al., 2000). However, Frings et al (2006) found precuneus activation on a declarative memory task when allocentric spatial memory was required. Although the finding of hippocampal activation during fixation is surprising, the authors acknowledge that hippocampal activation is present early on in the learning trials. Using an event related analysis, the spatial memory components of the task were analysed i.e. the initial orientation in the pool relative to the environment and this was associated with increased right hippocampal activity. It is likely therefore that some aspects of this task are not placing demands on allocentric spatial processing and thus not requiring substantial activation of the hippocampus.

Virtual MWM tasks have been used to demonstrate the effects of sex differences (Astur, et al., 1998; Sandstrom, et al., 1998) and age (Moffat & Resnick, 2002). Further these tasks have been used to investigate spatial learning and memory in schizophrenia (Folley, Astur, Jagannathan, Calhoun, & Pearlson, 2010; Hanlon et al., 2006; Weniger & Irle, 2008), Alzheimers (Cushman, Stein, & Duffy, 2008), mild cognitive impairment (Weniger, Ruhleder, Lange, Wolf, & Irle, 2011), and depression (Cornwell, Heller, Biggs, Pine, & Grillon, 2010; Gould et al., 2007); and conditions associated with damage to areas known to be implicated in MWM performance (the use of these tasks in schizophrenia is discussed later in this chapter).

4.4.4 Virtual Radial Arm Maze Studies

Several researchers have also sought to develop explicit analogues of the RAM (Abrahams, Pickering, Polkey, & Morris, 1997; Astur et al., 2005; Astur, Tropp, Sava, Constable, & Markus, 2004; Bohbot, Iaria, & Petrides, 2004; Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; R. Marsh et al., 2010). These tasks have been used to demonstrate sex differences (Astur, et al., 2004; Levy, Astur, & Frick, 2005; Rahman, Abrahams, & Jussab, 2005) and effects of age (Shukitt-Hale, McEwen, Szprengiel, & Joseph, 2004) in healthy volunteers and to investigate the effects of medial temporal lobe damage in patient groups (Abrahams, et al., 1997; Bohbot et al., 1998; Parslow et al., 2005).

Researchers have used these tasks to investigate the neural correlates of spatial learning and memory associated with performing a virtual RAM (vRAM) using fMRI. Iaria et al (2003) designed a human analogue of the radial arm maze using a commercially available computer game. The virtual environment was composed of an 8 arm RAM with a central start location. Surrounding the maze was a landscape (mountain and sunset) and two trees; a short wall separated the landscape from the trees. At the end of each arm, there was a staircase leading to the location where in some of the arms an object could be collected. This set up ensured that no object or cues could indicate the location of the target objects from the start location. There were three types of trial all of which were composed of two parts. In part one, four of the eight arms was accessible and objects were present in all four arms (e.g. arms 1, 3, 4 and 6). In part two, all arms were accessible and objects were present in the four arms previously blocked (e.g. arms 2, 5, 7, 8). Trials A and B are fundamentally the same but use a different sequence of blocked/accessible arms. Trial C is a probe trial where part 1 is the same as for trials A and B but in part 2 the wall was raised to conceal the landscape and the trees were removed. Following the experiment subjects were asked the strategy they had used to complete the task and were categorised as using a spatial strategy (used two or more landmarks), non-spatial strategy

(counted arms or assigned numbers to arms) or a "shift group" (started using a spatial strategy but shifted to a non-spatial strategy). Regardless of strategy, activation was observed in the posterior parietal cortex, premotor/motor cortices, cingulate gyrus, striatum (caudate and putamen), cerebellum, occipital gyrus and middle frontal gyrus. Subjects spontaneously adopted either a spatial or non-spatial strategy and those who adopted a spatial strategy had increased activation in the right hippocampus whereas the non-spatial strategy group was associated with increased activation of the caudate nucleus. Further, the caudate became involved in later trials with sustained activity from then on, confirming the role of the caudate in practice and habituation. Caudate activity was associated with better performance whereas the hippocampal activation in the spatial group was associated with impaired performance suggesting that habitual responding is more efficient and quicker than adoption of a spatial strategy throughout. However, this only applies to tasks which can be solved using any strategy.

These results were replicated by Etchamendy and Bohbot (2007) using the same task and administering it to 15 patients with medial temporal lobe (MTL) damage. The results demonstrated that as with healthy controls patients spontaneously chose a spatial or non-spatial strategy or switched from the former to the latter. Patients who chose a spatial memory strategy were impaired on the task as would be expected by their MTL damage but what is most striking is that they still attempted to use a spatial strategy. Other patients chose to either adopt a non-spatial strategy from the start or switched to a non-spatial strategy as the task progressed. This resulted in no impairments in performance which suggests that patients with damage to spatially necessary regions can choose to use an alternative strategy if they so wish however not all patients do this. This is intriguing and suggests that 1) spontaneous choice of strategy is random; 2) that there may be a genetic predisposition to adoption of a particular strategy or; 3) that there is an experience bias towards adoption of a particular strategy. Support for this latter interpretation come from further work that has demonstrated increased hippocampal grey matter

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volume in individuals who chose a spatial strategy and increased caudate volume in non-spatial strategy users (Bohbot, Lerch, Thorndycraft, Iaria, & Zijdenbos, 2007). This suggests long term preference for a particular strategy leads to neuroanatomical changes, which in turn supports this choice of strategy. This finding is in line with work by Maguire et al (2000) demonstrating a relationship between volumes of the hippocampus in taxi drivers and years of experience.

Astur et al (2005) created a VR version of the RAM in which subjects are placed on a central platform that has eight arms radiating out from it. The radial maze sits in the middle of a rectangular 'room' that has a variety of textures and landmarks throughout. Rewards are placed at either all eight platforms (visible condition) or four out of the eight platforms (spatial) and subjects instructed to collect all four rewards in the spatial condition and four out of eight rewards in the visible condition as quickly as possible without revisiting arms where rewards have previously been located. Areas associated with the spatial condition were the inferior, middle and superior frontal gyrus and fusiform gyrus whereas the hippocampus and parahippocampus were deactivated during the spatial condition (and conversely therefore active during visible) as were areas of the superior temporal gyrus, anterior cingulate and cerebellum. This is intriguing given the role of the hippocampus in spatial learning and memory however it is difficult to interpret this data due to the small sample size and extremely lenient threshold of fMRI activation (results are reported at a $p < 0.01$ uncorrected level). Additionally, subjects always begin from the central location with no movement of start location or extra maze cues such that stimulus response or other types of procedural learning may be used thus the spatial memory component of the test may not have differed significantly from the visible condition.

Marsh et al (2010) conducted a virtual reality based fMRI study of spatial learning and reward using a human analogue of a standard 8 arm radial maze with three conditions. The first condition (A) was a test of spatial learning and involved collecting 8 rewards (signalled by a

U.S. dollar sign) by using the extra maze cues to remember previously visited arms. Each trial began at the centre platform and subjects were returned to the centre after reaching the end of any arm with the initial viewing perspective randomly oriented which compelled subjects to use the extra maze cues to orient themselves for subsequent navigation. The randomised orientation at the start of each trial also prevented use of S-R strategies such as "chaining rules" (e.g. exploring arms to the left or right of the last arm entered) when performing the task. The second condition (B) was a control condition but differed from the first condition as the extra maze cues were randomised after each trial and the starting position randomly oriented preventing the use of a spatial strategy and procedural learning or S-R techniques. The third condition (C) was a "trail following" exercise where subjects had to follow a red arrow around the maze. Conditions B and C followed the same reinforcement schedule determined in condition A. Further trials were divided up into 4 events added as regressors in the fMRI model specification: 1. 'searching' – start of trial until 10% of an arm was traversed, 2. 'anticipation of reward' – after the first 10% of an arm was traversed and extended until reaching its baited area, 3. 'receipt of reward' was defined as comprising the images at the end of the trial when a reward was present, and 4. 'no receipt of reward' was the time when the end of the arm was reached but no reward was present. Spatial learning was associated with activation in the bilateral superior temporal gyrus, bilateral parahippocampal gyrus, right lateral inferior parietal cortex, posterior cingulate cortex and primary motor cortices. Rewarded trials were associated with increased activation of the left hippocampus and caudate nucleus whilst no reward was associated with increased activation of the right hippocampus and bilateral Putamen. This study was interesting as it demonstrates an involvement of the parahippocampal gyrus in the absence of hippocampal activation during the search phase of spatial learning. Several studies have suggested parahippocampal involvement in the processing of spatial layout and spatial scenes but not to single objects (Epstein & Higgins, 2007) and that the parahippocampal cortex is necessary for

the binding of objects to a particular environmental context rather than memory for particular objects themselves (G. Norman & Eacott, 2005). It is likely therefore that the requirement for the subjects to learn the spatial layout of the extra maze environment but not the precise features of the extra maze cues resulted in parahippocampal but not hippocampal activation.

4.5   The neural correlates of allocentric spatial memory in humans

Convergence from many diverse paradigms investigating allocentric spatial learning and memory in humans has suggested a spatial memory network including the hippocampus and associated structures as well as the parietal lobes, retrosplenial cortex, striatum and neocortical structures such as the prefrontal cortex. Although some of these regions are involved in egocentric spatial processing i.e. the parietal lobes and dorsal striatal regions such as the caudate, they also have been identified in tests of allocentric spatial memory and these shall be reviewed below. For the most part, the neural correlates of spatial memory will be discussed in relation to data acquired from human, rather than animal studies.

4.5.1   Hippocampus and related structures

The medial temporal lobes have long been implicated in the acquisition of new memories (Scoville & Milner, 1957), with the right hemisphere associated with spatial memory (M. L. Smith & Milner, 1981) and the left hemisphere associated with verbal and narrative memory(Frisk & Milner, 1990). The hippocampus has been hypothesised to be necessary for: 1) Construction and storage of spatial information in the form of allocentric spatial cognitive maps (O'Keefe & Nadel, 1978); 2) Declarative memory (conscious, explicit information) rather than procedural memory(Squire, 1987); and 3) disambiguating the relations between stimuli that combine to form unique representations of encoding and recall of information(Cohen & Eichenbaum, 1993).

The hippocampus and associated structures have become synonymous with spatial learning and memory. Neurophysiology studies in animals have identified place cells in the hippocampus(O'Keefe & Dostrovsky, 1971), head direction cells in Papez circuit structures (Taube, 1998) and grid cells in the entorhinal cortex (Hafting, Fyhn, Molden, Moser, & Moser, 2005). However, neurophysiological studies in humans are limited and restricted to clinical populations. Despite this, place cells and grid cells have been identified in the human medial temporal lobes particularly the hippocampus and adjacent entorhinal cortex (Doeller, Barry, & Burgess, 2010; Ekstrom et al., 2003; J. Jacobs, Kahana, Ekstrom, Mollison, & Fried, 2010) further supporting the role of the medial temporal lobe structures in spatial cognition.

Studies of patients with temporal lobe resections (Abrahams, et al., 1997; Feigenbaum, Polkey, & Morris, 1996; L. H. Goldstein, Canavan, & Polkey, 1989; Maguire, Burke, Phillips, & Staunton, 1996; R. G. Morris, Pickering, Abrahams, & Feigenbaum, 1996) and those with selective damage to the hippocampus and parahippocampal cortex (Bohbot, et al., 1998; Holdstock et al., 2000) on tests of spatial learning and memory supports the importance of these structures in spatial memory. Studies that have utilised functional MRI have demonstrated activation of the medial temporal lobes related to allocentric spatial memory performance whilst subjects navigate in virtual environments (G. K. Aguirre, Detre, Alsop, & D'Esposito, 1996; Maguire, et al., 1998; Parslow et al., 2004).

The parahippocampal cortex has been implicated in navigation in a virtual maze (Aguirre et al, 1996; Maguire et al, 1998; Parslow et al, 2004) and in processing of scene information (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Epstein & Higgins, 2007; Kohler, Bilker, Hagendoorn, Gur, & Gur, 2000). In a navigation task that involved memory for only one location in a room Bohbot & Colleagues (1998) found that the right parahippocampal cortex was involved in allocentric spatial memory without the necessary involvement of the hippocampus.

It is likely the parahippocampal cortex contributes to the establishment of a cognitive map of the environment by providing scene information to the hippocampus. Ekstrom et al (2003) recorded place sensitive neurons in the hippocampus whilst subjects navigated a virtual town reporting that place fields were found in the hippocampus more than any other region whereas cells in the parahippocampus responded more to views of target landmarks as opposed to views of people or background. The authors suggest this supports a model of human spatial navigation whereby a coarse representation of space is formed by the parahippocampus by extracting allocentric spatial information from salient visual landmarks. This visual and spatial information is then combined by the hippocampus via input from the parahippocampus into the flexible map like representations of space.

Comment should be made however as to the difficulty in segmenting the hippocampal and parahippocampal regions in fMRI and the different methods that researchers use for localising and labelling regions of activation. This complicates discussions of the functional division of labour within these regions. Further, navigational tasks are likely to involve subject movement within the scanner to a greater extent than other tasks that don't require movement in VR space. This further reduces the confidence a researcher can have about the exact location of neural activation using these tasks. An additional complicating factor is the regions researchers choose to include in the hippocampal formation/hippocampal complex including whether the entorhinal cortex is part of the hippocampal formation or the amygdala part of the hippocampal complex for example.

4.5.2 Parietal Lobes

The parietal lobes have typically been implicated in egocentric frames of reference (Colby & Goldberg, 1999). Damage to this region has been shown to impair egocentric spatial processing (Weniger et al., 2010). Bilateral parietal lesions are frequently related to a form of egocentric

navigational difficulties, implying deficits to localise visual space, to orientate towards objects in space, to track and reach objects in space or to form new topographical memories (Cogan, 1979; Kase, Troncoso, Court, Tapia, & Mohr, 1977; Wilson et al., 2005). Lesions to the parietal lobes have also been shown to impair allocentric spatial learning (Save & Moghaddam, 1996). Functional imaging studies have highlighted the role of the medial and posterior parietal cortices in computing egocentric spatial representations (N. Burgess, Maguire, Spiers, & O'Keefe, 2001; Spiers & Maguire, 2007) and route encoding (Janzen & Weststeijn, 2007; Wolbers, Weiller, & Buchel, 2004). The inferior parietal lobes have been associated with translation of allocentric spatial frameworks into egocentric representations (Burgess et al, 2002) and several studies have identified commonality between egocentric and allocentric conditions in activation of the parietal lobes (Iaria, et al., 2003; Maguire, et al., 1998; Parslow, et al., 2004). It has been suggested that visuo-spatial and self-motion cues are initially processed by the associative parietal cortex in an egocentric frame of reference with a subsequent transfer of these representations to an allocentric cognitive map by the hippocampus (Save & Poucet, 2000). Further, Burgess et al (2001) have proposed that the posterior parietal lobe has the specified role in recoding body centred representations into view independent ones.

4.5.3   Retrosplenial Cortex

The retrosplenial cortex is active during scene viewing, scene imagery and mental imagination of navigation through familiar environments and is likely involved in recovery of long term spatial knowledge about these environments (Epstein, 2008; Epstein, Parker, & Feiler, 2007). Navigational difficulties are often reported when this region is damaged by stroke in humans (Ino et al., 2007; N. Takahashi, Kawamura, Shiota, Kasahata, & Hirayama, 1997) and patients with this type of damage can identify scenes but cannot use them for the purposes of orientation(Osawa, Maeshima, & Kunishio, 2008; N. Takahashi, et al., 1997). The anatomical

connectivity of the retrosplenial cortex also supports its role in spatial cognition as the retrosplenial posterior cingulate is strongly connected with parietal lobe regions as well as the entorhinal cortex, subiculum and parahippocampal regions. Thus, the retrosplenial cortex is well placed to translate between egocentric spatial codes in the parietal lobes and allocentric spatial codes in the medial temporal lobes (Epstein, 2008). Indeed, part of the retrosplenial syndrome appears to be an inability to translate between egocentric and allocentric spatial representations (Bottini, Cappa, Geminiani, & Sterzi, 1990; Katayama, Takahashi, Ogawara, & Hattori, 1999). It has been suggested that the retrosplenial cortex complements the hippocampus in topographical orientation by updating the individual's location as the frame of reference changes. However, the retrosplenial complex may also encode its own representation of the spatial structure of familiar environment which may be sufficient to support navigation in very familiar environments or to support navigation when the hippocampus is damaged (Epstein, 2008).

4.5.4   Striatum

Functional activation of the caudate nucleus has been associated with speed of navigation (Maguire, et al., 1998) and route following (Hartley, Maguire, Spiers, & Burgess, 2003). In the Hartley et al (2003) study speed of route following was associated with activation of the caudate nucleus. The striatum, particularly the caudate and putamen, is typically involved in egocentric spatial learning and memory (Iaria, 2003; Bohbot et al, 2004; Etchamendy and Bohbot, 2007). It is typically active during a slower learning process that relies on stimulus-response behaviour i.e. gradually learning particular body turns in response to stimuli which allow the animal to reach a target location from any one starting position (Eichenbaum, Stewart, & Morris, 1990; Packard & Knowlton, 2002; Packard & McGaugh, 1996). Additionally, recruitment of the striatal systems increases with practice in navigating an environment (Iaria et al, 2003). This is in contrast to hippocampal systems which are most active during the early phases of trials (Astur

et al, 2005). The hippocampal and striatal systems may thus be active dependent on whether the subject is in the early or late phases of learning and environment (Packard & McGaugh, 1996; Iaria et al. 2003). Dissociation between striatal and hippocampal memory systems has also been demonstrated under scopolamine challenge on the Arena Task, a virtual Morris Water Maze task (Antonova et al., 2010). In this study hippocampal activation under placebo was accompanied by striatal deactivation whereas attenuated hippocampal activation under scopolamine was accompanied by a significantly stronger activation of the striatum. Given that the striatum is active during stimulus response strategies (reviewed above), increased activation of the striatum may reflect a use of egocentric strategies under scopolamine perhaps as a compensatory mechanism for attenuated hippocampal activation.

4.5.5 Prefrontal Cortex

Several neuroimaging studies have revealed increased activity in prefrontal areas during spatial navigation tasks (Gron, Wunderlich, Spitzer, Tomczak, & Riepe, 2000; Hartley, et al., 2003; Maguire, et al., 1998). It is proposed that the prefrontal cortex is involved in representing spatial goal locations and guiding navigation to these goals (Spiers, 2008) and prefrontal activity has been directly linked to goal processing (Spiers & Maguire, 2006, 2007). Furthermore, prefrontal activation has not only been found to be active during navigation tasks but that it is necessary for navigation (Ciaramelli, 2008). In this study, a patient with bilateral damage to the ventromedial prefrontal and rostral anterior cingulate cortices was asked to describe a set of routes between locations in his home town. He performed poorly but his performance improved if he was given the name of his destination or a cue to rehearse the destination at regular intervals. Analysis of the errors made by the patient including assessments of familiarity, route length, number of turns revealed only familiarity was related to number of errors. In fact, two thirds of error trials involved the route ending at one of a number of personally familiar locations. The authors

suggest that these locations acted as "attractor" locations distracting the patient from his true goal (Ciaramelli, 2008). Thus, the ventromedial may not only be necessary for maintaining the goal in memory but also to suppress irrelevant information. Other studies have reported a specific involvement of the PFC in spatial memory for example Spiers & Maguire (2006) who report that when subjects watched a replay of their performance on a navigation task and are asked what they were thinking during navigation; the most frequently reported thought was thinking about the goal and the route to it. These were associated with increased activity in anterior BA10 and in the medial prefrontal regions. It has been suggested that the medial prefrontal cortex is involved in maintaining goal representations whilst BA10 may be involved in the manipulation of information for planning (Koechlin, Basso, Pietrini, Panzer, & Grafman, 1999). Other authors have summarised the involvement of the PFC in spatial memory as a failure to maintain the intention to reach the destination in working memory and a reduced suppression of previously learned information (P. W. Burgess, Veitch, de Lacy Costello, & Shallice, 2000). Taken together, the literature suggests the PFC is necessary for representing goal locations, planning the route to the goal, suppression of irrelevant previously learned information and the ability to maintain the goal and the intention to reach the goal in working memory (Spiers, 2008).

Although it is possible that spatial learning and memory may occur in some instances in an almost exclusively allocentric or egocentric spatial manner; in everyday practice a conjoint usage of allocentric and egocentric information is likely. Even if a study is designed to assess allocentric spatial processing, a person may learn to navigate within this environment using egocentric cues and vice versa an egocentric task may be solved using survey perspectives for example, it has been suggested that humans can solve allocentric tasks by representing the egocentric position of target objects and updating these representations whilst moving (Wang et al 2003). From this perspective, rather than the use of a cognitive mapping strategy subjects

may learn associative rules which is consistent with the data suggesting that hippocampal lesions give rise to deficits in associative learning (Eichenbaum, Otto, & Cohen, 1992). Thus, the hippocampus may be involved in spatial learning and memory but not necessarily limited to allocentric spatial memory or cognitive mapping.

Taken together, however, the literature suggests that the hippocampus and parahippocampus are preferentially involved in allocentric spatial processing whereas the striatum is largely involved in egocentric spatial processing. The parietal lobes, retrosplenial cortex and prefrontal regions meanwhile are reportedly involved in both allocentric and egocentric processing; the parietal lobes and retrosplenial cortex are likely involved in the switching between allocentric and egocentric frames of reference whereas the prefrontal cortex is likely involved in the planning and decision making involved in choosing the correct navigational strategy to reach the goal.

4.6   Spatial learning and memory in schizophrenia and schizotypal personality.

Spatial learning and memory paradigms have also been applied to the study of schizophrenia although this represents a relatively small body of literature compared to other areas of cognition. Interest has been directed towards allocentric spatial memory particularly because of its dependence on structures implicated in schizophrenia namely the medial temporal lobes, basal ganglia and prefrontal cortex. Further, by successfully utilising paradigms that are comparable to those used in the animal literature this bridges the gap between animal and human research. Ultimately this will allow comparison between early preclinical findings and their later application to the disorder their modelling.

Hanlon et al (2006) were the first to use a virtual MWM to assess spatial memory in patients with schizophrenia. The virtual environment consisted of a room with a square floor-plan and a circular pool in the centre. All four walls are identical except for the landmarks (1 on each wall)

used as spatial cues. Landmarks are placed off centre vertically and horizontally by a fixed amount so that subjects could not follow a straight trajectory from the starting point to the platform. Subjects were able to view one to two landmarks at any one time. The surface of the pool was opaque blue and within the pool there is a square platform. Subjects could navigate forward and to the left and right and forward movement was accompanied by the sound of moving water. Two versions of the task were run: hidden and visible. In the hidden version, subjects had to search for a hidden platform which was always hidden in the same location. Subjects were started from various positions in the pool chosen using a pseudo-random sequence. Once the platform was found a bell sounded and a verbal message confirmed the platform had been found. If the platform was not found within 60 seconds an aversive tone sounded and the platform became visible for the participant to navigate towards. In the hidden probe trials the platform was no longer present in the pool and subjects swam for 45 seconds trying to locate the platform. In visible trials the platform was visible above the surface of the water and the participant just needed to swim towards it. This was a control for movement and motivation to escape the pool.

The results demonstrated poorer performance in patients during the hidden platform trials with patients taking longer to find the platform, spending less time in the correct quadrant of the pool and having longer path lengths. Additionally patients spent less time in the correct quadrant during the probe trial. Patients did not differ from controls on the visible platform version of the task. These results suggest that patients have impaired allocentric spatial memory performance. Although the authors link this to hippocampal dysfunction, other brain regions involved in spatial memory or cognition may also be involved. Additionally the authors do not report whether IQ or education was different between patients and controls, which limits the ability to draw conclusions regarding specific cognitive impairments. This is particularly true as the visible platform condition is not a truly comparable control as it is relatively simple and relies

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only on the ability to navigate to the platform. Comparing allocentric spatial memory to a cognitively similar task that does not require hippocampal involvement would have strengthened the results. Further, the requirement of this task to initially search for the hidden platform relies upon intact executive functioning and therefore worse performance on this task may not necessarily reflect poor allocentric spatial memory ability in schizophrenia. Worse performance could indicate a failure to form or implement an appropriate search strategy.

Weniger and Irle (2008) made the comparison between egocentric and allocentric spatial memory in patients with schizophrenia and controls using a virtual park (allocentric condition) and a virtual maze (egocentric maze). The virtual park environment comprised 9 points of two way intersection and 11 cul de sacs. Each cul de sac contained a pot, but only one pot contained money. Subjects were instructed to find the shortest way to the pot with the money in it. Landmarks (e.g. house, lake, playground, garden, bridge) were placed throughout the environment. The virtual maze environment compromised six points of two way intersection and 7 cul de sacs. Each cul de sac contained a pot but only one pot contained money. The maze consisted of brick walls, similar coloured ground and blue sky. All intersections seemed identical when approached from different directions. As the maze contained no landmarks it requires egocentric navigation to solve the task. In each trial of the virtual park and the virtual maze subjects started from the same location and the target (money pot) was the same in every trial. Subjects could not see the target from the start position or from any other vantage point in the environment. Performance was measured as the number of errors committed by going to a pot that did not contain money. Subjects were debriefed afterwards to ascertain what strategy they had used to solve the task.

Results revealed that patients committed significantly more errors on the virtual park (allocentric spatial memory) compared to controls. Patients however did have a lower IQ and covarying for

this within the results revealed a significant effect of IQ on virtual park performance. Patients and controls did not differ on performance in the virtual maze (egocentric spatial strategy). The authors interpret this finding as evidence of allocentric spatial memory impairment and suggest that the deficit in patients with schizophrenia to use and store navigationally relevant landmark information may be related to a compromised ventromedial declarative memory system and reduction in hippocampal size demonstrated in other studies and in unpublished data from their own laboratory. This study also demonstrates the sparing of egocentric spatial strategies in patients with schizophrenia. Not only did subjects not differ from controls but they also reported using more egocentric strategies across both tasks revealing a preference for this type of strategy. Speculatively, this would suggest that the neural circuitry underlying egocentric navigation, the parietal, thalamic/striatal and temporal cortices, are less affected that the ventromedial temporal cortices including the hippocampus and parahippocampal gyrus in early schizophrenia.

Whilst these two studies reveal allocentric spatial memory deficits in patients with schizophrenia the latter suffers from confounding factors of IQ and education and the former does not report whether groups differed in this respect or not. This has been addressed by Girard, Rizvi and Christenson (2010) using a virtual reality task termed the nine-box maze test (Abrahams et al., 1999; Abrahams, et al., 1997).

This task comprises nine visually identical containers with detachable lids affixed in a circular formation on a large, square, black board covering the top of a table. Surrounding the table were four identical chairs one of each side situated in a room with various environmental features i.e. artwork, a computer, a desk. To assess object memory, nine everyday items were derived from the Fuld (1980) object-memory evaluation: a golf ball, bottle, button, playing card, scissors, ring, key and book of matches. Test materials included an object recognition booklet (nine pages of

digital photographs of the objects) and a cancellation test (11 randomly ordered geometric shapes).

Eight trials were performed, four trials were allocentric and involved observing the experimenter hiding the objects and then walking around the table to a different chair. Once re-seated the subjects performed the cancellation task and then were asked to recall what objects were hidden (object memory), which containers they were hidden in (location memory) and what objects were in which containers (object-location memory). Subjects remained seated for four out of the eight trials (egocentric condition). Subjects were asked to remember four objects and four locations per trial. Two of these objects and locations had been presented in the practice task and were present across all eight trials thus they served as consistent items to tap reference memory; two additional objects and bins were presented varied across trials to measure recent event memory. Self-report strategies were recorded and coded into five categories a) no reported strategy b) watching closely/temporal order c) visual imagery d) object based e) location based f) object and location based and g) object-location associations.

Results on location memory revealed that controls and patients performed similarly on egocentric trials whereas the patient group remembered fewer locations on allocentric trials. Additionally spatial memory deficits in the patient group were most pronounced under event memory but not reference memory. These results support the hypothesis of preferential impairment in hippocampal-dependent forms of memory in schizophrenia. Additionally the weaker results of event versus reference memory is consistent with a suggestion by Abrahams (1997) that cognitive mapping theories of hippocampal function may be more relevant than event versus reference memory distinctions (Girard et al, 2010). The matching of IQ and education between the patient and control group allow these distinctions to be assessed free from

additional psychometric factors, therefore building upon the findings of the Hanlon et al (2006) and Weniger and Irle (2008) papers.

These studies demonstrate that allocentric, but not egocentric, spatial memory is impaired in patients attributing this to dysfunction in the structure and function of the hippocampal and parahippocampal cortices. However, none of the studies presented so far directly test this hypothesis.

Investigating the neural circuitry underlying allocentric and egocentric learning and memory in schizophrenia can be done using functional neuroimaging. Folley et al (2010) conducted a study using functional neuroimaging to elucidate the neural circuitry underlying performance on a virtual MWM task similar to the design employed by Hanlon et al (2006). A block design was employed using visible and hidden conditions. Subjects are presented with a virtual environment with them placed in a pool within a square room. In HIDDEN, furniture and objects were at fixed locations along the walls. In VISIBLE, a cylindrical wall masked these cues. In both, four equidistantly-spaced yellow balls hovered over the water surface as reference points to possible platform locations, with one being placed in the centre of each of the four quadrants. The platform lay beneath one of these balls. Subjects manoeuvred around the environment using a joystick until they found the platform. In VISIBLE, the platform could be easily seen between one ball and the water surface, and the platform was in the same location during each trial. In HIDDEN, the platform was 'hidden' beneath the surface of the water at the same ball location throughout the experiment. For each trial, subjects began from a pseudo randomly determined North, South, East or West location, navigating the pool using a joystick.

The results demonstrated that patients found less platforms, travelled further, took longer and made more errors than controls on both visible and hidden conditions. Independent components analysis (ICA) revealed 5 components of neural activation during this task. Component 1

included the insular, inferior, medial and superior frontal gyrus, anterior and posterior cingulate, superior and middle temporal gyrus, inferior parietal lobule, parahippocampal gyrus, hippocampus and the amygdala. Component 2 included anterior cingulate, inferior, medial, middle and superior frontal gyrus, uncus, paracentral lobule and inferior parietal lobule. Component 3 included insula, middle, superior and transverse temporal gyrus, hippocampus and parahippocampus and amygdala. Component 4 included cingulate gyrus, paracentral lobule, insula, superior, inferior, middle and transverse temporal gyrus, caudate, fusiform gyrus, parahippocampal gyrus, hippocampus and amygdala. Component 5 included the parahippocampal gyrus, hippocampus, amygdala, uncus, superior temporal gyrus and anterior cingulate gyrus. Component 1 was associated preferentially with VISIBLE. Component 5 was a general processing component that was active across conditions and groups. While locating the visible platform, patients preferentially recruited Components 1, 2, and 4, comprising hippocampus, cingulate, insula, and basal ganglia. Controls preferentially recruited Component 3 during VISIBLE, comprising temporal, frontal, and mesial temporal regions. Component 4 was associated with strategies employed during HIDDEN for controls and VISIBLE for patients, including a prominent temporal lobe focus that extended to other frontal and subcortical regions. Left and right hippocampal BOLD signal was associated with better performance in controls. No correlation was observed between BOLD activation and behaviour in patients. Investigations into grey matter volume (GMV) resulted in significant coupling between behaviour and GM concentrations in hippocampus subregions, indicating greater concentrations associated with efficient performance in controls. No association between GMV and performance in patients. Using a standard general linear model (GLM) analysis they also demonstrated significant BOLD signal increases in the superior and inferior temporal gyri bilaterally, the right transverse and left medial temporal gyri, bilateral postcentral, cingulate, middle occipital gyri, left fusiform gyrus, right insula, and inferior parietal lobules in controls

compared to patients. Patients exhibited impaired performance on the HIDDEN and VISIBLE conditions of the task, related to negative symptom severity. The significant relationships observed between BOLD signal variation, GMV, and better performance on this task suggests appropriate coupling between activation of neural networks, regional neuroanatomy and behaviour associated with the task in control subjects. Patients meanwhile activated different neural circuitry and this was not associated with GMV or behaviour. GLM analysis elucidated several regions comparable to the results observed for the ICA analysis however no differences in BOLD activation was observed in the hippocampus and parahippocampal gyrus between patients and controls. The authors interpret a lack of association between mesial temporal lobe regions and behaviour, as well as consideration of previous literature on disrupted frontal-temporal connectivity in schizophrenia, as indicative of inefficient hippocampal recruitment. Thus inefficient allocentric learning and memory in patients may be related to an inability to recruit appropriate task dependent neural circuits (Folley et al, 2010).

Contrary to what has been observed in the behavioural studies is impairment on the visible condition of the task. As subjects need only to swim to a visible platform during this condition, the finding that patients perform worse during visible trials as well as on HIDDEN trials would indicate impairment in spatial navigation not specific to allocentric spatial memory. Further, the inclusion of proximal cues (yellow balls) situated above the platforms may have led subjects to use an alternative strategy based on these proximal cues rather than using the environmental distal cues. What this study does highlight is the role of several brain regions that are differentially activated by patients during performance of an allocentric spatial memory task, highlighting the need to consider other brain regions as well as the hippocampus when discussing aberrant performance on these tasks. Further, patients did not select task/condition appropriate neural circuitry and there was a decoupling of performance and function and structure in patients indicating the need to move beyond just assessing whether a region is active

or not. However, this study utilised the same task as the Hanlon et al (2006) study and thus is subject to the same concerns regarding executive dysfunction underlying performance differences as the Hanlon et al study reported above.

To date no studies have looked at spatial ability in schizotypal personality using VR tasks of allocentric and egocentric spatial memory. As outlined in Chapter 2 several studies have found modest impairments on spatial *working* memory paradigms, but it should be emphasized that these tasks tap into cognitive processes different from those concerning the spatial orientation tasks reviewed above, which have a long term episodic memory or spatial learning component. Furthermore, a limitation of standard 2 dimensional pen and paper tasks and their computer based counterparts is that they are inherently egocentric (Girard, et al., 2010) and do not mimic the cognitive demands of real life spatial cognition.

4.7   Summary

In this chapter I have introduced the different spatial strategies and frames of reference animals and humans use to navigate the environment. An important distinction is made between allocentric and egocentric frames of reference and the subsequent spatial behaviour elicited from information coded within these reference frames. Tasks used in animals such as the MWM and RAM are designed to measure allocentric spatial memory processes whereas human studies, using more established psychometric paradigms, have focused on desk-top egocentric designs. However, the advancement of VR software has allowed versions of these tasks to be more easily created for use in humans. A spatial memory network has been identified using this task comprised of the hippocampus and parahippocampus, parietal lobes, striatum, retrosplenial cortex and prefrontal regions. Whereas the hippocampus and parahippocampus are required primarily in tasks of allocentric spatial memory the striatum and parietal lobes are activated by egocentric paradigms. Further significant overlap between the two frames of reference occurs in

the parietal, retrosplenial and prefrontal cortices. These tasks have been applied to schizophrenia, a condition known to have structural and functional alterations of regions necessary for successful MWM performance. However, they have not been used to study spatial cognition in schizotypal personality. In this thesis, spatial learning and memory will be investigated in schizotypal personality using two human analogues of the MWM and RAM, the Arena Task and Platform Task, respectively. These tasks will now be introduced in Chapter 5 and discussed in depth in experimental chapters 7 and 8.

4.8   Aims, Objectives and Hypotheses

This section outlines the general aim of this thesis and the motivation for the work undertaken. General hypotheses are presented. Specific hypotheses relating to each task/investigation are presented in the relevant experimental chapters.

4.8.1   Overall aims of this thesis

The main aim of this thesis was to assess allocentric spatial memory in high schizotypy scorers compared to average schizotypy scorers (from here on referred to as the control group). Allocentric spatial memory has been demonstrated to be impaired in schizophrenia using human versions of tasks known to be sensitive to this in animals whilst egocentric spatial memory is reportedly spared (Hanlon et al, 2006; Weniger & Irle, 2008). No studies to date have investigated allocentric spatial memory in psychometrically defined schizotypy or in individuals with schizotypal personality disorder. This thesis sought to address this gap by using two tasks of allocentric spatial memory, the Arena and Platform Task, which have been developed based on the Morris Water Maze and Radial Arm Maze, respectively. The Nback task was included in this thesis as a general cognitive activator sensitive to attentional ability to determine if a much used task can discriminate the groups.

There is a paucity of research into brain function in schizotypal personality. Evidence is accumulating that suggests schizotypal personality is associated with differential activation compared to controls. However, no study to date has used fMRI to explore the correlates of allocentric spatial memory in psychometrically defined schizotypy. A second aim of this study was to assess brain function in high schizotypy during performance of the two allocentric spatial memory tasks. Previous literature suggests these tasks are thought to be dependent on successful

activation of the medial temporal lobes specifically the hippocampus and parahippocampal gyrus as well as the prefrontal cortex. As these are areas that have been consistently implicated in psychosis, the function of these regions was explored in psychometric schizotypy. Further, the relationship between functional activation and cognitive performance was explored.

Previous research has highlighted structural abnormalities in schizotypal personality disorder and schizophrenia however few studies have assessed grey and white matter volume in psychometrically defined schizotypal personality. White matter especially is under studied in schizotypal personality despite increasing evidence to suggest its involvement in psychotic disorders. Therefore a third aim of this study was to assess grey and white matter volume in schizotypal individuals.

4.8.2   General Hypotheses

Specific hypotheses pertaining to each task (and structural scan) will be presented in the relevant experimental chapters. The general hypotheses of this thesis are:

1. Allocentric spatial learning and memory will be impaired in high schizotypy as evidenced by worse performance on the two allocentric spatial memory tasks compared to the control group.

2. The control group will activate regions associated with spatial memory including activation of the hippocampus and/or parahippocampus, parietal lobes and prefrontal cortex.

3. Performance on the two allocentric spatial memory tasks will be related to the degree of activation in the hippocampus.

4. Allocentric spatial memory in high schizotypes will be associated with a different pattern of brain activation compared to control subjects specifically lower activation of the hippocampus and parahippocampal gyrus.

5. Increased activation in prefrontal regions will be observed in high schizotypy during performance on the allocentric spatial memory tasks compared to the control group.

6. Working memory will be impaired in high schizotypy and associated with a differential pattern of brain activation specifically lower activation of the dorsolateral prefrontal cortex.

7. Increased activation will be observed in anterior frontal pole area (BA10) compared to the control group on the working memory task.

8. High schizotypy will be associated with grey and white matter volume differences compared to controls.

Chapter 5:   General Methodology

This chapter outlines the general methodology for the thesis as a whole including the selection and allocation of subjects, study design, and statistical analysis. Specific details (demographic, behaviour and imaging) pertaining to each task will be presented in the relevant results chapters.

5.1   Selection of subjects

The Schizotypal Personality Questionnaire Brief (SPQ-B; Raine & Benishay, 1995) was used to identify subjects. This shortened version of the SPQ was thought to be more suitable for initial online recruitment of subjects, using 22 items rather than the 74 items in the full SPQ version. The 22 items deemed the most informative from the complete questionnaire are included in the SPQ-B (Raine, 1991; Raine & Benishay, 1995). Respondents select a yes or no response for each item and scores are then summed to provide a total score and cognitive perceptual, interpersonal and disorganized subscale scores. Inter-correlation between the SPQ-B and full SPQ is reported as 0.89 for the cognitive perceptual scale, 0.90 for interpersonal and disorganized scales and 0.94 for the total score (Raine & Benishay, 1995). The SPQ-B questionnaire is presented in Appendix I.

The SPQ-B was placed online and anyone who was interested in taking part completed the questionnaire. Subjects were asked to confirm they lived within reasonable travel distance of London where the study was conducted. Advertisements and circular college emails distributed an online link to this questionnaire and subjects could also request a copy by email or by post. Respondents with total SPQ-B scores in the range of 7-12 inclusive were classified as average schizotypes and invited to participate in the study. Respondents with scores ≥15 were classified as high schizotypes and invited to participate in the study. Scores were derived from a published

mean of 9.6 and SD deviation of 5.5 (Raine & Benishay, 1995); the control group (average schizotypy) was calculated as ½ standard deviation above and below the mean and the high group cut off starts at 1 standard deviation above the mean. Respondents with scores outside of these ranges were not invited to participate further in the study. Completion of the questionnaire was taken as consent to be contacted further about the study.

5.1.1 Inclusion Criteria

Subjects had to meet the following inclusion criteria to be able to take part in the study:

- SPQ-B score 7-12 inclusive ('average') or ≥15 (high)

- SPQ score 21-36 inclusive ('average') or ≥43 (high)

- Male or Female aged 18-45 years inclusive at assessment visit

- Fluent English Speakers

- For female subjects surgically sterile or abstinent or, if sexually active, practicing an effective method of birth control before entry and throughout the study. Confirmed by negative pregnancy test prior to scanning.

- Acceptable weight as defined by a BMI of between 18- 30 inclusive (weight [kg]/height$[m]^2$)

- Normotensive with sitting blood pressure between the range of 100 and 140mmHG systolic and 60-90mmHG diastolic, inclusive.

- Healthy on the basis of medical history and a pre-study psychological and physical examination

- Non-smoker or light smoker (≤5 cigarettes a day).

- Willing to follow prohibitions and restrictions, as outlines in 5.1.3.

- Signed informed consent prior to the first study related procedure.

5.1.2 Exclusion Criteria

Subjects were excluded if they met any of the following criteria:

- History of alcohol or substance dependence. Confirmed by negative urine drugs test and alcohol breath test prior to testing.

- Consumption of large amounts of caffeinated drinks (no more than 8 cups of standard caffeinated drinks (tea, instant coffee) or 6 cups of stronger coffee or other drinks containing methylxanthines such as coca cola or red bull per day).

- Relevant history or presence upon clinical examination, of cardiac, ophthalmologic, pulmonary, endocrine (diabetes), cancer, blood disease, gastro-intestinal, hepatic or renal disease or other condition which could interfere with test procedures.

- History or presence of significant neurological or psychiatric conditions.

- Have received medication within 14 days prior to testing (apart from the contraceptive pill

- Have received over the counter medicine within 48 hours prior to testing day.

- Have received an experimental drug and/or used an experimental medical device within 30 days of testing or within a period less than 5 times the drug's half-life, whichever is longer.

- If female, pregnant or trying to get pregnant or currently breastfeeding.

- Have a history of, or current condition of, migraine headaches or have undergone operations to the head.

- Significant hearing impairment which in the opinion of the investigator could interfere with the performance of the tasks

- Significant visual impairment including colour blindness, or history of ocular treatment including corrective laser eye surgery or ongoing condition which in the opinion of the investigator could interfere with the performance of the tasks.

- Left handedness.

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- Unable to comply with MR patient declaration.

- Unable or unwilling to comply with study procedures.

5.1.3   Prohibitions and Restrictions

Subjects also complied with the following lifestyle restrictions:

- Attend the research unit for the screening and testing visit

- Not to consume beverages containing alcohol for the 24 hours prior to the testing visit and for the duration of the testing visit.

- Not to consume any psychoactive substances between the screening day and the testing visit.

- Not to smoke in the two hours prior to the testing visit. Heavy nicotine users (>5 cigarettes per day) were not included in this study. Therefore it was not anticipated that this restriction on nicotine consumption would lead to nicotine withdrawal.

- Drink only their normal intake of coffee or tea on the morning of the testing visit. Not to consume caffeinated drinks two hours prior to the testing visit and throughout the visit. Heavy caffeine consumers were excluded from taking part in this study. Therefore it was not anticipated that this restriction on caffeine consumption would lead to caffeine withdrawal.

- Refrain from taking prescription medicine in the 14 days prior to the testing visit and throughout the visit (apart from the contraceptive pill)

- Refrain from taking any over the counter medicine in the 48 hours prior to the assessment visit and throughout the visit.

5.1.4   Allocation to schizotypy groups

Schizotypy group allocation was decided based on responses on the *full* SPQ (Raine, 1991) conducted on the screening visit. As outlined in Chapter 1, the SPQ is a 74 item self-report

measure based on DSM-III-R criteria for SPD. Scores can be derived for nine subscales: ideas of reference, odd beliefs/magical thinking, unusual perceptual experiences, odd thinking and speech, suspiciousness/paranoid ideation, inappropriate/constricted affect, odd behaviour, lack of close friends and excessive social anxiety. These subscales can be summed to give a total score and scores for three composite scales: cognitive perceptual (ideas of reference, magical thinking, unusual perceptual experiences and paranoid ideation), interpersonal (social anxiety, no close friends, blunted affect and paranoid ideation) and disorganized (odd speech and odd behaviour).

The full SPQ scale was used to define two groups as follows: 1. The control group. These were subjects with SPQ scores within the average score range of 21-36 inclusive, hence representative of the majority of the general population; 2. The high group. Their score was 43 and above. These ranges were derived from published norms and based on reports of a normal distribution of SPQ scores in the general population (Avramopoulos, et al., 2002; Bora & Baysan Arabaci, 2009; Fossati, et al., 2007; Raine, 1991). By definition, subjects who scored outside of these ranges were excluded from the study. From here on in, the groups will be referred to as the control group and the high schizotypy group.

Thus, the SPQ-B was used to identify schizotypes who may be interested in taking part in the study whilst the full SPQ was used to confirm eligibility once subjects had been invited to take part. A copy of the full SPQ is provided in appendix II.

5.1.5 Sample Size

42 subjects were recruited for the investigations in this thesis; 21 average and 21 high schizotypes. As no details were available for the Platform task previous data acquired on young and older subjects using the Arena Task was used to generate power calculations to determine the sample size used in this thesis. Using the following means: Young subjects = 12.25 (SD =

5.92) and Older subjects = 21.27 (SD = 5.38), t_{17} = 3.542, p = 0.003 (Antonova et al., 2009), at 80% power and alpha level 0.05 a one tailed power calculation revealed 4 subjects in each groups were required to detect a difference. However, it is unknown whether the differences observed in schizotypy will be of the magnitude of that detected when comparing young to older subjects. As such the power calculation was redone to detect half the difference observed in the previous study ([21.27-12.25]/2 = 4.51) at 80% and with an alpha level of 0.05; these calculations revealed 16 subjects were required in each group.

This was raised to 21 subjects in each group to account for higher variability in brain signals/volumes in schizotypy.

Power calculations were performed using www.stats.ubc.ca/~rollin/stats/ssize/n2.html.

5.2   Study Procedures

5.2.1   Recruitment

Subjects who had completed the online questionnaire (the short version of the SPQ for recruitment purposes) and had scores in the correct ranges (on the short version of the SPQ) were contacted for a telephone screening (see section 5.1). This was to ensure that only subjects who were likely to score in the correct ranges on the *full* SPQ (completed at the face to face screening visit) were invited for screening. This was to limit the cost and time of screening large numbers of people. The telephone screening was used to determine medical and lifestyle history, basic demographic information and to check MR suitability.

Subjects were sent a participant information sheet prior to the telephone screen. Before any questions were asked, subjects were asked to confirm they had read the information sheet and were given the opportunity to ask questions. Verbal consent was obtained to carry out the

telephone screen and subjects were informed that they could withdraw from the telephone screening at any time.

Subjects who were eligible for the study following the telephone screen were asked to attend a screening visit at the Centre for Neuroimaging Sciences, Institute of Psychiatry. Subjects who agreed to a screening visit were sent a copy of the prohibitions and restrictions (see section 5.1.3) and asked to adhere to these requests.

5.2.2   Screening Visit

The screening visit took place within 6 weeks of the testing visit. After signed informed consent had been obtained, the inclusion and exclusion criteria were reviewed (see section 5.1.1 and 5.1.2 for details of inclusion and exclusion criteria). Subjects were asked to confirm they had adhered to the prohibitions and restrictions set out in section 5.1.3.

Subjects then completed a computerized version of the *full* SPQ (programmed in Matlab) situated within an experimental testing room. Completion of the *full* SPQ was to determine allocation to the groups. It was necessary to conduct the SPQ in an experimental setting as responses to personality questionnaires may differ between online completion and completion under laboratory conditions. This ensured that the questionnaire was completed accurately. Subjects who fell within the correct score ranges were assigned to either the control group or high schizotypy group and subjects who fell outside of these ranges were excluded (see section 5.1.4 for full details of schizotypy scoring criteria).

Subjects were screened for mental health issues using the MINI International Neuropsychiatric Interview (Sheehan et al., 1998). The MINI is a short, structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders. Subjects who endorsed any of the main criteria for diagnosis were excluded from the study and had the opportunity to discuss their experiences

with a trained medical professional if they so wished. A copy of the MINI is provided in Appendix IV.

Verbal IQ was assessed using the National Adult Reading Test- Restandardised (H. Nelson & Willison, 1991). Subjects were asked to read out a list of irregularly spelt words. Pronunciation was scored as correct or incorrect. The verbal IQ score was calculated with the equation 129-(0.92 x no. of incorrect words). A copy of the NART-R is provided in appendix III.

Subjects were medically screened using the following procedures:

- Relevant medical history (taken by a medical doctor)

- Height and weight (to determine BMI)

- Vital signs (sitting and standing blood pressure, heart rate and temperature)

- Brief physical examination (performed by a medical doctor)

- Alcohol breath test

- For females only, a urine pregnancy test

- Drugs of abuse urine test

If the results of these screening tests were acceptable then subjects were taken into the mock scanner suite to experience the noise and enclosed environment of the scanner to determine whether they would be happy to take part in the testing day. Additionally subjects practiced the three tasks used in this study to ensure they were comfortable with the virtual reality environment and were able to use the MR joystick and tracker ball proficiently. Standardised instructions were used to train the subjects and these are provided in Appendices V – VII. The tasks are described briefly later in this chapter and in detail in the relevant experimental chapters.

5.2.3   Testing Day

Subjects who were eligible for the study following the screening visit procedures were invited to a testing day. Before testing, subjects confirmed that they still wanted to take part and the information taken on the screening day was reviewed to ensure no significant changes in medical history or psychological wellbeing had occurred. Subjects also confirmed they had adhered to the prohibitions and restrictions as set out in section 5.1.3.

Subjects then underwent the following medical procedures:

- Vital signs (sitting and standing blood pressure, heart rate and temperature)

- Alcohol breath test

- For females only, a urine pregnancy test

- Drugs of abuse urine sample

- Subjects were asked to confirm they had not smoked for 2 hours prior to the scanner visit.

All subjects completed a practice run of the three tasks and signed an MR patient declaration form to confirm safety for being scanned. A radiographer co-signed the MR safety form and placed the participant within the scanner. All subjects then completed the three tasks along with a set of structural scans within the MR scanner. The scanning session lasted approximately 1.5 hours.

5.3   The Tasks

This is a brief summary of the three tasks used in this thesis. Full task details will be given in the relevant experimental chapters.

5.3.1 The Arena

5.3.1.2 Task Design

The Arena Task consists of a virtual reality circular arena with coloured patterns on the walls as visual cues to aid navigation (Parslow et al, 2004; Antonova et al, 2009). Subjects use a joystick, manipulated with their right hand, to navigate around the virtual arena. The participant is required to move from the periphery of the arena to a pole situated in the central space during the encoding phase. After a delay, filled with a blank screen, the participant re-enters the arena from a different entry point. During the retrieval phase, the pole is removed and the participant has to use the patterns around the arena as cues to find the previous location of the pole. When they have located where they believe the pole was located, they stop and the computer records this finished position at the end of the 30 second block. The task requires allocentric spatial memory because no single pattern can indicate position, but rather the combined vectors associated with different patterns around the arena are required. Following retrieval, the subjects are presented with a blank screen (rest) and a coloured screen (visual control) before moving onto the next trial. The trials are repeated six times during a single fMRI experiment.

5.3.1.3 Behavioural Measures

Dependent variables of interest are mean linear deviation (distance between the true and estimated pole location) and mean angular deviation (distance between the angle of the true and estimated pole location). These are expressed in terms of arbitrary "virtual" units calibrated in relation to the virtual size of the arena. Illustrations of the behavioural measures are provided in the results section for this task (Chapter 7, section 7.3). Imaging measures of interest are BOLD activation associated with each of the 6 epochs (encoding, rest, retrieval, rest, control and rest).

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5.3.2 The Platform

5.3.2.1 Task design

The Platform task incorporates a circular arena which contains a randomly arranged array of circular platforms positioned on the floor. Surrounding the area are visual cues (e.g. cottage, trees, castle) to help the participant navigate around the central space using a tracker ball, manipulated with the subjects right hand. The number of platforms is titrated to determine the difficulty level and trials include 4 platforms, 6 platforms and 8 platforms. The task is to select each platform in turn visiting each platform only once. When a platform is selected the participant is transported to that location and the computer indicates whether this was correct (never been visited before) or incorrect (been visited before). Subjects are required to remember which platforms they have already visited so that they only visit each platform once. This task measures allocentric spatial memory as subjects move to each platform they select altering their starting position for locating the next platform.

5.3.2.2 Behavioural Measures

Dependent variables of interest are accuracy as determined by number of between and within search errors and time to complete each set of 4, 6 and 8 platforms. Imaging measures of interest are BOLD activation during each set of 4, 6 and 8 platforms and BOLD activation and deactivation as spatial memory load increases.

5.3.3 The N-back

5.3.3.1 Task design

In this task there are three levels of increasing difficulty of working memory load. Subjects view a stream of letters. In the easiest level (1-back) subjects are asked to respond when two letters which follow one another are the same i.e. the participant has to hold online the previous letter they had seen and determine whether it was the same as the one they are currently viewing. In the 2-back condition subjects have to hold two letters presented one after the other in their memory and determine whether the current letter matched the letter they saw two letters ago. In the 3-back they have to hold three letters in mind to determine whether the letter they are currently viewing matched one they saw three letters ago. There is also a control condition for attention. Subjects are asked to press a button each time they see the letter 'X'. Subjects are prompted at the start of each block about which of the task levels they are about to perform. This is a screen reading "one back" for example written in black letters on a white background in the same typeface as the stimulus letters.

5.3.3.2 Behavioural Measures

Dependent variables of interest are number of correct responses, errors of omission (failing to respond when they should) and errors of commission (responding when they should not) and latency of correct and incorrect (commission errors) responses. Imaging measures of interest are BOLD activation for each set of 1, 2 and 3-back trials compared to the 0-back attention trial and BOLD activation and deactivation as working memory load increases.

5. 4   Magnetic Resonance Imaging

5.4.1   Scanning Order

The study was conducted on a 3-Tesla GE HDx scanner located in the Centre for Neuroimaging Sciences, Institute of Psychiatry. Subjects completed the MR patient declaration and were placed inside the MR scanner by a trained radiographer. Subjects then completed the three functional tasks. Task order was counterbalanced in the order of A) Arena – N-back – Platform or B) Platform – N-back – Arena.

After completing the first two tasks a structural brain scan was performed to exclude gross deviations from normal in the morphology of the brain. This scan was also used to assess group differences in grey and white matter volume between the control and high schizotypy group.

5.4.2   Functional Image Acquisition

For BOLD responses, T2* weighted gradient echo planar images were obtained. A total of 38 axially oriented 3 mm thick contiguous slices were acquired for each volume with a TR of 2s, TE 30ms, flip angle 75° and matrix size 64 x 64. This was the same for each task.

5.4.3   Structural Image Acquisition

A SPoiled Gradient Recalled Echo (SPGR) scan was acquired with a TR of 7.104s and a TE of 2.824s, flip angle 20, and matrix size 256 x 256.

5.5   Data Analysis Methods

In this section general data analysis methods will be covered including testing for normality, homogeneity of variance and independence of observation. Data transformation and outlier

identification will be discussed as well as the parametric and non-parametric statistical tests used in this thesis.

Demographic, behavioural and questionnaire data was analysed using Statistics for Social Sciences (SPSS) version 18. Significance was defined as $p < 0.05$.

5.5.1 Exploratory Data Analysis

Parametric tests are statistical tests which make certain assumptions about the parameters of the full population from which the sample is taken; it is assumed, for example, that the data show a normal distribution, and that, where populations are compared, they show the same variance. If these assumptions are not met, non-parametric tests are more appropriate for the data.

Assumption of Normality

Normality was checked in two ways; by visual inspection of histograms with a normal distribution curve and using the W statistic derived from the Shapiro Wilk test for normality. The Shapiro Wilk test tests the null hypothesis that a sample came from a normally distributed population (Shapiro & Wilk, 1965). If the p-value is less than the chosen alpha level (in this case 0.05) then the null hypothesis is rejected and it is concluded that the data are not from a normally distributed population. If the p-value is greater than the chosen alpha level then the null hypothesis is retained and it is concluded that the data came from a normally distributed population. The Shapiro Wilk test is the preferred test of normality for small samples ($N < 50$) and has good power properties compared with a wide range of alternative tests (Conover, 1999; Royston, 1995; Shapiro, Wilk, & Chen, 1968).

Assumption of Homogeneity of Variance

Levene's test of equality of variances (Levene, 1960) is used to test if k samples have equal variances. In SPSS, Levene's test for equality of variances can be included and produced alongside the results from the statistical test chosen. If the p-value provided by the test is greater than the chosen alpha level (in this case 0.05) then the variances are assumed to be equal. If the p-value is less than the chosen alpha level then variances are assumed to be unequal. For t-tests used in this thesis, if the variances are unequal then the t-statistic, adjusted degrees of freedom and significance are reported from the column labelled "equal variances not assumed". For ANOVA's used within this thesis, violation of the assumption of equal variances is addressed by attempts to transform the data, removal of outliers and the use of non-parametric tests if these attempts proved unsuccessful.

Assumption of independence

In order for parametric tests to be used observations must be independent. This assumption cannot be tested but is met if the design of the study is such that each subject is only measured once. However, if repeated measures designs are to be used this independence assumption is violated and the test statistic becomes unreliable. To test for the assumption of sphericity in repeated measures designs, Mauchly's test of sphericity (Mauchly, 1940) were performed in SPSS. If Mauchly's test statistic is significant (i.e. has a probability value less than 0.05) it is concluded that there are significant differences between the variance of differences, ergo the condition of sphericity has not been met. If, however, Mauchly's test statistic is nonsignificant then it is reasonable to conclude that the variances of differences are not significantly different. For variables that violated the assumption of sphericity, a Greenhouse-Geisser (Greenhouse & Geisser, 1959) correction was applied.

Assumptions of linearity and homoscedascity in correlation analysis

The assumptions, underlying the coefficient of correlation are those of linearity, normality, and homoscedascity. Linearity was assessed using scatterplots overlaid with a trend line. Homoscedascity refers to the same construct as homogeneity of variance and was assessed using the same methods outlined above. Normality was assessed using the same methods as above.

Outlier analysis

Outliers were identified in the data by visual inspection of box plots and extreme values tables produced in SPSS. Any outliers were inspected to ensure that they were valid data points and not data input errors. Outliers that were identified as extreme but valid data points were removed from the data if they significantly improved the distribution i.e. normalized a non-normal variable. However, if removal of the outlier did not significantly improve the distribution then in the interests of maintaining an adequate sample size, they were retained in the analysis.

Transformation of non-normal variables

Generally parametric analysis is considered more powerful than non-parametric analysis therefore transformation of non-normal data so that parametric tests can be used is thought to be a better strategy than using non-parametric tests (Rasmussen & Dunlap, 1991). Data that was identified as non-normal and which did not possess outliers or did not significantly improve with outlier removal was transformed using log transformations or squared in order to normalize the data.

5.5.2   Statistical Analysis Tests

5.5.2.1 Parametric tests

For independent, continuous interval data that meets the assumption of normality and homogeneity of variance independent t-tests were used to determine group differences. For repeated measures designs, repeated measures ANOVA were performed. For repeated measures designs with covariates repeated measures ANCOVA was performed.

5.5.2.2 Non-parametric tests

For non-parametric data that would have been analysed using an independent t-test the equivalent non-parametric test, the Mann Whitney U test was performed.   For non-parametric data that would have been analysed using repeated measures ANOVA, the non parametric equivalent Friedman's test of repeated comparisons was performed. Before selecting a non-parametric test, steps were taken to normalize the data so that parametric tests could be used. Non-parametric tests were used when normalization of the data was unsuccessful.

5.5.2.3 Analysis of Nominal Data

For analysis of nominal data for example gender and ethnicity, a chi square was performed. Ethnicity was biased towards Caucasian subjects in both groups and therefore some cells had a count of less than 5. Collapsing ethnicities together did not provide a count of more than 5 for one category. Chi square tests with low sample sizes have very little power and so the test result should be treated with caution.

5.5.3 Functional Image Analysis

Details common to all tasks are presented below. Structural analysis is presented in the relevant experimental chapters. Specific details pertaining to the imaging analysis of each task are presented in the relevant experimental chapters.

5.5.3.1 Preprocessing

Functional MRI data from the Arena, N-back and Platform Task were pre-processed and analysed using SPM5 (Statistical Parametric Mapping, developed by University College London http://www.fil.ion.ucl.ac.uk/spm/).

<u>Realignment</u>

Each image was realigned to the first image in the dataset to correct for subject movement in the scanner. Sinc interpolation was used to reslice each image after the transformation had been applied and a mean EPI image created from the resliced images. Movement less than 3mm was deemed acceptable.

<u>Normalisation</u>

The anatomical MRI image was co-registered to the mean EPI image created in the realignment step. The co-registered MRI image was then normalised to the International Consortium for Brain Mapping (ICBM152) T_1 weighted template.

<u>Smoothing</u>

The resultant time series realigned and spatially normalised images were smoothed with an 8mm FWHM Gaussian kernel.

5.5.3.2 Model Specification

Details specific to each experimental task or investigation are reported in the relevant experimental chapter. Here, I will discuss the general model specifications and the justifications for their use in this thesis.

In a fixed effects analysis one cannot generalise the results to the population from which the subjects were drawn; the results are only a description of the subjects included in the experiment. Thus, if two groups are compared using fixed effects analysis any differences found may result from particular subjects rather than underlying differences between the two populations. To generalise a result to a population a random effects analysis is used. The random effects model is necessary to make valid inferences from group fMRI data and for the purposes of group fMRI analysis it is important that subjects are treated as random effects in the model so that the results can be generalised to the population in which the subjects were sampled and not limited to each individual subject. In effect the single subject analysis controls the within subject variance whereas the group level analysis controls the between subject variance (Holmes & Friston, 1998). This is a standard group level design for comparing two groups i.e. patients and controls and is the necessary design for group comparisons in fMRI using the Statistical Parametric Mapping (SPM) software (R.A. Poldrack, Mumford, & Nichols, 2011).

This random effects analysis is carried out in multiple stages so for example let's assume that we have a single run of fMRI data and there are multiple subjects. The subjects belong to two different groups and the goal of the study is to see whether the activation when viewing one condition versus another condition is different between the two groups. In this case there would be two levels to the model. The first level involves modelling the data for each subject separately; the output of this model is subject specific estimates of the contrast and within subject variance estimates for this contrast. The second level model then takes as input the

subject specific estimates from the first level model. The model then estimates a mean for each group and the contrast tests which of the conditions is stronger in the first group compared to the second group and is an example of a two sample t-test. If several contrasts and their interactions are of interest then an ANOVA can be performed to test these. Details specific to the analysis used in this thesis are given below and in the relevant experimental chapters.

First Level Analysis

The onset and duration were entered for each task and for each subject, and a box car model convolved with the hemodynamic response function was selected (specific parameters for each task are given in the relevant experimental chapters). Six rotational and translational movement parameters generated by the realignment procedures for each subject were entered as regressors (i.e. nuisance covariates). A high pass filter of 128Hz was used and the hemodynamic response function was used as a low pass filter. Following estimation of the statistical model, contrast images were generated for each task comparison, and for each subject.

Second Level Analysis

Smoothed contrast images were analysed using a one-sample t-test to show the main effect of task in each group and a two-sample t-test was used to show differences in activation between schizotypes and controls. For some tasks a full factorial ANOVA was used to demonstrate the main effect of group, condition and the interaction between the two.

5.5.3.3 Significance

Inferences can be made either at the voxel or cluster level. Voxel level inference involves testing each and every voxel individually so for example two voxels may be above the statistical height threshold and these two voxels will be individually defined as significant. Alternatively, we can identify clusters of activated voxels and test the significance of each cluster, which is referred to

as cluster level inference. In cluster level inference, a single cluster of 10 voxels may be significant where as none of the 10 voxels are individually significant but together they comprise a single cluster.

Voxel level inference makes no use of the spatial information in the image and given that fMRI data is spatially smoothed we would expect that signals in fMRI will be spatially extended. To take advantage of the knowledge about the spatial structure of fMRI signals we can use cluster level correction. Although cluster level inferences are thought to be more sensitive that voxel level inferences for standard MRI data they are reliant on an arbitrary cluster forming threshold and they lack spatial specificity (R.A. Poldrack, et al., 2011). This means that too small a threshold and the result will be large clusters but too high a threshold results in a break up of the large clusters but excludes many smaller clusters. Cluster level inferences also lack specificity to the exact location of a signal and all that can be concluded is that one or more voxels within a cluster have evidence against the null hypothesis

In this thesis voxel level inferences are reported to determine the precise location of the activated signal and correction for multiple testing is applied using family wise error correction.

Across tasks, images were thresholded at a voxel-level p<0.001 uncorrected and significance defined as p < 0.05 family wise error (FWE) corrected to control for multiple comparisons. FWE was selected for several reasons: 1) It is the gold standard level of significance at which true results are observed; 2) it is more appropriate than alternative methods e.g. false discovery rate (FDR) for the level of smoothing used in this thesis (8mm) and the degrees of freedom (>20); 3) It is a better option than FDR for group data as group data is usually highly smoothed due to anatomic variability and FDR performs best at lower levels of smoothing (< 6mm)(Nichols & Hayasaka, 2003).

In order to control the multiple testing problem a correction needs to be applied to control the false positive risk. If a statistical image has 100, 000 voxels and we declare all voxels with p < 0.05 to be significant then on average 5% of the 100, 000 voxels – 5000 voxels – will be false positives. The most common measure of Type 1 error over multiple tests is the "family wise error rate", which determines the chance of one or more false positives anywhere in the image. A valid procedure with αFWE= 0.05 will result in at most a 5% chance of any false positives anywhere in the map.

The most widely known method for controlling FWE is the Bonferroni correction. However, although it will control FWE for any dataset, the Bonferroni procedure becomes very conservative when there is a strong correlation between tests. Functional imaging data has a degree of spatial correlation that comes from the way the scanner collects and reconstructs the image, physiological signal and spatial pre-processing and thus Bonferroni corrections are normally very strongly conservative and not applicable to neuroimaging data. Instead correction for multiple comparisons in fMRI data is based on random field theory (RFT), which takes into consideration the inherent and applied smoothing of the data and thus the spatial dependence between voxels. Random field theory corrections attempt to control the FWE rate by assuming that the data follow certain specified patterns of spatial variance – that the distributions mimic a smoothly varying random field (Nichols & Hayasaka, 2003). RFT corrections work by calculating the smoothness of the data in a given statistic image and estimating how unlikely it is that voxels with particular statistic levels would appear by chance in data of that local smoothness. Random field theory corrections are the default option in SPM software.

As well as corrected p-values, voxel level uncorrected statistics at a threshold of p < 0.001 will also be reported for information as is convention in imaging studies. These results will be presented in tables but are not discussed further. In the case of uncorrected results that have a

strong hypothesis, the results will be discussed but emphasis will be placed on their uncorrected status.

5.5.3.4 ROI selection

If a study is focused on a particular region of the brain, then it is possible to limit the search for activations to a region of interest, which reduces the stringency of the correction for multiple testing. As FWE correction methods adapt to the number of tests performed, limiting your correction to an area of interest rather than the whole brain, reduces the number of tests performed and results in a less severe correction. Small volume correction is applied in SPM5 by selecting the small volume correction option and specifying either an ROI mask or applying a sphere around a point (a set of coordinates for the ROI). SPM then recalculates the corrected p-statistics using family wise error correction for that specified region only.

For *a priori* regions of interest, small volume corrections (SVC) were applied derived from the WFU pick atlas (Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Kraft, & Burdette, 2003) installed as part of the SPM5 toolbox. The WFU pickatlas software toolbox developed at Wake Forest University School of Medicine provides a method for generating ROI masks based on the Talairach Daemon database (Lancaster, Summerln, Rainey, Freitas, & Fox, 1997; Lancaster et al., 2000) and other human and non-human atlases for example AAL (Tzourio-Mazoyer et al., 2002). The advantage of using the WFU pickatlas to generate ROIs is that they are anatomically rather than functionally derived, providing an unbiased ROI mask. This is considered a more independent method of generating ROIs than using small volume correction around the peak of the activation derived from the whole brain analysis. It has the advantage that mask/s can be created at the start of the analysis and then applied to subsequent analyses obtaining a consistency of ROI used. The disadvantage of using an anatomical ROI is that they are relatively large such that truly active voxels will make up a relatively small proportion of any

anatomic region (R. A. Poldrack & Mumford, 2009). However, this approach is conservative and allows true significant differences to be ascertained.

For unbiased extraction of BOLD parameter estimates for use in correlation analyses in SPSS, independent ROIs were constructed in MarsBar (Brett, Acton, Valabregue, & Poline, 2002), part of the SPM5 toolbox and applied to the individual subject activation maps. Full details of these methods are given in the individual results chapters. ROIs were selected based on previous literature and are provided in each experimental chapter; co-ordinates for the ROIs were taken from previously published literature.

5.5.3.5 Reporting of imaging results

MNI coordinates provided by SPM were converted into Talairach space using the Brett et al (2002) method (see http://imaging.mrc-cbu.cam.ac.uk/imaging/Mnitalairach). Anatomical regions were identified using the Talairach Daemon (Lancaster, et al., 1997; Lancaster, et al., 2000) and approximate Brodmann areas are reported for information.

For each task, results from the image analysis are first presented at a FWE corrected level of $p < 0.05$. Following this, a less conservative threshold at a voxel-level uncorrected $p<0.001$ are presented for reasons discussed above. Results of region of interest investigations using small volume correction will then be reported. Small volume corrections will be reported if they are significant at a corrected level of $p < 0.05$. Brain regions activated are presented in tables and BOLD activation maps are illustrated on glass brains and images derived from SPM5.

Chapter 6:   Investigation into brain structure in schizotypal personality using voxel based morphometry.

In this chapter, results will be presented from whole brain voxel based morphometric assessment of brain volumes in healthy volunteers with schizotypal traits. Few studies have been conducted to investigate brain structure in this group. Firstly I will introduce the different methods used for investigating volumetric differences in psychosis and why voxel based morphometry has been chosen for this thesis. Secondly, I will present the results from this investigation and discuss it in light of the previous literature.

6.1   Introduction

Previous studies have explored regional gray matter (GM) differences in schizotypal personality have employed region of interest (ROI) approaches to manually delineate GM volumes (e.g. Suzuki, et al., 2005). A major limitation of ROI based techniques to determine morphometric brain changes is the need for an *a priori* decision concerning which structures to evaluate. This leads to certain brain regions being studied extensively as hypotheses are generated from previous work whilst in comparison some regions remain understudied. Practically, manually based ROI analysis is limited by its reliance on the user to trace the ROI which introduces potential errors, is time consuming and unlikely to be used on large datasets. Laboratory specific ROIs also limit comparisons between data acquired at different institutions. An alternative method to ROI analysis is voxel based morphometry (VBM).

At its simplest, VBM involves a voxel wise comparison of focal differences in tissue volumes using the statistical approach of statistical parametric mapping (Ashburner & Friston, 2000). Generally, the VBM method comprises of spatial normalisation of all subjects' data into stereotactic space, segmentation of brain tissue into GM, white matter (WM) and CSF, smoothing of the image and finally comparison of the segment of interest (e.g. GM) between groups on a voxel by voxel basis (Ashburner & Friston, 2000). This provides statistical maps comprised of the location and statistically significant values of the regions where differences in volume are present. Correction for multiple comparisons is then applied using Gaussian Random Field Theory (RFT) (Ashburner & Friston, 2000). Several different methodologies have been developed over the years from standard VBM analysis to optimised VBM (Good et al., 2001) implemented in SPM99/2 to unified segmentation introduced in SPM5 (Ashburner & Friston, 2005) and lastly to the recently developed Diffeomorphic Anatomical Registration Through Exponential Lie Algebra (DARTEL; Ashburner, 2007) implemented in SPM8. For the most part these differ in their treatment of segmentation and modulation. Good et al (2001) highlighted the advantages of using Optimised VBM and the benefits of modulating normalised images. Spatial normalisation expands and contracts some brain regions; modulation involves scaling by the amount of contraction, so that the total amount of grey matter in the modulated grey matter remains the same as it would in the original images. The advantage of a modulated analysis over an unmodulated one is that differences between groups can be specified in terms of volume rather than 'concentration'. However, optimised VBM was inherently circular in its approach (registration required an initial tissue classification and the tissue classification required an initial registration) and thus, SPM5 introduced a unified segmentation approach (Ashburner & Friston, 2005). Here, segmentation, bias correction and spatial normalisation are combined into a simple generative model. This model also includes parameters that account for image intensity non-uniformity. Estimating the model parameters involves alternating among classification, bias

correction and registration steps providing better results than simple serial application of each component (Ashburner & Friston, 2005). See Figure 4 for schematic overview of unified segmentation in SPM5. Further, VBM can be combined with region of interest investigations using small volume correction methods to spatially constrain analysis to *a priori* regions of interest. SPM5 is used in this thesis as it was the latest, most readily available and widely supported analysis package at the time of data analysis.
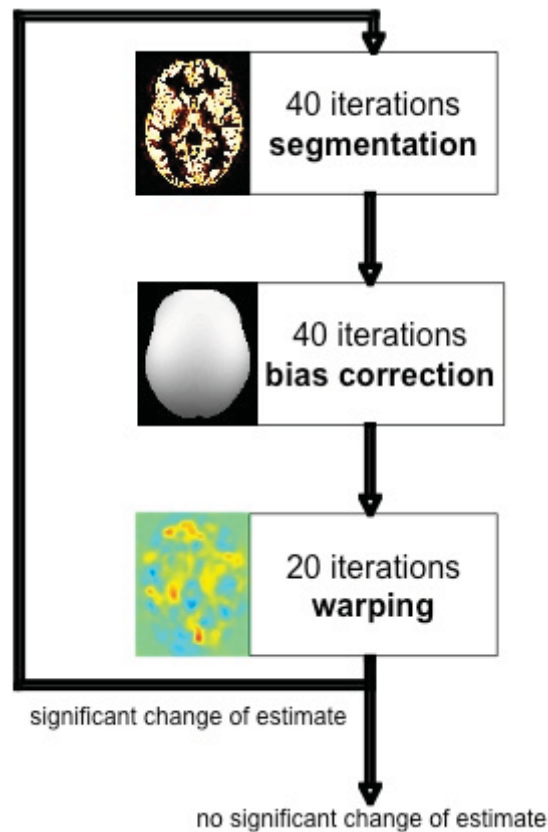
Figure 4 Schematic overview about the unified segmentation approach in SPM5

The first 40 iterations of the initial segmentation estimation are followed by 40 iterations of bias field correction and finally 20 iterations are made for warping the prior image to the data. This iterative scheme is repeated until no significant changes occur.

As discussed in Chapter 3 of the introduction, schizophrenia is associated with alterations in grey matter of the medial temporal lobes, superior temporal gyrus, prefrontal cortex, parietal lobes and basal ganglia (for review see Shenton, et al., 2010). Schizotypal personality disorder meanwhile has been associated with volume reductions in the medial temporal lobes (hippocampus, entorhinal cortex; Kawasaki et al, 2004; Yoneyama et al, 2003), superior temporal gyrus (Goldstein et al, 2009), parietal lobes (Zhou et al, 2007), insula (Yoneyama et al, 2003) and thalamic nuclei (Byne et al, 2001). Studies of healthy volunteers with schizotypal traits have revealed lower volumes in the hippocampus (Flaum & Andreasen, 1995) superior and medial frontal gyrus, anterior cingulate gyrus, insula, middle and superior temporal gyrus and rolandic operculum (U. Ettinger, et al., In press). Meanwhile, increases have been observed in global brain volume and grey matter volume of the precuneus and posterior cingulate cortex (Modinos, et al., 2010). Several researchers have suggested that the discontinuity between schizophrenia and schizotypal personality is a relative sparing of the frontal lobes, or at least some regions of the prefrontal cortex (i.e. BA10) in schizotypal personality (Siever & Davis, 2004; Siever, et al., 2002). The temporal lobes meanwhile are affected across the schizophrenia spectrum and the volume alterations observed in this region in chronic and first episode patients with schizophrenia, healthy volunteers with schizotypal traits, patients with clinical SPD, individuals at clinical and/or genetically at risk for the disorder suggests it is a neurobiological marker of vulnerability to psychotic disorders.

The tasks used in this thesis have been shown to be dependent upon regions that have demonstrated volume alterations in schizotypal personality expression including the hippocampus, prefrontal cortex, and parietal lobes. Thus, the aim of this chapter of the thesis is to ascertain whether high schizotypy as measured using the SPQ is associated with structural alterations of these regions. A secondary aim is to investigate the specificity of previously reported grey matter volume alterations in the hippocampus by exploring the volumes of the

hippocampal subregions in schizotypal personality. Significant structural findings will be taken forward into the functional chapters to explore the relationship between structure and cognition.

6.2 Specific Hypotheses

Specific hypotheses are as follows:

1. High schizotypy will be associated with a reduction in regional tissue volume in the medial temporal lobe structures specifically the hippocampus compared to the control group in line with previous schizotypy findings.

2. There will be no differences in regional tissue volume of the prefrontal cortex between the control group and high schizotypy.

3. In line with previous studies and Siever & Davis's model of schizotypal personality, increases in volume will be observed in anterior frontal pole region (BA10) in the high schizotypy group.

4. There will be no differences in global tissue volume (grey matter, white matter or CSF) between the control group and high schizotypes.

6.3 Methods

6.3.1 Subjects

Overall 42 participants completed the study through to follow up. Table 3 demonstrates the number of participants contacted, telephone screened, screened and tested as well as the number of participants excluded as per the reasons outlined in the inclusion/exclusion criteria (section 5.1.1 and 5.1.2).

Table 3 Number of participants contacted, screened and assessed

Telephone Screened	136
Excluded	73
Reasons for exclusion:	
Did not want to participate	10
Psychiatric History	4
Medical	2
MRI incompatible	10
Not GP registered	6
Drug Use	3
Smoker	4
Age	1
Unable to schedule/did not attend	33
Screened	63
Excluded:	21
Reasons for exclusion:	
Drug Use	2
MRI incompatible	5
Unable to Schedule	5
SPQ score in incorrect range	9
Assessed	42

42 subjects were included in the structural VBM analysis, 21 control subjects and 21 high schizotypy subjects. Demographics and schizotypy scores for this group are reported in the results section of this chapter.

Screening procedures, inclusion and exclusion criteria, schizotypy group allocation and selection of subjects is as discussed in Chapter 5. Image acquisition details are presented in Chapter 5, section 5.4.2).

6.3.2   Preprocessing of the structural images

Visual Inspection of the MRI Images

Images were visually inspected using MRIcro 1.35 (C. Rorden www.mricro.com, 2002). Images were rejected if the image quality was judged as poor. No images were rejected from the final analysis.

Reorientation of the images to the AC/PC line

Images were re-orientated to the AC/PC line to ensure compatibility with the pre-processing steps. This is to ensure the affine registration has better starting estimates.

Unified segmentation using VBM5

Preprocessing of the images was done using unified segmentation in SPM5. Data was segmented into grey, white matter and CSF, modulated and normalised with bias correction and thoroughly cleaned of non-brain matter. Images were then smoothed with a 12mm kernel. This smoothing size is in line with previous studies in schizotypal personality that have observed volumetric changes in the medial temporal lobes (Kawasaki et al, 2004)(Yoneyama, et al., 2003) and has been used to determine volumetric differences in healthy volunteers with schizotypal traits (Modinos et al, 2010).

6.3.3   Model Specification

Global tissue volumes

Global tissue volumes were extracted from the pre-processed images using a script written by John Ashburner (2000) available via (http://www.jiscmail.ac.uk/cgi-bin/webadmin?A2=ind0010&L=spm&P=R36678&D=O&I-1).   The values for total grey and white matter, and CSF were entered into SPSS and total brain volume was calculated by

summing grey and white matter. Global tissue volumes were investigated using an ANCOVA design in SPSS 18 with appropriate nuisance covariates of age and total intracranial volume.

Regional tissue volumes

Differences in regional tissue volumes were investigated using the general linear model in SPM5 with appropriate nuisance covariates (determined using the same method as for global tissue volumes). No grand mean scaling or global calculation was applied as global differences were accounted for by including global volume as a covariate in the analysis.

6.3.4 Region of interest

A region of interest analysis was conducted using the WFU pickatlas part of the SPM5 toolbox. See chapter 5 for discussion of the WFU pickatlas. To address the hypotheses listed in 6.2, *a priori* regions of interest were the left and right prefrontal cortex and medial temporal lobe structures: left and right hippocampus, left and right amygdala and left and right parahippocampal gyrus. Only regions that are significant $p < 0.05$ small volume corrected will be reported.

If significant volumetric differences of the hippocampus is observed in high schizotypy subregions of the hippocampus will be explored further using a probabilistic cytoarchitechtonic atlas to construct ROIs of the hippocampal formation sub-regions including the Cornu Ammonis (CA), Subiculum (SUB), Fascia Dentata (FD), Entorhinal Cortex (EC) and Hippocampal-Amygdaloid Transition Area (HATA). The probabilistic cytoarchitechtonic maps are accessible via an SPM toolbox developed by Eickhoff et al (2005). Coordinates for the hippocampal ROIs are derived from Amunts et al (2005) and are available on the probabilistic anatomy toolbox website. The probabilistic cytoarchitechtonic maps for medial temporal lobe regions are derived from histological cell-body staining of 10 post mortem brains (Amunts et al., 2005). Using

MarsBar(Brett, et al., 2002), volume estimates for each of these subregions was extracted for each subject and entered into SPSS. Group differences were ascertained between the groups using the general linear model with appropriate nuisance covariates.

6.4 Results

6.4.1 Demographics

Gender and ethnicity were evaluated using chi-square. Age had a non-normal distribution (Control Group: W = .798, df =21, p < 0.001; High Group: W = .873, df = 21, p = 0.011). Transformation of this variable did not significantly improve the distribution therefore a non-parametric Mann Whitney test was performed. The variable education had three missing values therefore a series mean calculation was performed to replace these values. The new education variable was normally distributed (Control Group: W =.921, df = 21, p = 0.089; High group: W = .918, df = 21, p = 0.077). IQ (NART-R score) was also normally distributed (Control Group: W = .954, df = 21, p = .405; High Group: W = .959, df = 21, p = .492). Education and IQ were investigated using independent t-tests. Schizotypy groups did not differ on age, gender, IQ, years in education or ethnicity (demographic data is presented in Table 4).

Table 4 Demographics for each schizotypy group in the VBM analysis.

	Control Group	High Schizotypy	Statistical Test
Age Range	24.95 (6.64) 19-42	23.57 (4.95) 18-37	U = 200.50, p = .613
Gender Ratio (M:F)	8:13	10:11	χ^2 = .389, df = 1, p = .756
Ethnicity (N) White Black Asian	 17 0 4	 15 3 3	 χ^2 = 3.268, df = 2, p = .302
Education	15.43 (1.77) 13 – 20	15.55 (1.75) 11 - 18	t = -.221, df = 40, p = .827
NART-R IQ score Range	116.35 (4.37) 107.84 – 123.48	116.50 (4.07) 107.84 – 123.08	t = -.111, df =40, p = .912

6.4.2 Schizotypy Scores

Schizotypy scores were determined by total score on the SPQ. Allocation to the average schizotypy group included scores 21-36 and allocation to the high group included scores of 43 and above.

Total SPQ score was not normally distributed (Control Group: W = .861, df =21, p = 0.007; High Group: W = .866, df = 21, p = 0.008) and the cognitive perceptual subscale was not normally distributed in the average group (Control Group: W = .905, df = 21, p = 0.043; High Group: W = .973, df = 21, p = 0.792) therefore for these two variables a Mann Whitney test was used. The SPQ subscale Interpersonal was normally distributed (Control Group: W = .983, df = 21, p = 0.961; High Group: W = .961, df = 21, p = .536) and the SPQ subscale Disorganised was also normally distributed (Control Group: W = .976, df = 21, p = .860; High Group: W = .910, df = 21, p = 0.056). Therefore, these variables were investigated using independent t-tests. Schizotypal personality scores in each group are presented in Table 5.

Table 5 Schizotypy scores across both groups included in the VBM analysis

	Control Group	High Schizotypy	Statistical Test
SPQ total score Range	26.42 (4.94) 21 – 36	48.14 (4.91) 43.58	U = 441.00, p =0.001
Cognitive Perceptual Range	9.80 (6.63) 1-29	19.81 (5.15) 10-29	U = 390.50, p = 0.001
Interpersonal Range	11.52 (4.80) 1-23	21.76 (5.68) 8-31	t = -6.306, df = 40, p =0.001
Disorganised Range	8.52 (3.23) 3-15	12.71 (2.90) 6-16	t = -4.420, df = 40, p = 0.001

Data represents means (SD) unless otherwise stated.

6.4.3 Global Tissue Volumes

Determining Nuisance Covariates

Twenty one high schizotypes were compared to 21 control subjects in the VBM analysis. From previous work (Good et al, 2001) it is known that between subject variance of tissue volume in the brain is largely accounted for by total intracranial volume, age and sex. Sex differences in brain volume are largely accounted for by total intracranial volume and thus age and intracranial volume are included as nuisance covariates.

<u>Group Comparison</u>

Age and intracranial volume were included as nuisance covariates for grey matter total volume, white matter total volume and CSF total volume. Results are presented in Table 6.

Table 6 Global tissue volumes for grey matter, white matter and CSF between schizotypy groups

	Control Group (N = 21)	High Schizotypy (N = 21)	Statistical Comparison
Grey Matter Volume/ml	754.27 (92.51)	740.00 (64.84)	$F_{(1,38)} = 0.23$, p = .687
White Matter Volume/ml	481.38 (74.26)	466.04 (51.31)	$F_{(1,38)} = 0.64$, p = .802
CSF Volume/ml	425.62 (104.71)	415.67 (119.08)	$F_{(1,38)} = .168$, p = .684

Data represents means (SD) unless otherwise stated.

6.4.4 Regional Tissue Volumes

The general linear model was used to investigate tissue grey matter and white matter volume differences between the two groups. Age and total brain volume were included as nuisance covariates. This allows for localisation of differences not explained by these factors. Across tissue types there were no regions that survived correction for multiple comparisons at the p < 0.05 family wise error (FWE) level, therefore the following results are presented at the p < 0.001 uncorrected level. Results are presented at an uncorrected p < 0.001 level for completeness but it should be noted that not correcting for multiple comparisons increases the risk that the SPM maps contain more false positives. Grey matter and white matter results are presented below.

6.4.4.1 Grey Matter Volume

Decreased grey matter volume was observed in the right hippocampus, bilateral middle frontal gyrus (BA6) and right middle temporal gyrus (BA21). Increased grey matter volume was observed in left occipital regions (cuneus and inferior occipital gyrus), left inferior temporal gyrus (BA20), bilateral superior temporal gyrus (left – BA22 and right – BA39), right inferior frontal gyrus (45) and right superior frontal gyrus (8) and right medial frontal gyrus (BA10). Results are presented in Table 7 and Figures 5 and 6.

Table 7 Grey matter volume differences between average and high schizotypes

Location	BA Equivalent	Cluster Size	Z score	Maximum Co-ordinates (x, y, z)
Decreased regional grey matter in high schizotypes compared to controls				
Hippocampus (R)		78	3.85	30 -42 0
Middle Frontal Gyrus (R)	BA6	15	3.84	26 -12 62
Middle Temporal Gyrus (R)	BA21	71	3.52	68 -2 -22
Middle Frontal Gyrus (L)	BA6	7	3.49	-26 -12 64
Increased regional grey matter in high schizotypes compared to controls				
Cuneus (L)	18	100	5.28	-18 -96 12
Inferior Occipital Gyrus (L)	19	18	3.97	-42 -80 -10
Inferior Temporal Gyrus (L)	20	15	3.84	-50 -10 -24
Medial Frontal Gyrus (L)	6	8	3.57	-10 -22 62
Superior Temporal Gyrus (L)	22	6	3.52	-52 -6 -6
Inferior Frontal Gyrus (R)	45	9	3.42	50 24 18
Posterior Cingulate (R)	30	9	3.32	30 -76 8
Medial Frontal Gyrus (R)	10	6	3.27	16 60 -4
Superior Frontal Gyrus (R)	8	5	3.26	22 20 54
Superior Temporal Gyrus (R)	39	10	3.25	44 -54 28

All regions reported at the $p < 0.001$ level uncorrected. L = left hemisphere, R = right hemisphere.
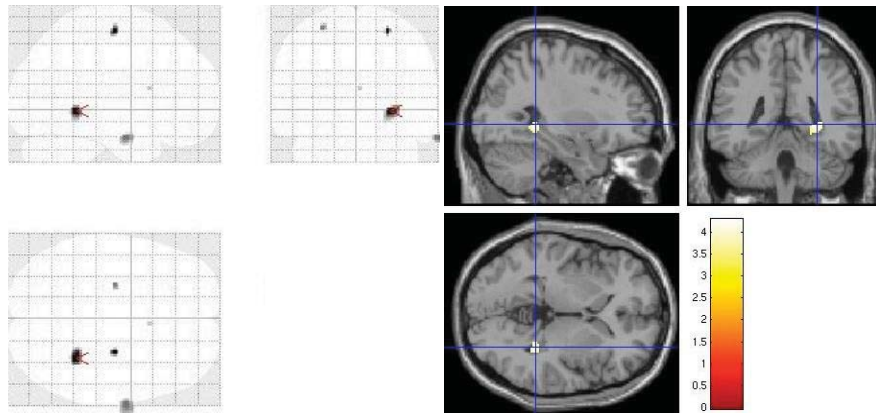
Figure 5 Grey matter decreases in high schizotypes compared to controls (p < 0.001 uncorrected)
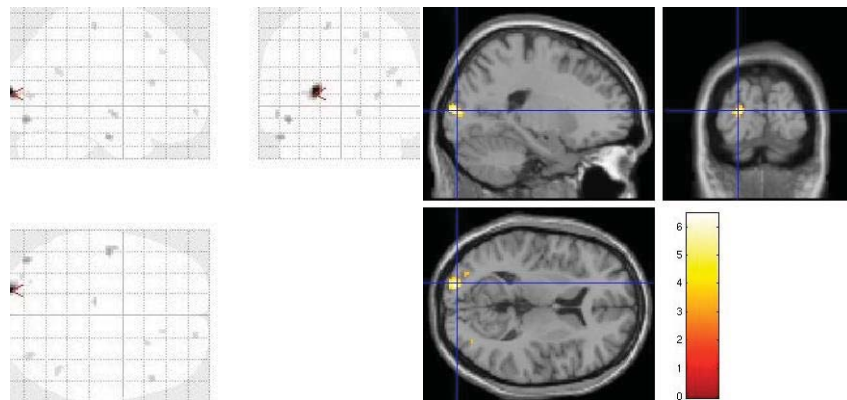
Figure 6 Increased grey matter in high schizotypy compared to controls (p <0.001 uncorrected)

6.4.4.2 White Matter Volume

Decreased white matter was observed in the left fusiform gyrus, right supramarginal gyrus, left parahippocampus, right inferior frontal gyrus and left superior temporal gyrus. Increases in white matter were observed in the right parahippocampus, right lingual gyrus, right fusiform gyrus, left middle frontal gyrus and left lingual gyrus. Results are presented in Table 8 and Figures 7 and 8.

Table 8 White matter volume differences between controls and high schizotypes.

Region	Cluster Size	Z score	Maximum Co-ordinates (x, y, z)
Decreased regional white matter in high schizotypes relative to controls			
Fusiform gyrus (L)	40	3.81	-52 -8 -26
Supramarginal Gyrus (R)	15	3.52	46 -51 28
Parahippocampus (L)	7	3.43	-30 -5 -20
Inferior Frontal Gyrus (R)	21	3.40	51 26 15
Superior Temporal Gyrus (L)	8	3.31	-50 -4 -7
Increased regional white matter in high schizotypes relative to controls			
Parahippocampus (R)	79	4.02	24 -42 -4
Lingual Gyrus (R)	75	3.91	14 -58 1
Fusiform Gyrus (R)	32	3.57	50 -67 -12
Middle Frontal Gyrus (L)	6	3.39	-16 9 55
Lingual Gyrus (L)	8	3.35	-24 -72 -8

All regions reported at the p <0.001 level uncorrected. L = left hemisphere, R = right hemisphere
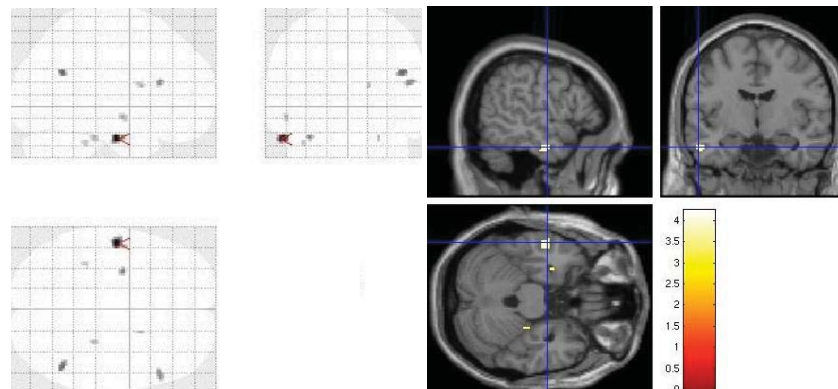
Figure 7 Decreases in white matter volume in high schizotypy compared to controls (p < 0.001 uncorrected)
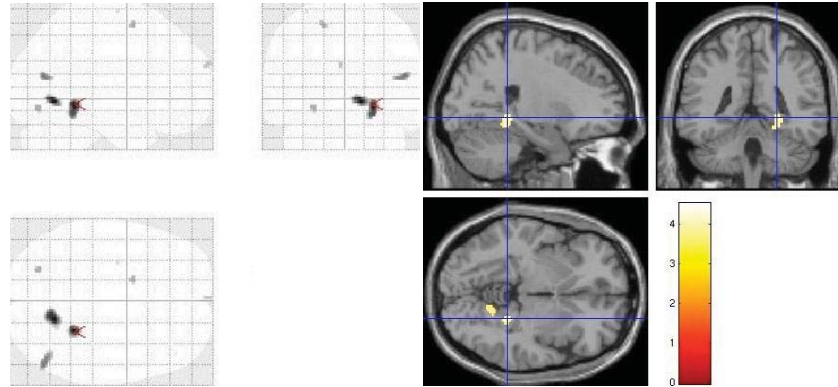
Figure 8 Increases in white matter volume in high schizotypy compared to controls (p < 0.001 uncorrected)

6.4.5 Regions of Interest

Region of interest analysis using WFU pickatlas did not reveal any regions across tissue types and groups that were above the p < 0.05 small volume corrected threshold. As no significant differences were observed in the hippocampus or parahippocampus between the two groups at either the whole brain or small volume corrected level, the subregions of the hippocampus were not explored further.

6.5 Discussion

Global brain volumes

There were no differences between controls and high schizotypes in total grey matter volume, total white matter volume or total CSF volume. Although a small global volume reduction has been reported in schizophrenia (Wright et al, 2000) it has not been consistently reported in schizotypal personality. Modinos et al (2010) reported a small increase in global brain volume in high schizotypy using the CAPE, a measure of positive schizotypy. However, Ettinger et al (In press) did not find any differences in global tissue volume in high schizotypy using the RISC, another measure of positive schizotypy.

<u>Regional brain volumes</u>

There was no regional volume differences observed at the $p < 0.05$ FWE corrected level but several regions were identified at a lower threshold of $p < 0.001$ uncorrected. This is considered a more liberal threshold but reporting of uncorrected statistics is often reported in the imaging literature. There is however an increased risk of obtaining false positives and this must be taken into consideration when assessing the results. Regions that were observed at an uncorrected level but had a clear hypothesis will be discussed but emphasis is placed on these results being uncorrected. Grey matter volume reductions were observed in the right hippocampus, bilateral medial frontal gyrus and right middle temporal gyrus in high schizotypes compared to controls. Grey matter increases were observed in the left cuneus, left inferior and bilateral superior temporal gyrus, right inferior frontal gyrus, left occipital gyrus, right posterior cingulate and right frontal pole. White matter volume decreases were observed in the left inferior frontal gyrus, right supramarginal gyrus, left parahippocampus extending into the amygdala, right inferior frontal gyrus and left superior temporal gyrus. Increased white matter was observed in the right parahippocampal gyrus, bilateral lingual gyrus, right fusiform gyrus and left middle frontal gyrus. There were no areas where CSF was lower in high schizotypes than controls.

In line with the hypothesis, smaller volumes of the hippocampus were observed in high schizotypy. This is in line with previous literature in schizotypy (Flaum & Andreasen, 1995) and schizotypal personality disorder (Suzuki, et al., 2005). Further, hippocampal volume reductions are observed in chronic and first episode schizophrenia patients (eg. Velakoulis et al., 1999; Witthaus et al., 2009), clinical high risk groups (Fusar-Poli et al., 2011) and relatives of patients with schizophrenia (eg. Seidman, et al., 1999; Seidman et al., 2002). Positive schizotypal traits have been associated with lower hippocampal volumes (Flaum & Andreasen, 1995) and both the Modinos et al (2010) and Ettinger et al (in press) reported volume alterations associated with positive schizotypy. In this thesis, the underlying factors of schizotypy are not

investigated and the hippocampal differences between the two groups do not survive correction for multiple comparisons. Using a measure specific to positive schizotypy such as the RISC or PAS or utilising a design where the positive dimension of the SPQ is used may have elicited stronger hippocampal differences between the two groups. The results observed in this study suggests that the hippocampus is a region worth exploring further in schizotypal personality.

Grey matter volume reductions were also observed bilaterally in the medial frontal gyrus which has also been observed previously in schizotypy (Ettinger et al, In press) and relatives of patients with schizotypal traits (R. A. Honea et al., 2008) however these did not survive correction for multiple comparisons. No reductions were observed in any other prefrontal regions. However, several regions of increased volume were observed in high schizotypy including right frontal pole region BA10 as hypothesised. However, this also did not survive correction for multiple comparisons. An increased volume of BA10 in never-medicated patients with schizotypal personality disorder has also been reported (Hazlett, et al., 2008) and this has been suggested as a key protective factor in SPD alongside sparing of temporal regions (BA 20 and 22). Consistent with this we also found volume increases in these regions in high schizotypy with volume decreases in the middle temporal gyrus (BA21) also reported in the Hazlett et al (2008) study. However, given that the results obtained in this thesis did not survive correction for multiple comparisons further exploration of these regions in schizotypal personality are needed to investigate this further. Other studies of schizotypal personality disorder and healthy volunteers with schizotypal traits have found volume alterations of the superior temporal gyrus (K. E. Goldstein, et al., 2009). It has been suggested that volume decreases in the superior temporal gyrus and inferior frontal gyrus are related to transition to psychosis and may underlie the clinical onset of the disorder (Fusar-Poli, et al., 2011). Therefore, a lack of gray matter volume decreases in these regions in the high schizotypy group may reflect the psychological health of this volunteer sample.

Methodological Considerations

Although the unified segmentation of SPM5 is an improvement on the optimised VBM procedure implemented in SPM99/02 it still has considerable difficulty in segmenting CSF from total gray and white matter. Conducting the analysis in SPM8 with the recently implemented DARTEL may improve registration and strengthen the conclusions drawn from this study.

The schizotypy groups recruited in this study were recruited on the basis of the total score on the SPQ and not the underlying dimensions. Negative schizotypal traits such as asociality and blunted affect are underrepresented in schizotypy samples as individuals high in these traits are unlikely to volunteer for research studies. Further some traits associated with schizotypy such as odd non-verbal communication and odd speech may go unrecognised by the schizotypal subjects. Thus, structural alterations that are associated with negative or disorganised schizotypal traits may have been less prominent in this schizotypy sample.

Conclusions

The results obtained from the VBM analysis were small and not significant when corrected for multiple comparisons. It is not surprising that high schizotypes do not evince significant volume decreases to the same magnitude as patients with schizophrenia, or SPD and to those who are at enhanced risk for the disorder as these are healthy volunteers. Nonetheless, the results demonstrate small volume alterations associated with schizotypal trait expression and suggest that the right hippocampus and bilateral medial frontal gyrus may be particularly vulnerable to structural abnormalities along the psychosis spectrum.

Several regions were identified as increased in volume in high schizotypy including the inferior frontal gyrus (BA47), medial frontal gyrus (BA10) and superior temporal gyrus (BA20 and BA22). However again these results were not significant corrected for multiple comparisons.

The pattern of volumetric decreases and increases in individuals high in schizotypal traits likely reflects a complex pattern of vulnerability to psychosis and compensatory, protective factors. This is in line with Siever & Davis's model of schizotypal personality (Siever & Davis, 2004) which suggests structural abnormalities of the medial temporal lobes with relative sparing of the prefrontal cortex and evidence of compensatory regions of volume increase. Further, it extends this model to include healthy volunteers with schizotypal trait expression and supports the idea that the medial temporal lobe may be particularly vulnerable to structural abnormalities along the psychosis spectrum.

Chapter 7: Functional Imaging Results – Arena Task

In this chapter I will present results from the Arena Task, a human analogue of the Morris Water Maze (MWM) developed by Robin Morris and David Parslow in 2004 (Parslow et al, 2004). I have briefly outlined this task in the methods section (Chapter 5) and will present it here in more depth.

7.1   Introduction

As discussed in Chapter 4 the Morris Water Maze (R. Morris, 1984) has been extensively used in the animal literature as a test of spatial navigation, learning and memory (D'Hooge and De Deyn, 2001). The task requires subjects to navigate to a hidden platform in a pool of opaque water. Subjects use distal contextual cues to map platform locations and need to flexibly retrieve and update these maps enabling successful navigation regardless of start position within the pool. Hence it is an excellent paradigm for assessing allocentric spatial learning and memory.

Several human analogues of the MWM has been developed recently (reviewed in Chapter 4) including the one chosen for this thesis, the Arena Task (Parslow et al, 2004). The Arena Task has been established as a measure of egocentric and allocentric spatial memory in healthy volunteers (Parslow et al, 2004). It has well established neural correlates including activation of the medial temporal lobes, frontal and parietal cortices, occipital lobe and basal ganglia (Antonova, et al., 2009). The task related activations have been replicated twice, with consistent posterior hippocampal activation. In comparisons between allocentric and egocentric conditions, the hippocampus and parahippocampal regions are reported to be active during allocentric, but not egocentric, spatial learning and memory using this task (Parslow et al, 2004). The

hippocampus and parahippocampal regions have been shown to be active during encoding (Parslow et al, 2004) and during encoding and retrieval (Antonova, et al., 2009) when compared to rest during this task. In a study investigating hippocampal functioning in young and older adults, this region was found to only be actively recruited by the young subjects.

This is the first study to investigate allocentric spatial learning and memory in schizotypy. An MWM analogue, the Arena, was chosen on the basis that it provides a robust measure of neuronal activity in regions putatively involved in psychosis and that, based on prior literature, warrant investigation in schizotypal personality. Additionally, the Arena Task is designed to separate the encoding (learning) and retrieval (memory) processes allowing different aspects of spatial memory to be explored. Little is known about these separable components of memory and their neural correlates in schizotypal personality. Furthermore spatial cognition using virtual environments has not been investigated in schizotypy and only one study to date has investigated allocentric spatial memory in schizophrenia using functional neuroimaging (Folley et al, 2010) (reviewed in Chapter 4).

7.2 Specific Hypothesis

Specific hypotheses explored using this task was as follows:

1.   Based on previous studies of allocentric spatial learning and memory in schizophrenia individuals high in schizotypal traits will perform worse of this task compared to control subjects.

2.   The control group will demonstrate a pattern of activation in line with previous studies of spatial learning and memory using the Arena Task including activation of the hippocampus and parahippocampal gyrus, parietal lobes, prefrontal cortex, cingulate gyrus, occipital lobes, thalamus and basal ganglia.

3.   As performance on the allocentric spatial memory component of the Arena Task is thought to rely on activation of the hippocampus and parahippocampal gyrus, BOLD activation

in these regions will be negatively correlated with performance (as BOLD activation increases, the difference between the estimated and true pole location will be reduced).

4.   High schizotypy will be associated with different patterns of brain activation specifically reduced BOLD signal in the hippocampus and parahippocampal gyrus.

5.   In line with Siever & Davis (2004) model of schizotypal personality disorder (see Chapter 3), high schizotypy will be associated with increased activation of prefrontal compared to control subjects.

7.3   Methods

7.3.1   Subjects

Forty two subjects completed the studies in this thesis but only thirty-nine subjects were included in the final analysis of this task. One subject was excluded due to poor coverage of the temporal lobes in the functional images. One subject was excluded due to excessive movement during performance of the task (movement cut-off defined as > 3mm translation and rotation). A third subject was identified as an extreme outlier on behavioural performance of the task and excluded from the overall analysis. In total, <u>18 control subjects</u> and <u>21 high</u> schizotypes were included in the analysis.

Screening procedures, inclusion and exclusion criteria, schizotypy group allocation and selection of subjects is as discussed earlier in Chapter 5. Image acquisition is reported in the Chapter 5, section 5.4.2.

7.3.2   Task Design

<u>Programming</u>

The task was programmed in virtual reality (VR) format by Third Dimension (Dorset, United Kingdom) using Superscape VR software (Superscape, Hampshire, UK). Images were displayed

via a projector onto a Perspex screen at the foot of the scanning table. For navigating around the VR environment, the participant used a Magnetic Resonance (MR) compatible analogue joystick specifically designed for the experiment.

The task employs a VR circular arena, with a circular wall providing a peripheral boundary for the overall workspace. Abstract patterns are rendered onto the walls of the arena, faded into one another to produced one large seamless pattern. The floor of the arena has markers randomly distributed to enhance perception of motion and perspective during navigation. The patterns were constructed of semi-random mixes of three primary colours and were considered abstract in the sense that they did not resemble everyday objects. This encourages subjects to use spatial rather than object memory. Blending of the patterns together prevented borders being used as cues.

The subject moves around the arena using an MR compatible joystick. Forward movement is initiated by pushing the joystick forward to accelerate, the opposite achieved by pulling backwards on the joystick. Tilting sideways is used to change trajectory either to the left or right. The range of motion and the relative height of the walls assist in the feeling of immersion in the arena.

<u>Start relocation and pole positions</u>

In order to programme the position of the subject start positions, relocation positions and the pole positions two hidden 'inner' circles were used to accommodate these. The circles were termed hidden because they literally could not be seen and were simply a geometric device for specifying the various locations. Allocations of starting and relocation positions were restricted to circle A. The arena and circles A and B were divided into 18 radials, each 20° apart. Intersections of the circles and radials defined the possible set of starting, relocation and pole

positions.
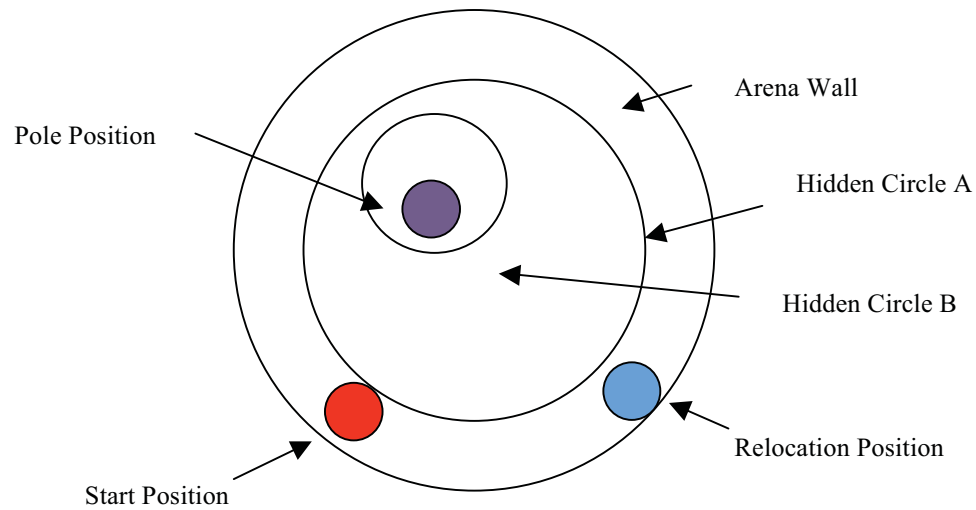
Figure 9 Illustration of the design of an allocentric spatial memory trial

7.3.3   Procedure
For each trial there are six epochs as follows:

1. Encoding: Subjects start from the periphery of the arena with the pole visible in their field of view. Subjects navigate towards the pole, using the patterns on the wall to remember the pole location. The pole has a 'puck' at the base to guide their final movement, such that they 'bump' into the puck and stop immediately in front of the pole. At this point the screen freezes for the remainder of a 30 second epoch. Movement within the arena is paced, such that all subjects move at the same speed.

2. Rest: The monitor is blank for 30 seconds.

3. Retrieval: Subjects are returned to the arena in a different start location in the periphery with the pole removed. They move to where they estimate the pole location was during the encoding

condition using the arena wall patterning to guide them.   When they arrive at this judged location they have to stop moving until the end of the epoch.   Again, movement is paced so that all subjects travel through the arena at the same speed.

4. Rest: The monitor is blank throughout for 15 seconds.

5. Visual Control: An amalgam of the patterns used on the walls of the arena is presented for 30 seconds. Subjects are asked just to fixate on the screen.

6. Rest: The monitor is blank for 15 seconds.
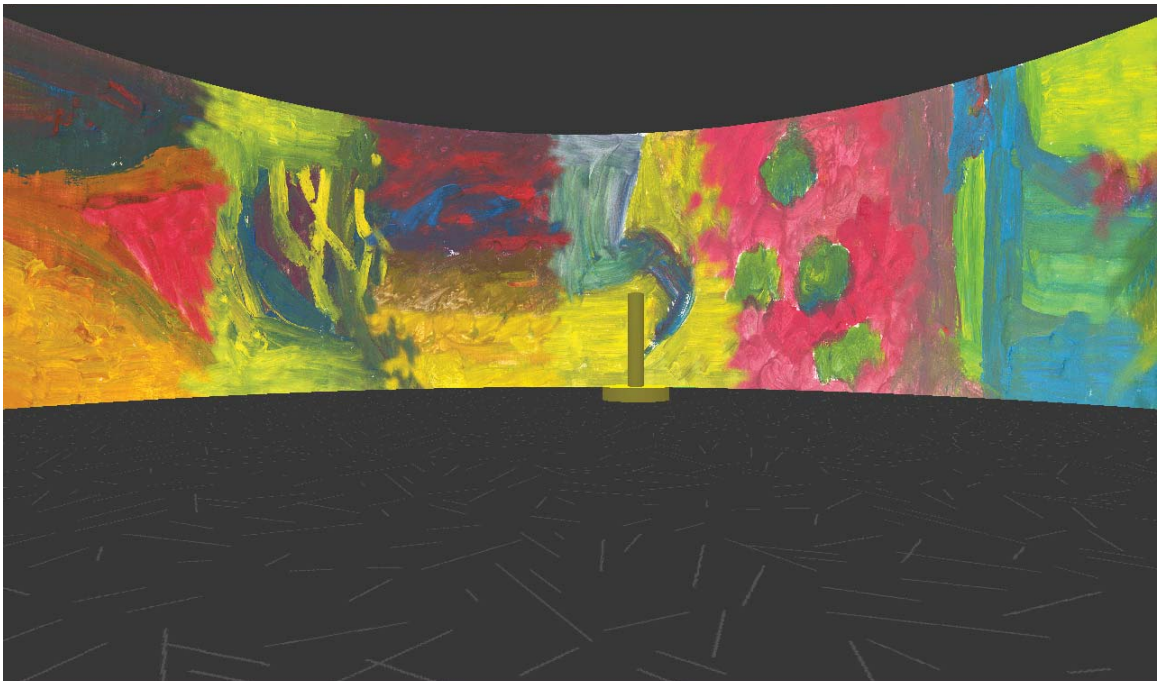
Figure 10 Encoding condition: Start position with pole visible in periphery
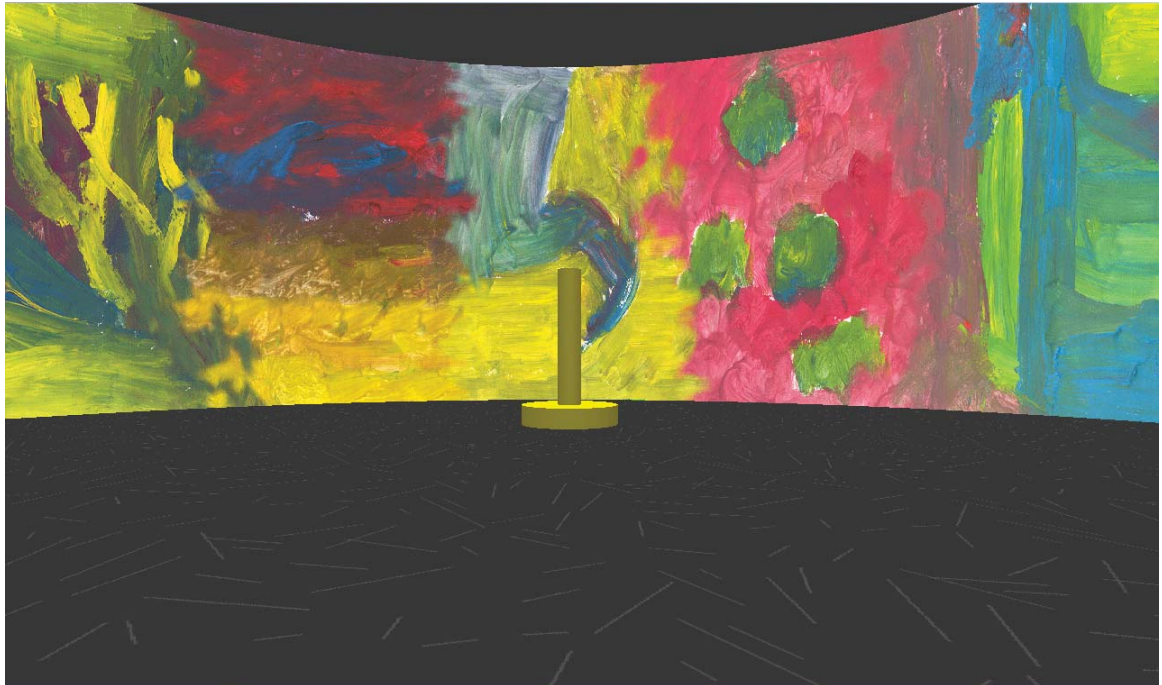
Figure 11 Encoding condition: Subject on trajectory towards pole
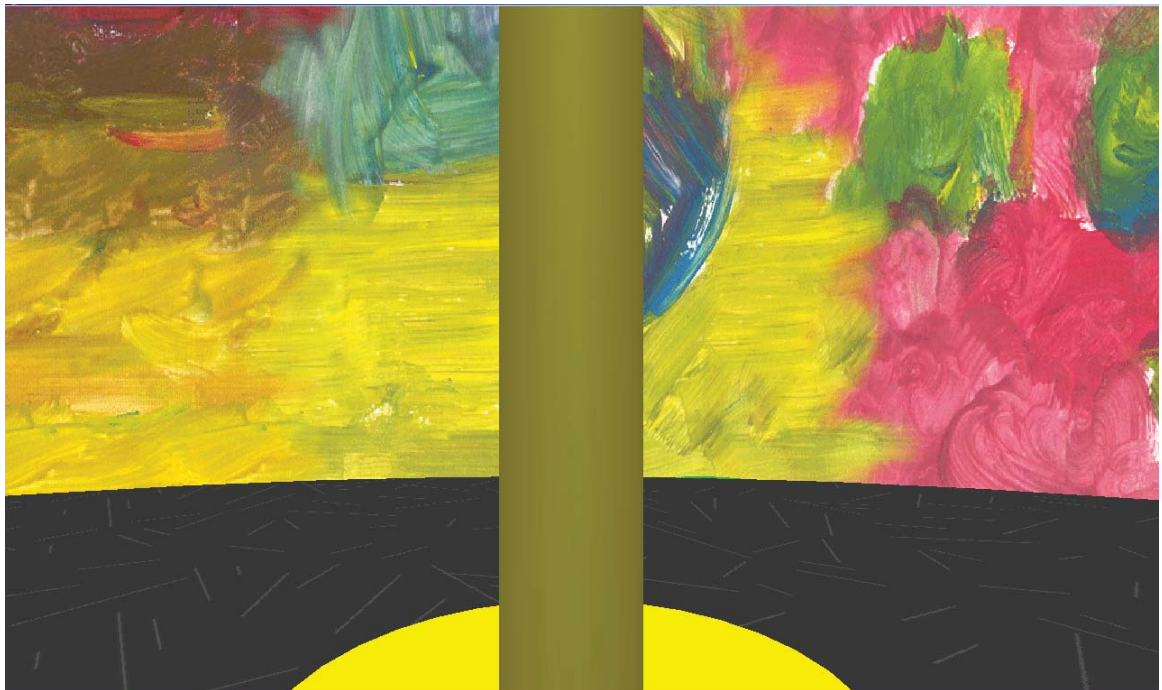
Figure 12 Encoding condition: Subject has successfully located the pole
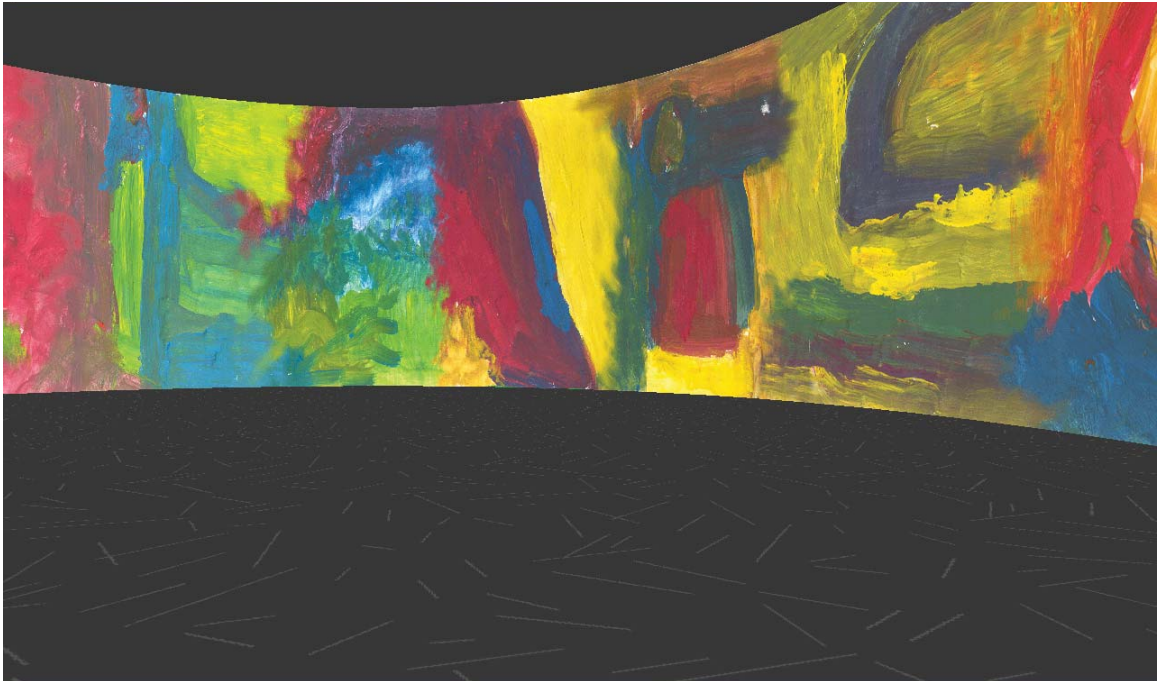
Figure 13 Retrieval condition: Start position on re-entering the Arena
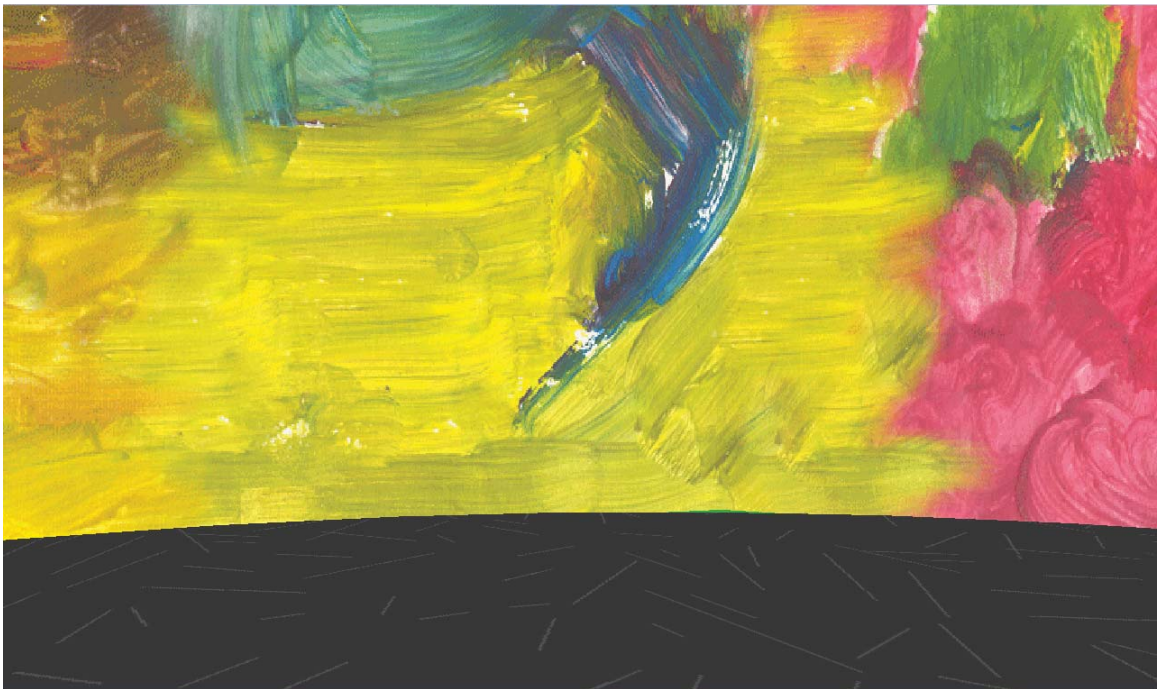
Figure 14 Retrieval condition: Subject's estimate of the previous pole location
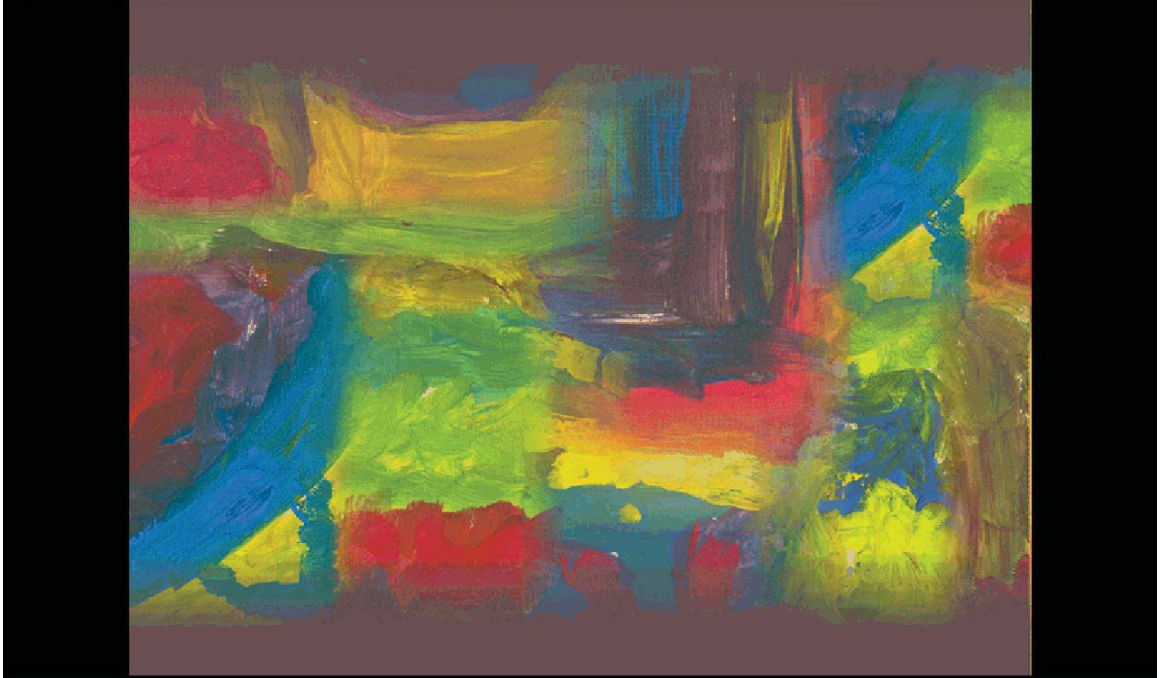
Figure 15 Example of the visual control condition

The task requires allocentric spatial memory because when retrieving the pole location from a different starting position no single pattern can indicate position but rather the combined vectors associated with different patterns around the arena are required. Hence, subjects cannot navigate successfully to the pole location using a simple egocentric or cue guidance strategy (Parslow et al, 2004).

The Arena Task differs from other human analogues and from the original MWM as the target is immediately visible and thus it does not require an initial search component which complicates the interpretation of other human analogues.

7.3.4   Data Analysis

7.3.4.1 Behavioural Data

The computer recorded the finish location at the retrieval phase. Task accuracy was defined as linear and angular deviation. Mean linear deviation refers to the distance between the true pole location and estimated pole location. Mean angular deviation refers to the difference in angle between the true and estimated pole location (see Figure 16).

Independent t-tests were used to assess differences between the groups on linear and angular deviation. Angular displacement was measured because the known propensity to systematic directional bias that can occur in spatial navigation tasks. For example, in path integration, there is a right sided bias in terms of return to the target location which has been observed across species (Healy, 1998), and this is seen in humans, although more variable (e.g. Loomis et al. 1993). Although there was no reason to predict a directional bias specifically on the Arena task, an angular displacement measure was included to determine whether inaccurate location was sporadic or due to systematic directional error.

Location of Pole   Possible Response

Linear
Deviation

Angular Deviation

Target
Distance

Starting Position   Subject Relocation
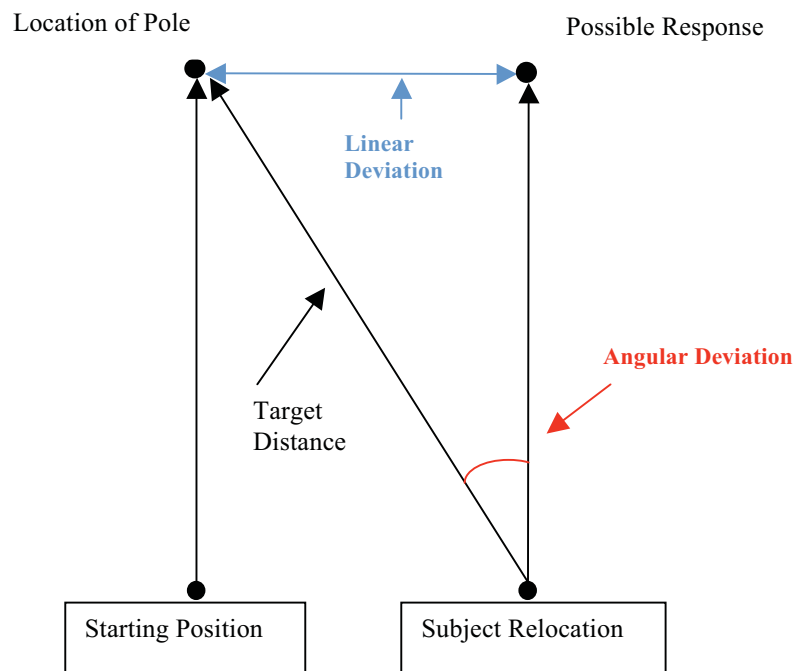
7.3.4.2 Functional Imaging Data

<u>Preprocessing of the functional images</u>

Preprocessing steps were the same for all tasks and are presented in Chapter 5 (section 5.5.3.1).

<u>Model Specification</u>

A random effects analysis was applied to investigate the main effect of the task and differences in brain activations between controls and high schizotypes. This involved a 1st level fixed effect (single subject) model of task contrasts and parameter estimates taken to a 2nd level group analysis.

<u>First Level Analysis</u>

For each subject, a model encoding six conditions (encoding, rest, retrieval, rest, control and rest) was created. All variables were modelled by convolving the resulting boxcars with the hemodynamic response function. No parametric modulation, temporal derivatives or interactions between trials were required. Six rotational and translational movement parameters generated by the realignment procedure for each subject were entered as regressors (nuisance covariates). Following estimation of the statistical model, contrast images were generated for each task comparison and for each subject. Whilst there are numerous potential contrasts within this paradigm design I have focused on encoding > rest and retrieval > rest to address the hypotheses set out at the beginning of this chapter.

<u>Second Level Analysis</u>

Contrast images were analysed using a one sample t-test to show the main effect of task in each group and a full factorial ANOVA model with 2 factors (group and condition) and two levels per

factor (group: control and high schizotypy; condition: encoding and retrieval) was applied to test for differential responses to these task conditions in these two groups.

fMRI statistical inference

Differences between groups and task conditions were assessed at the voxel level and significance defined as $p < 0.05$ FWE corrected. Following this a less conservative threshold of $p < 0.001$ uncorrected was also investigated. These results are reported for information but uncorrected fMRI maps are at risk of containing a high proportion of false positives. Uncorrected results will be presented but not discussed. Coordinates were converted from MNI space to Talairach space using the Brett et al (2002) method. Thus, all coordinates reported in this thesis are converted into Talairach space. Images are presented in neurological orientation; left side of the brain is presented on the left side of the image.

Small Volume Correction (SVC)

Based on previous studies of allocentric spatial learning and memory in humans and animals *a priori* regions of interest were both the left and right hippocampus and left and right parahippocampal gyrus. Based on previous studies of schizophrenia and schizotypal personality additional *a priori* regions of interest were the prefrontal cortex and anterior cingulate cortex. For *a priori* defined ROIs, small volume corrections were applied anatomically derived from the WFU pickatlas (Maldjian et al, 2003). Full details are given in Chapter 5 (section 5.5.3.5).

Performance correlations

To specifically evaluate the role of the hippocampal-parahippocampal regions in performance, BOLD signal beta estimates were extracted using the MarsBar Toolbox in SPM5 (Brett, Acton, Valabregue & Poline, 2002). Region of interest coordinates were derived from a previous paper

by Antonova et al (2009) and included the left and right hippocampus (-36 -52 0 and 25 -30 -3). Areas that emerge as significantly related to performance will be plotted graphically.

7.4   Results

7.4.1   Demographics

Gender and ethnicity were evaluated using chi-square. Age had a non-normal distribution (Control Group: W = .859, df = 18, p = 0.012; High Group: W = .873, df = 21, p = 0.011). Transformation did not significantly improve the distribution therefore the non-parametric Mann Whitney test was performed. The variable education had three missing values therefore a series mean calculation was performed to replace these values.   The new education variable was normally distributed (Control group: W = .943, df = 18, p = .325; High group: W = .918, df = 21, p = .77). IQ (NART-R IQ score) was also normally distributed (Control group: W = .958, df 18, p = .558; High group: .959, df = 21, p = .492). Education and IQ were investigated using independent t-tests. Groups did not differ on age, gender, IQ, years in education or ethnicity (data presented in Table 9)

Table 9 Demographics in the control and high schizotypy group (data is presented as means [SD])

	Control Group	High Schizotypy	Statistical Test
Age	23.44	23.57	U = 184.00, p =.887
Range	19-33	18-37	
Gender (Ratio M:F)	6:12	10:11	χ^2 = .818, df =1, p =.283
Ethnicity (N) White Black Asian	15 0 3	15 3 3	χ^2 = 2.78, df = 2, p=.379
Education	15.50 (1.48)	15.55 (1.75)	t = -.411, df = 37, p=.684
NART-R IQ	115.72 (4.28)	116.50 (4.07)	t = -.576, df = 37, p =.568

7.4.2   Schizotypy Scores

Schizotypy scores were determined by total score on the SPQ. Allocation to the control group included scores 21-36 and allocation to the high schizotypy group included scores of 43 and

above. Total SPQ score was not normally distributed (Control group: W = .353, df = 18, p = 0.009; High group: W = 19.80, df = 21, p = 0.008). Therefore a non-parametric Mann Whitney test was performed. The SPQ subscale *cognitive perceptual* was normally distributed (Control group: W = .915, df = 18, p = .105; High group: W = .973, df = 21, p = .792) as was *interpersonal* (Control group: W = .972, df = 18, p = .830) and *disorganised* (Control group = .978, df = 18, p = .928; High group = .910, df = 21, p = .056) therefore independent t-tests were used. Schizotypal personality scores in each group are presented in Table 10.

Table 10 Total SPQ scores and scores for each of the schizotypal personality scales in each group

	Control Group	High Schizotypy	Statistical Test
SPQ Total	26.44 (5.18)	48.14 (4.90)	U = 378.00, p <0.001
Cognitive Perceptual	9.22 (5.02)	19.80 (5.15)	t =-6.47, df =37, p < 0.001
Interpersonal	11.5 (4.93)	21.76 (5.68)	t = -6.13, df = 37,p <0.001
Disorganised	8.4 (3.27)	12.71 (2.90)	t = -4.53, df = 37,p< 0.001

Data represent means (SDs) unless otherwise stated.

7.4.3 Behavioural Results

Performance measures were linear and angular deviation between the true and estimated pole location. See Table 11 for means and standard deviations and section Figure 16 for illustration of these measures.

Linear Deviation

Linear deviation was normally distributed (control group: W = .973, df 18, p = .849; high schizotypy group: W = .957, df 21, p = .457). Visual inspection of box plots produced by SPSS did not identify any outliers. There were no significant differences between the control and high schizotypy group on estimated distance from the true location of the pole (t = .715, df = 37, p = .479).

Angular Deviation

Angular Deviation was not normally distributed (Average group = W .793, df 18, p =.001; High group: W = .891, df 21, p = 0.024). Transformation of this variable did not significantly improve the distribution. A Mann Whitney was therefore used to investigate group differences on this measure revealing no significant differences between groups on angular deviation (U = 205.00, p = .652).

Table 11 Behavioural performance on the Arena Task

	Control Group	High Schizotypy
Linear Deviation	7.35 (3.02	6.76 (2.12)
Angular Deviation	.32 (4.95)	1.70 (5.52)

Data represents means (SD).

7.4.4   Functional Imaging Results

7.4.4.1 Group Maps

7.4.4.1.1   Control Group

Encoding

Control subjects activated areas the middle occipital gyrus bilaterally, the right superior occipital gyrus, bilateral fusiform gyrus, left inferior parietal gyrus, left precuneus and right cerebellum during the encoding condition compared to rest, correcting for multiple comparisons. Significant activations are reported in Table 12 and SPM maps presented in Figure 17.

Table 12 Significant activations during the encoding condition compared to rest in the control group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinate x, y, z
Middle Occipital Gyrus (L)	18	431	5.82	-28 -84 -3
Middle Occipital Gyrus (R)	18	727	5.69	28 -88 -6
Superior Occipital Gyrus (R)	19	167	5.49	32 -74 26
Fusiform Gyrus (L)	19	72	5.33	-28 -66 -7
Fusiform Gyrus (R)	20	30	5.07	30 -36 -18
Fusiform Gyrus (L)	37	5	4.87	-30 -47 -13
Inferior Parietal Lobe (L)	40	40	4.97	-32 -50 56
Precuneus (L)	7	14	4.84	-24 -72 31
Cerebellum (R)		9	4.89	28 -47 -13
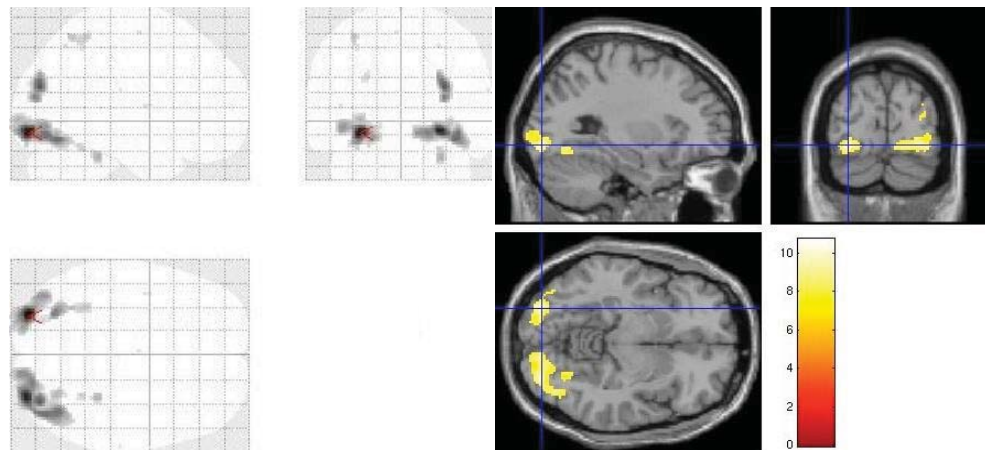
Figure 17 Significant activations during the encoding condition of the Arena Task compared to rest in the control group

Lowering the threshold to p < 0.001 uncorrected revealed additional activations in the left occipital gyrus, right inferior frontal gyrus, right paracentral lobule, right superior temporal gyrus, right parahippocampal gyrus, right middle frontal gyrus and left insula. Uncorrected level activations are reported in Table 13 and SPM maps presented in Figure 18.

Table 13 Uncorrected activations during the encoding condition of the Arena Task compared to rest in the control group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinate x, y, z
Inferior Frontal Gyrus (R)	BA46	33	3.64	48 38 12
Paracentral Lobule (R)	BA5	35	3.49	16 -30 46
Superior Temporal Gyrus (R)	BA22	1231	4.52	48 12 -4
Superior Temporal Gyrus (R)	BA41	92	3.78	-44 -30 16
Postcentral Gyrus (R)	BA40	542	4.76	64 -20 22
Middle Frontal Gyrus (R)	BA8	17	3.30	40 38 38
Parahippocampal Gyrus (R)	BA28	134	3.66	22 -18 -6
Insula (L)	BA13	2210	4.78	-42 0 10

All activations are reported at the p < 0.001 uncorrected level. L = left hemisphere, R = right hemisphere.
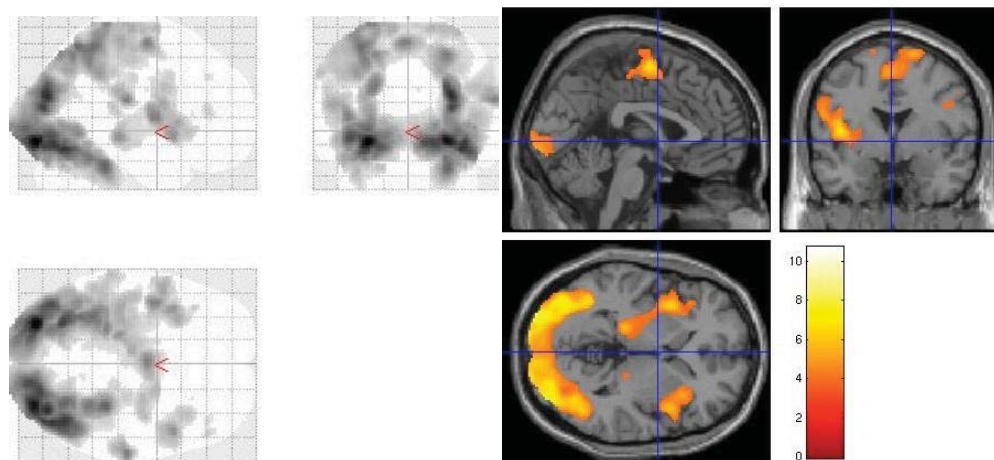
Figure 18 Uncorrected activations during the encoding condition of the Arena Task compared to rest in the control group

To ensure sufficient activation of the hippocampal-parahippocampal regions during spatial encoding a final spatially constrained analysis was performed using WFU pickatlas (details in methods section). This revealed bilateral activation in the hippocampal-parahippocampal region. Small volume corrected regions of interest are reported in Table 14 and SPM maps presented in Figure 19.

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Table 14 Hippocampal activations during memory encoding compared to rest in the control group (small volume corrected)

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinate x, y, z
Hippocampus (L)		40	4.34	-20 -28 -6
Hippocampus (R)		27	3.66	24 -22 -10

All activations shown at p < 0.05 small volume corrected. L = left hemisphere, R = right hemisphere.
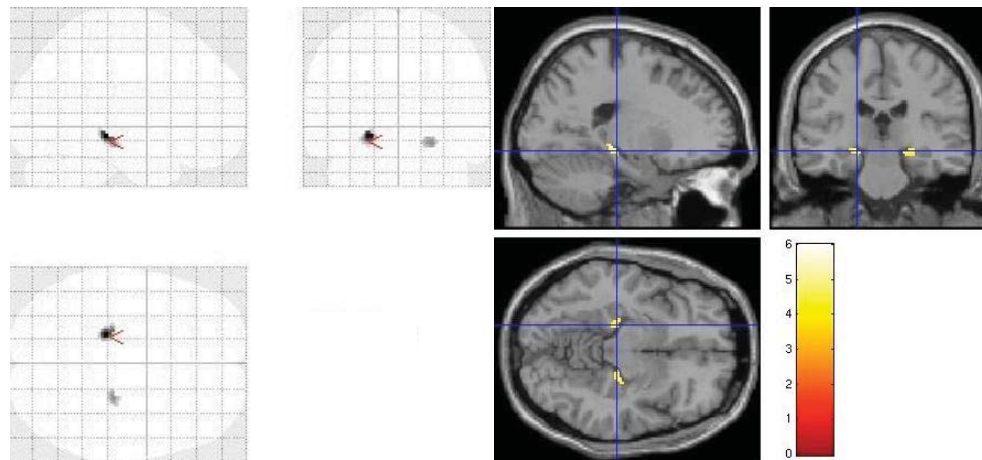
Figure 19 Hippocampal activation during the encoding condition compared to rest in the control group (small volume corrected)

Retrieval

Activation was observed in bilateral middle occipital gyrus, right fusiform gyrus, left posterior parietal lobe, left precuneus, left postcentral gyrus, and left cingulate gyrus in the control group when contrasting retrieval to the rest condition, corrected for multiple comparisons.

Table 15 Significant activations during the memory retrieval condition in the Arena Task compared to rest in the control group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinate x, y, z
Middle Occipital Gyrus (R)	18	582	5.50	28 -85 1
Middle Occipital Gyrus (L)	18	319	5.37	-28 -93 6
Middle Occipital Gyrus (R)	19	40	5.11	32 -76 28
Fusiform Gyrus (R)	19	11	4.86	34 -66 -3
Posterior Parietal Lobe (L)	40	44	5.19	-40 -37 41
Precuneus (L)	7	89	5.10	-20 -65 29
Postcentral Gyrus (L)	40	153	5.02	-34 -36 57
Precuneus (L)	7	14	5.00	-18 -65 51
Cingulate Gyrus (L)	24	64	5.09	-18 0 48

All activations are reported $p < 0.05$ FWE corrected for multiple comparisons. L = left hemisphere, R = right hemisphere.
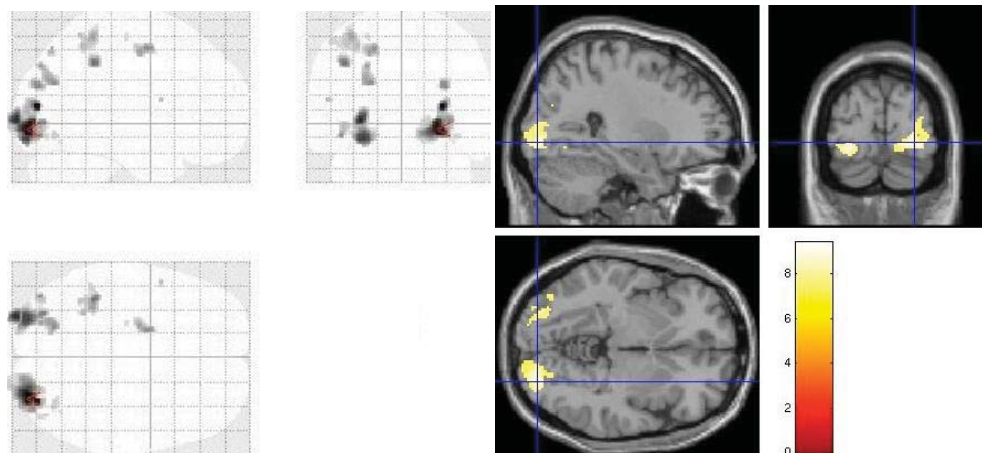
Figure 20 Significant activations during the memory retrieval condition of the Arena Task compared to rest in the control group

Lowering the threshold to $p < 0.001$ uncorrected revealed additional activation in right middle occipital gyrus, left inferior frontal gyrus, right inferior frontal gyrus, middle frontal gyrus, left fusiform gyrus, left superior temporal gyrus, inferior parietal lobule, bilateral striatum (left – global pallidus; right – putamen) and left cerebellum.

Table 16 Uncorrected activations during the memory retrieval condition of the Arena Task compared to rest in the control group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinate x, y, z
Inferior Frontal Gyrus (R)	9	388	4.20	50 9 27
Middle Frontal Gyrus (R)	10	146	3.89	40 36 24
Fusiform Gyrus (L)	9	8	3.27	-38 27 26
Superior Frontal Gyrus (L)	37	32	3.45	-44 -43-11
Inferior Frontal Gyrus (L)	6	6	3.30	-16 5 66
Inferior Parietal Lobe (R)	40	6	3.32	44 -42 57
Basal Ganglia (L)	Globus Pallidus	114	4.10	-18 -12 -6
Basal Ganglia (R)	Putamen	139	3.67	22 23 -6
Cerebellum (L)		52	3.76	-36 -32 -26

All activations are reported at the $p < 0.001$ uncorrected level. L = left hemisphere, R = right hemisphere.

Lowering the threshold to $p < 0.001$ uncorrected revealed activation in right middle occipital gyrus, left inferior frontal gyrus, right inferior frontal gyrus, middle frontal gyrus, left fusiform gyrus, left superior temporal gyrus, inferior parietal lobule, bilateral striatum (left – global pallidus; right – putamen) and left cerebellum.   For the most part encoding and retrieval activated regions in the prefrontal cortex, parietal lobe, occipital gyrus and temporal regions. However, the parahippocampal gyrus was activated during encoding but not retrieval in the control group whereas the cingulate gyrus was activated during retrieval but not during encoding.

Small volume correction using WFU pickatlas did not demonstrate activation in the left or right hippocampus or left and right parahippocampal gyrus in control subjects when contrasting retrieval to the rest condition.

7.4.4.1.2   High Schizotypy

Encoding

Activation was observed in bilateral middle occipital gyrus, left precentral gyrus, right precentral gyrus, left superior frontal gyrus, right inferior frontal gyrus, left fusiform gyrus, bilateral cerebellum and right insula in the high group when contrasting encoding to the rest condition, corrected for multiple comparisons. See Table 17 for table of activations for the contrast encoding > rest and SPM maps are presented in Figure 21.

Table 17 Significant activations during the encoding condition of the Arena Task compared to rest in the high schizotypy group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinate x, y, z
Middle Occipital Gyrus (R)	18	2076	6.27	34 -90 4
Middle Occipital Gyrus (L)	18	783	5.94	-30 -94 6
Precentral Gyrus (L)	6	5167	6.29	-26 -14 62
Precentral Gyrus (R)	6	479	5.88	34 -10 48
Precentral Gyrus (R)	6	13	4.92	52 2 30
Superior Frontal Gyrus (L)	11	43	5.07	-30 50 -22
Inferior Frontal Gyrus (R)	46	31	4.92	44 42 6
Fusiform Gyrus (L)	37	57	5.30	-44 -62 -14
Cerebellum (R)		64	4.97	24 -42 -26
Cerebellum (L)		17	4.89	-36 -34 -36
Insula (R)	13	158	5.72	44 6 14

All activations are reported at p < 0.05 FWE corrected. L = left hemisphere, R = right hemisphere.
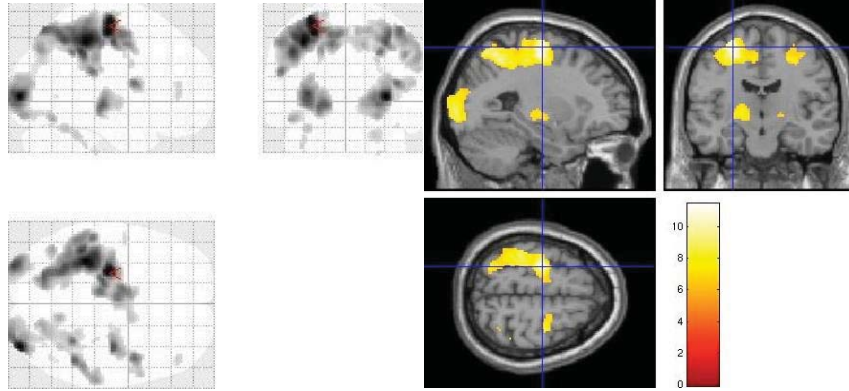
Figure 21 Significant activations during the encoding condition of the Arena Task compared to rest in the high schizotypy group

Lowering the threshold to p < 0.001 uncorrected revealed additional activation in the middle frontal gyrus in the high group when contrasting the encoding condition to rest the rest condition These results are presented in Table 18 and Figure 22.

Table 18 Uncorrected activations during the encoding condition of the Arena Task compared to rest in the high schizotypy group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinate x, y, z
Middle Frontal Gyrus (R)	BA9	258	4.57	-38 30 32

All activations reported at the p < 0.001 uncorrected level. L = left hemisphere, R = right hemisphere.
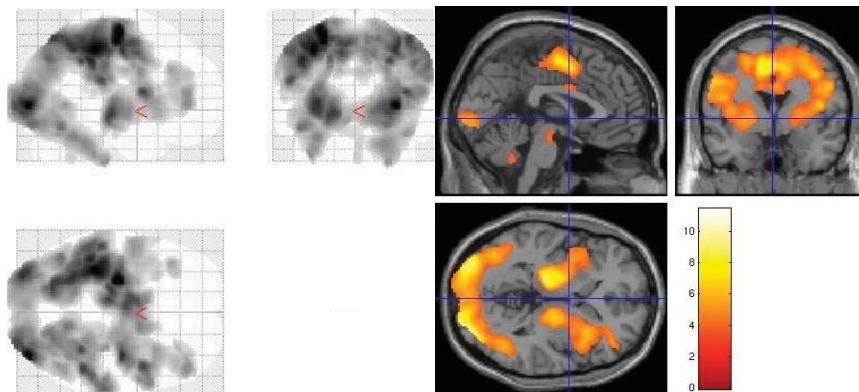
Figure 22 Uncorrected activations during the encoding condition of the Arena Task compared to rest in the high schizotypy group

Small volume correction using WFU pickatlas revealed bilateral activation of the hippocampus

in the encoding condition contrasted to rest in the high schizotypy group.

Table 19 Significant hippocampal activations during the encoding condition of the Arena Task compared to rest in the high schizotypy group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinate x, y, z
Hippocampus (L)		145	5.16	-22 -24 -8
Hippocampus (R)		108	4.08	24 -22 -10

Activations reported at p <0.05 small volume corrected. L = left hemisphere, R = right hemisphere.

Retrieval

Activation was observed in the left precentral gyrus, right middle occipital gyrus, right inferior

frontal gyrus, left insula, left fusiform gyrus and bilateral striatum (left – lateral globus pallidus;

right – medial globus pallidus) in high schizotypy group when contrasting retrieval to rest,

corrected for multiple comparisons. See Table 20 for significant activation during memory

retrieval contrasted to rest in the high schizotypy group. See Figure 23 for SPM maps displaying

this activation.

Table 20 Significant activations during the memory retrieval condition of the Arena Task compared to rest in the high schizotypy group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinate x, y, z
Precentral Gyrus (L)	6	2401	6.78	-28-13 52
Middle Occipital Gyrus (R)	19	1907	6.62	32 -92 14
Precentral Gyrus (L)	6	5106	7.01	-28 -16 56
Inferior Frontal Gyrus (R)	47	288	5.27	30 27 -3
Inferior Frontal Gyrus (R)	9	56	5.18	57 9 24
Middle Occipital Gyrus (R)	9	7	4.75	34 38 26
Insula (L)		120	5.42	-36 25 1
Fusiform Gyrus (L)	37	22	4.95	-42 -61 -9
Basal Ganglia (L)	Lateral Globus Pallidus	151	6.09	-16 -2 -2
Basal Ganglia (R)	Medial Globus Pallidus	146	5.36	12 -4 -5

All regions are reported at the $p < 0.05$ level corrected for multiple comparisons. L = left hemisphere, R = right hemisphere.

Lowering the threshold to $p < 0.001$ uncorrected revealed additional activation in the left middle occipital gyrus, right cerebellum and right parahippocampus. Encoding and retrieval activated regions in the occipital gyrus, prefrontal cortex, fusiform gyrus and cerebellum. However, retrieval was associated with activation of the striatum and parahippocampus which was not observed in the encoding condition (see Table 21 and Figure 24).
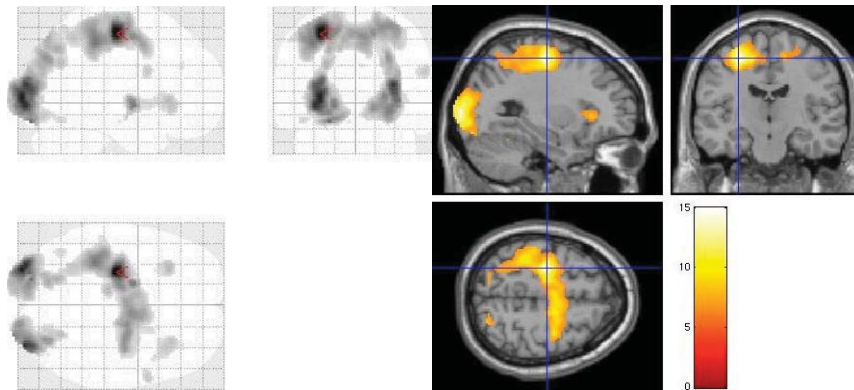
Figure 23 Significant activations during the retrieval condition of the Arena Task compared to rest in the high schizotypy group

Table 21 Uncorrected activations during the retrieval condition of the Arena Task compared to rest in the high schizotypy group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinate x, y, z
Middle Occipital Gyrus (L)	9	140	3.48	-42 31 30
Cerebellum (R)		57	3.75	0 -43 -38
Parahippocampal Gyrus (R)	28	28	3.46	22 -22 -12

All regions reported at a p < 0.001 uncorrected level. L = left hemisphere, R = right hemisphere
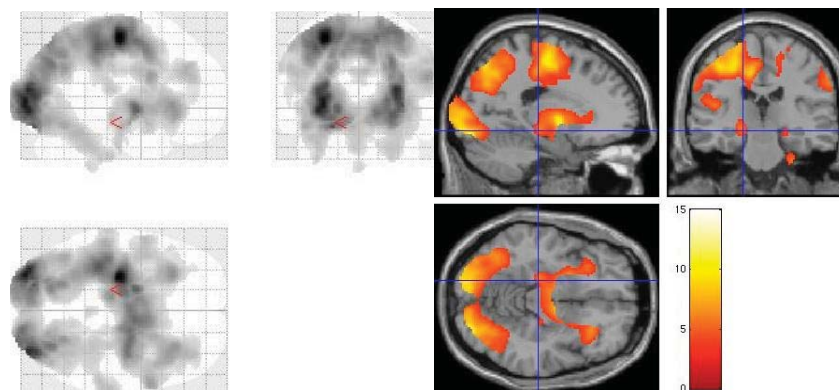
Figure 24 Uncorrected activations during the retrieval condition of the Arena Task compared to rest in the high schizotypy group

Small volume correction using the WFU pickatlas revealed bilateral activation of the hippocampus when contrasting memory retrieval to rest in the high schizotypy group.

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Additionally there was a peak of activation in the right hippocampus extending into the right amygdala (18 -8 -12). These medial temporal lobe activations are reported in Table 22 and SPM maps are presented in Figure 25.

Table 22 Medial temporal lobe activations during the retrieval condition compared to rest in the high schizotypy group (small volume corrected)

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinate x, y, z
Hippocampus (L)		62	4.27	-20 -24 -7
Parahippocampus (R)	BA28/Amygdala	9	3.75	18 -8 -12
Hippocampus (R)		9	3.41	22 -24 -9

All regions are reported at the p <0.05 level small volume corrected. L = left hemisphere, R = right hemisphere.
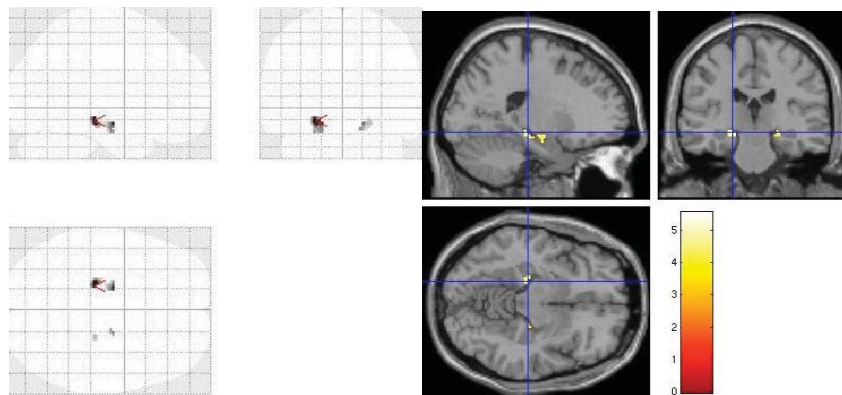
Figure 25 Medial temporal lobe activations during memory retrieval condition compared to rest in the high schizotypy group (small volume corrected)

7.4.4.2   Group Differences

Group differences in functional activation between and across conditions were investigated using a full factorial ANOVA (see methods of this chapter, section 7.3.4.2 for full details).

7.4.4.2.1   Effect of group

There was a main effect of group across memory conditions in temporal, frontal and limbic regions at an uncorrected level of p<0.001. Investigations into the positive effect of group

(controls > high schizotypy) revealed no areas of greater activation in control subjects compared to high schizotypes. The inverse contrast (high schizotypy > controls) revealed increased activation in temporal, frontal and limbic regions in high schizotypy compared to the control group at the p < 0.001 uncorrected level. No areas survived correction for multiple comparisons. Uncorrected level activations are reported in Table 23 and Figure 26.

Table 23 Main effect of group across task conditions (p < 0.001 uncorrected)

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x, y, z
Control Group > High Schizotypy Group				
None				
High Schizotypy Group > Control Group				
Middle Temporal Gyrus (R)	41	56	3.56	50 -36 13
Middle Frontal Gyrus (R)	6	60	3.56	22 -11 47
Cingulate Gyrus (R)	24	18	3.27	14 4 42

All activations are reported at the P < 0.001 uncorrected level. L = left hemisphere, R = right hemisphere.
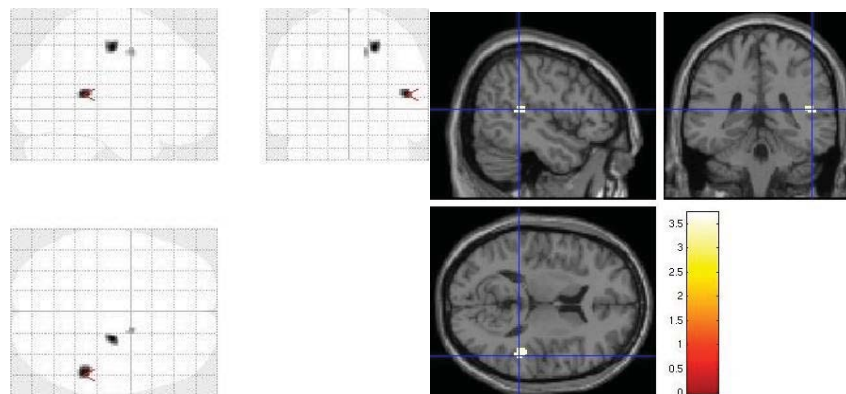
Figure 26 Main effect of group across task conditions (High Schizotypy > Controls)

7.4.4.2.2   Effect of condition

There was a main effect of condition across groups with encoding associated with greater activation in the parietal, frontal, occipital, temporal and striatal regions and retrieval associated with increased activation in frontal and striatal regions. See Table 24 and Figure 27.

Table 24 Main effect of condition across groups (p < 0.001 uncorrected)

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x, y ,z
Encoding > Retrieval				
Inferior Parietal Lobe (L)	40	431	4.11	-57 -35 29
Inferior Frontal Gyrus (R)	46	55	3.81	48 41 2
Precentral Gyrus (L)	6	9	3.31	-42 -14 34
Inferior Frontal Gyrus (L)	46	9	3.31	-48 31 6
Cuneus (L)	19	63	3.67	-4 -90 27
Middle Temporal Gyrus (L)	22	254	3.63	-53 -48 4
Superior Temporal Gyrus (R)	39	14	3.30	48 -54 20
Insula (L)	13	33	3.55	-30 -40 19
Retrieval > Encoding				
Precentral Gyrus (L)	BA6	938	4.95	-28 -13 52
Basal Ganglia (R)	Caudate	212	4.03	12 20 4
Basal Ganglia (L)	Putamen	80	3.78	-20 19 -3

All regions reported at the P < 0.001 uncorrected level. L = left hemisphere, R = right hemisphere.
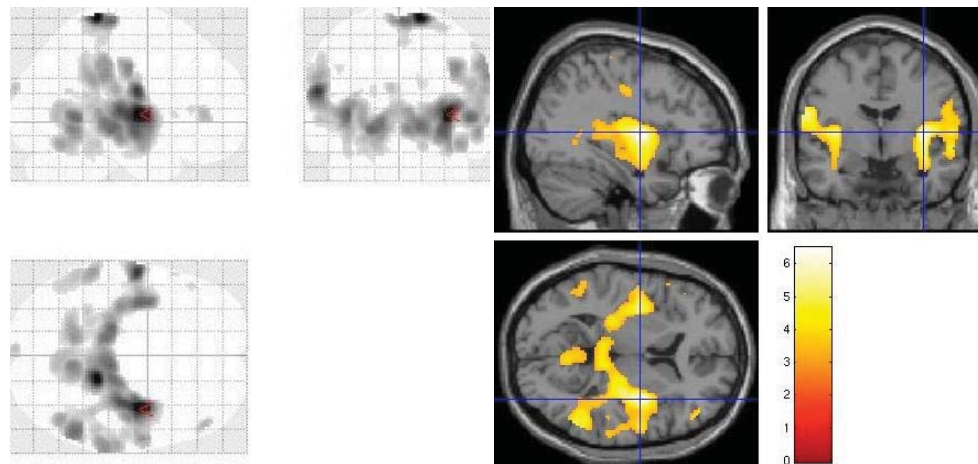
Figure 27 Main effect of condition across groups (Encoding > Retrieval)

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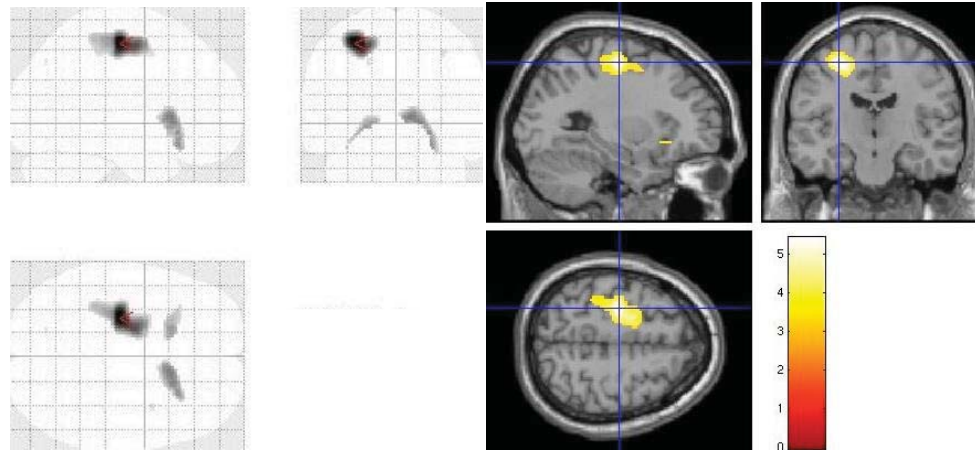
Figure 28 Main effect of condition across groups (Retrieval > Encoding)

7.4.4.2.3   Interaction between schizotypy group and task condition

An interaction between schizotypy group and condition was identified in the right hippocampus and left insula at a FWE corrected level of p < 0.05. See Table 25 and Figure 29 and 30. At an uncorrected level of p < 0.001 additional interactions were found in the left hippocampus, fusiform gyrus, medial temporal gyrus, dorsolateral prefrontal cortex, inferior frontal gyrus and anterior cingulate regions (see table 26). Significant interactions will be shown pictorially and accompanied by signal percent plots to demonstrate activation at each level of group and condition.

Table 25 Schizotypy x Condition interaction demonstrating significant interaction between group and condition in the right parahippocampal gyrus and left anterior insula (corrected for multiple comparisons)

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x,y,z
Hippocampus (R)		201	4.69	20 -13 -20
Insula (L)	13	396	4.60	-38 0 4

All activations are reported P < 0.05 FWE corrected. L = left hemisphere, R = right hemisphere.
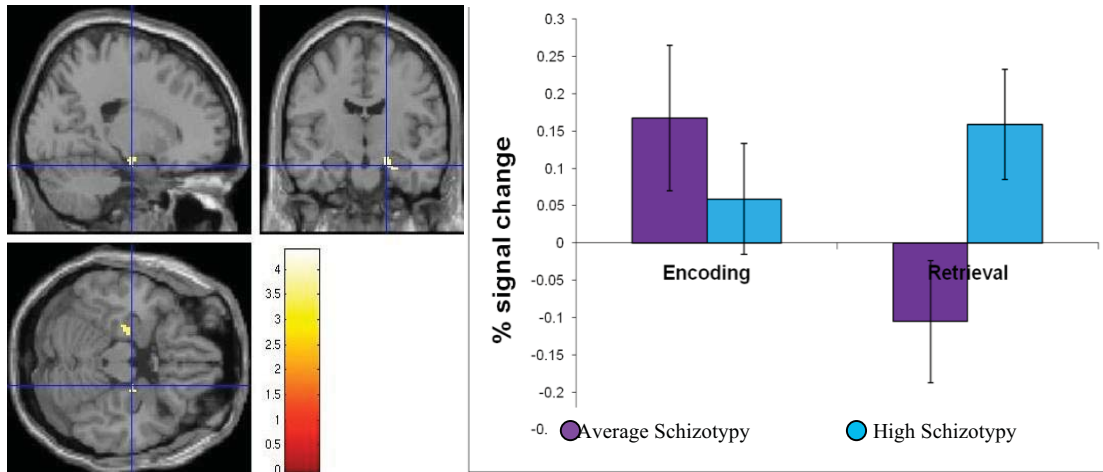
Figure 29 Schizotypy x task condition interaction in the right hippocampal region
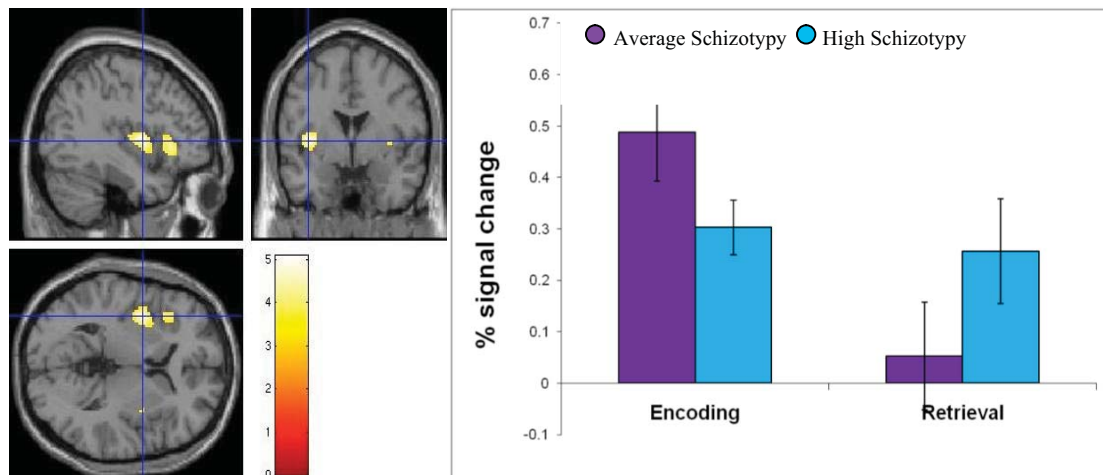
Figure 30 Schizotypy x task condition interaction in the left anterior insula

Table 26 Schizotypy x Condition interaction in inferior and middle frontal gyrus, left parahippocampal gyrus, temporal gyrus and anterior cingulate cortex (p < 0.001 uncorrected)

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x,y, z
Inferior Frontal Gyrus (L)	47	202	4.20	-36 -25 1
Middle Frontal Gyrus (R)	46	7	3.33	53 28 21
Fusiform Gyrus (L)	37	39	3.79	-46 -60 -18
Parahippocampal Gyrus (L)	28	46	3.53	-22 -18 -16
Superior Temporal Gyrus (R)	22	50	3.50	50 -22 -9
Traverse Temporal Gyrus (R)	42	26	3.41	63 -9 10
Anterior Cingulate (R)	32	46	3.41	6 36 26
Cingulate Gyrus (L)	23	14	3.38	12 -24 29

<u>Regions of interest</u>

As defined in the methods chapter regions of interest are the hippocampus and parahippocampal gyrus, anterior cingulate cortex and dorsolateral prefrontal cortex. ROI analysis was applied to the interaction between schizotypy and task conditions and revealed significant interactions in the left and right hippocampus and right anterior cingulate gyrus. Beta estimates are extracted for the significant regions and plotted to illuminate the activation for each group and condition. See Table 27 for hippocampal parahippocampal activations and Figure 31 for images of left hippocampal-parahippocampal activation (the results for the right hippocampus are presented above).

Table 27 Interaction between schizotypy group and condition in the hippocampus (small volume corrected)

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x,y,z
Hippocampus		109	4.69	20 -13 -20
Hippocampus		37	3.53	-22 -18 -16

All regions reported $p < 0.05$ small volume corrected. L = left hemisphere, R = right hemisphere.
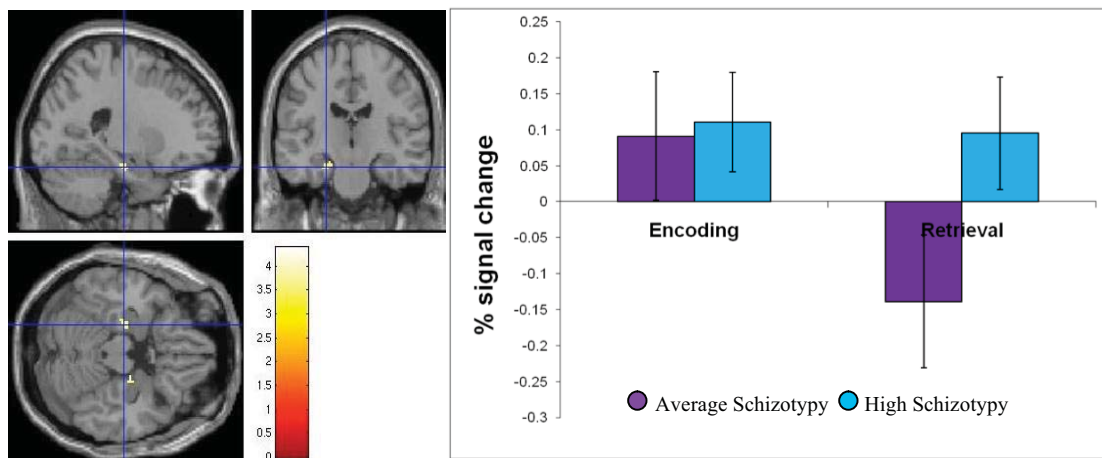
Figure 31 Schizotypy x task condition interaction in the left hippocampal region

Small volume correction revealed a significant interaction between schizotypy group and activation of the right anterior cingulate gyrus presented in Table 28 and Figure 32.

Table 28 Interaction between schizotypy group and task condition in the right anterior cingulate gyrus (small volume corrected)

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x,y,z
Anterior Cingulate (R)	32	33	3.41	6 36 22

Activation reported at the p < 0.05 level, small volume corrected. L = left hemisphere, R = right hemisphere.
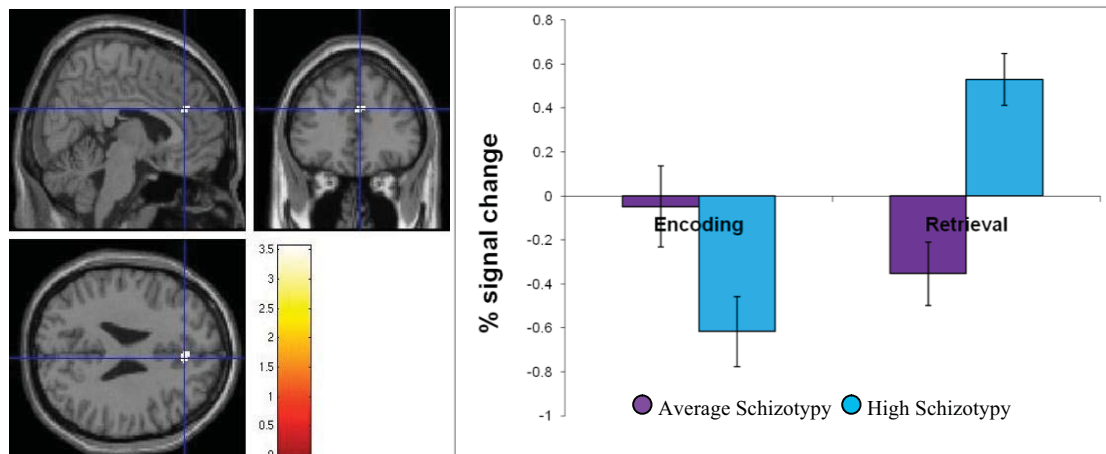
Figure 32 Schizotypy x task condition interaction in the right anterior cingulate gyrus (small volume corrected)

7.4.4.3 Performance Correlations

7.4.4.3.1 Relationship between hippocampal function and performance

As the left and right hippocampus are thought to be involved in allocentric spatial memory and performance on spatial navigation tasks (see Chapter 4) the relationship between activation of this region and performance was investigated. Previous studies have highlighted that the relationship between activation of the hippocampus and performance of these tasks is different in patients with schizophrenia compared to controls (Folley et al, 2010).

In order to investigate the relationship between hippocampal functioning and performance in average and high schizotypes, correlational analysis was performed using the beta estimates derived from the individual subject maps (SPM maps created at the single subject level) using independently derived ROIs. One tailed significance was selected for the correlation as it is hypothesised that there will be a relationship between hippocampal recruitment and performance on this task such that the greater the hippocampal recruitment the better the performance.

<u>Relationship between hippocampal recruitment during encoding and performance</u>

Right hippocampal BOLD signal was normally distributed (Control group: W = .977, df 18, p = 0.817; High Schizotypy: W = .941, df 21, p =.876) as was linear deviation (reported in section 7.4.5) so a parametric Pearson's correlation was performed. As the hypothesis is directional one-tailed significance is reported. <u>Right</u> hippocampal recruitment during <u>encoding</u> was associated with better performance (decreased distance between true and estimated pole location) during the retrieval condition in the control group (r = -.563, df 18, p = 0.007, one-tailed) but no relationship was observed between right hippocampal recruitment and performance in high schizotypes (r = .020, df = 21, p = .294). See Figure 33.

There was a trend level inverse relationship between linear deviation and left hippocampal recruitment at encoding in the control group (r = -.369, df = 18, p = 0.066, one tailed) but no relationship was observed between hippocampal recruitment and performance in high schizotypes (r = .126, df = 21, p = 0.294, one tailed). See Figure 34.
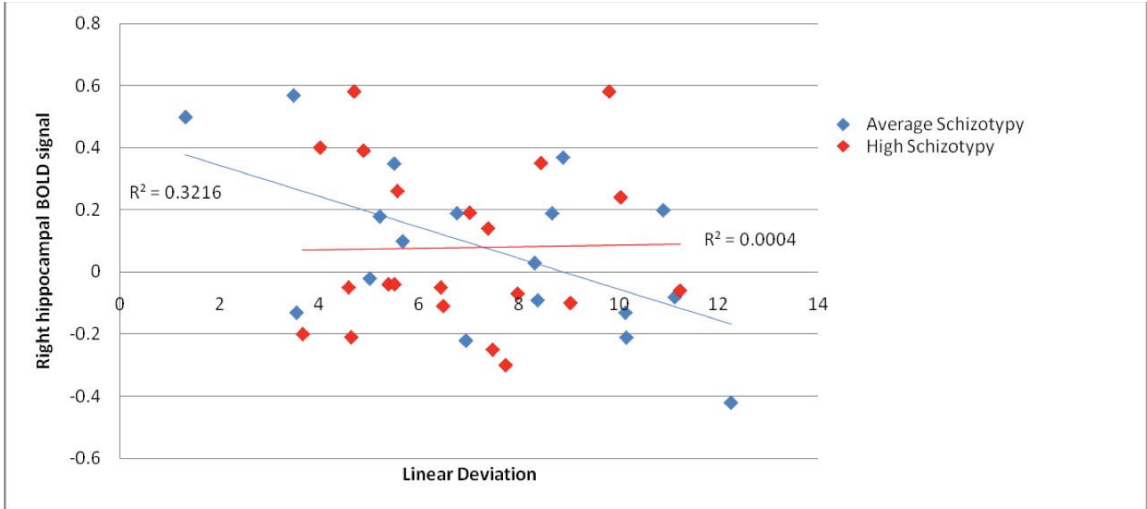
Figure 33 Relationship between right hippocampal recruitment at encoding and performance in the control group and high schizotypy group
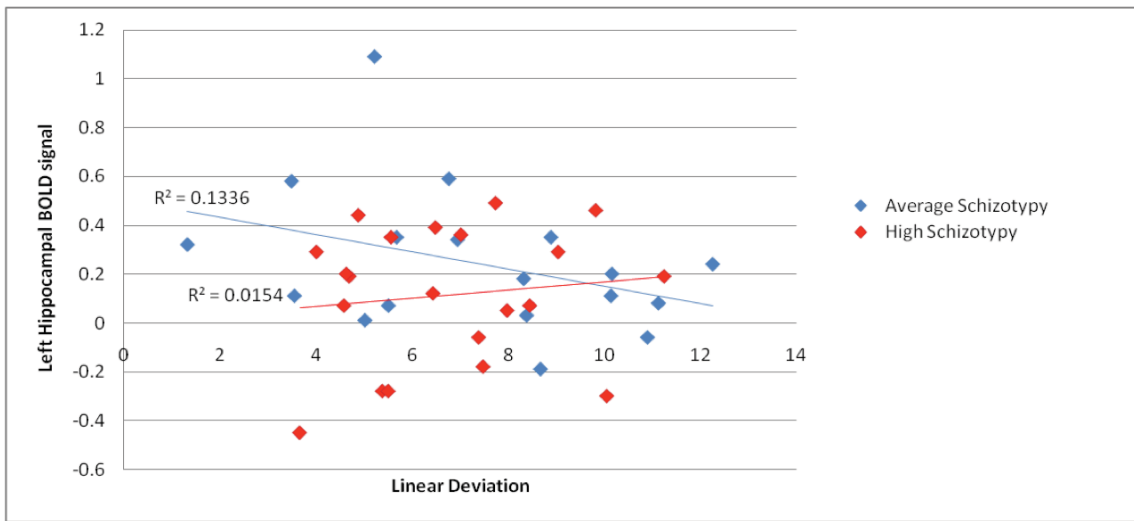
Figure 34 Relationship between left hippocampal signal and performance at encoding in control group and high schizotypy group

Relationship between hippocampal recruitment at retrieval and performance (linear deviation)

In contrast, there was a significant relationship between <u>right</u> hippocampal recruitment during memory <u>retrieval</u> and performance in the high schizotypy group (r = .398, df 21, p = 0.049, one tailed) but no relationship was present in control subjects (r = -.298, df = 18, p = .115).

The direction of the relationship in high schizotypy was positive indicating that increased right hippocampal recruitment at retrieval was associated with worse performance on the task (as hippocampal signal increased so did the deviation from the true pole location). See Figure 35. No relationship was observed between left hippocampal BOLD signal at retrieval and performance in either group.
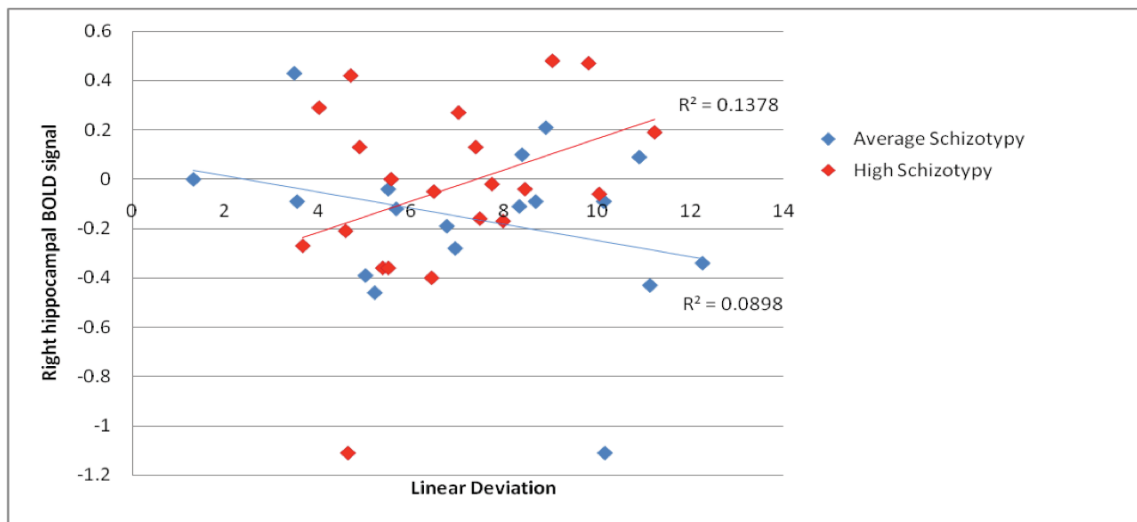
Figure 35 Relationship between hippocampal activation at retrieval and performance in the control group and high schizotypy group

7.5 Discussion

7.5.1 Summary of results

There were no differences in performance on this task between the control and high schizotypy groups on either linear or angular deviation. Both groups activated a neural network consistent

with allocentric spatial memory including activation of the hippocampal-parahippocampal regions bilaterally, parietal cortex and occipital lobes, striatal-thalamic and cingulate and frontal regions during encoding and retrieval. There was an effect of schizotypy group in the motor cortex (BA6), superior temporal gyrus (BA41) and cingulate gyrus (BA24) across encoding and retrieval conditions with these regions being hyperactive in high schizotypes compared to average controls. Further, there was a significant interaction between schizotypy group and condition in hippocampal-parahippocampal regions bilaterally (BA28) as well as the left insula (BA13) and right anterior cingulate cortex (BA32). Lowering the threshold revealed significant interactions in the fusiform gyrus (BA37), superior temporal gyrus, inferior frontal gyrus (BA47) and dorsolateral prefrontal cortex (BA9). Notably, these interactions largely revealed increased activation during memory retrieval in the high schizotypes and to a lesser extent lower activation at encoding compared to controls. Hippocampal-parahippocampal recruitment in each group and performance on the task was investigated revealing a significant relationship between better performance and right hippocampal recruitment at encoding in the average control group but no relationship in the high schizotypes. Recruitment of the right hippocampal-parahippocampal region during memory retrieval in high schizotypes was related to worse performance. Recruitment of the left hippocampus was unrelated to performance in both groups.

7.5.2   Behavioural Data

There were no behavioural differences between the two groups on performance on this task. This is surprising giving the extensive body of literature on cognitive impairments in individuals with high schizotypal trait expression (for review see Raine, 2006). The performance of both groups is in line with previous literature using this task in healthy, young volunteers (Parslow et al, 2004; Antonova et al, 2009). Several reasons may underlie the lack of behavioural differences observed in this group. Firstly, subjects were extensively trained on the task prior to

performance in the scanner which may have masked cognitive differences. Opportunity for practice may allow high schizotypes to improve to a satisfactory level whereas controls may have stable performance from the start. A second explanation could be that the schizotypes in this sample are high functioning with comparable IQ and educational status. Whilst this is an advantage in terms of having an appropriate comparative control group it may have reduced our ability to identify cognitive differences between the two groups. Related to this, the strict exclusion criteria excluded individuals who had significant alcohol, nicotine or recreational drug intake. Schizotypy is associated with elevated use of these substances (Barkus & Murray, 2010; Esterberg et al, 2007) and as such our sample may not reflect the entirety of the schizotypy profile. A final suggestion is that high schizotypes possess a differential pattern of neural activation that compensates for impairments in other regions (Siever et al, 2002; Siever & Davis, 2004).

7.5.3   Task related activations across groups

Both groups activated a network of neural activation in line with that reported in the spatial cognition literature (e.g. G. K. Aguirre, et al., 1996; N. Burgess, et al., 2002; Maguire, et al., 1998) and in previous literature using this task (Parslow et al, 2004; Antonova et al, 2009). Across groups there was activation in the hippocampal-parahippocampal regions, parietal cortex, striatum, occipital regions, motor cortices, cingulate gyrus and prefrontal cortex during memory encoding and memory retrieval. As described in the literature, the recruitment of the right hippocampus is essential for allocentric spatial memory (Maguire, et al., 1998) and this was evidenced in this study by its recruitment in both groups and its relationship with navigation accuracy in the control group. This is in line with previous literature that has demonstrated a relationship between right hippocampal recruitment and successful spatial navigation in healthy volunteers (Maguire et al, 1998; Gron et al, 2000; Hartley et al, 2003). Hippocampal-

parahippocampal activation was bilateral in this study. Several studies have reported bilateral activation during allocentric spatial memory tasks (G. K. Aguirre & D'Esposito, 1997). Several explanations are proposed for the involvement of the left hippocampus in spatial memory tasks. It may be that the left hippocampus is involved in verbal recoding of visual or spatial information (Parslow et al, 2004) consistent with its specified involvement in verbal learning and memory (Frisk & Milner, 1990). Bohbot et al (1998) identified spatial memory deficits in patients with damage to the right hippocampus whereas verbal memory deficits were observed in patients with left hippocampal damage. More generally, Burgess et al (2002) have proposed that the left hippocampus is involved in episodic memory and the non-geometric aspects of spatial memory. Maguire et al (1998) also report left hippocampal involvement during spatial navigation but this was unrelated to navigational accuracy; similarly we found the left hippocampus was not related to performance across groups. A pattern of activation was also identified consistent with general navigation through virtual environments including the parietal and striatal regions. In this task, subjects are asked to first navigate towards a pole during encoding and then to retrieve the encoded location and navigate to the remembered location. It is likely that during encoding, the requirement of the subject to navigate to a pole they can plainly see in the periphery may elicit egocentric processing i.e. the only requirement is to move towards the visible pole location whereas the allocentric spatial memory requirement is to use the distal cues to then remember this pole location for later navigation. At retrieval, once this information is retrieved from memory it may be recoded into an egocentric framework to allow navigation towards the remembered goal.

7.5.4   Group comparisons

The main group difference was observed bilaterally in the hippocampal-parahippocampal region. Average schizotypes had increased activation of the right anterior hippocampal-

parahippocampal region during spatial encoding compared to high schizotypes. Conversely, there was a marginal increase in activation of the left hippocampus in high schizotypy during memory encoding compared to the control group. However, the real difference lies in their recruitment of the hippocampal-parahippocampal region during memory retrieval. Average schizotypes did not recruit this region during memory retrieval in line with previous literature using this task (Parslow et al, 2004 but also see Antonova et al, 2009). High schizotypes on the other hand recruited this region bilaterally and this was related to worse performance on the task suggesting recruitment of this region is anomalous and not pertinent to successful completion of the task. Recruitment of this region by high schizotypes may reflect a sustained use of cognitive mapping at retrieval as a compensatory mechanism for an inefficient encoding strategy. Evidence for inefficient encoding is suggested by the reduced hippocampal activation and lack of a relationship between right hippocampal activation and performance in high schizotypes. Inefficient encoding strategies related to hippocampal dysfunction are reported in both schizophrenia (Heckers, 2001)and at risk mental states (Allen et al., 2009). Studies have also demonstrated that impaired encoding is associated with hyperactivation at retrieval in the prefrontal cortex, cingulate regions and other medial temporal structures (Hall, et al., 2010; Heckers, et al., 1998; M. R. Johnson et al., 2006) which is also reported in this study.

The left anterior insula was also an area of significant difference between the two groups. Whilst the two groups activated this region during encoding the high schizotypy group had decreased activation at encoding and increased activation of this region during retrieval compared to average schizotypes. The insula has been implicated in several functions including processing of visceral sensations and information, vestibular function, attention, pain, empathy, pain, emotion, speech and verbal learning and memory, and processing of gustatory, olfactory, visual, auditory and tactile data (Shelley & Trimble, 2004). Although its role in cognition is understudied, the insula cortex has also been demonstrated to be involved in declarative memory

(Bermudez-Rattoni, Okuda, Roozendaal, & McGaugh, 2005; S. Chen, Li, Xu, & Liu, 2009; Miranda & Bermudez-Rattoni, 2007) and the left insula has been implicated in verbal learning and memory (Awh et al., 1996; E. E. Smith & Jonides, 1999). Increased activation of this region during retrieval may therefore be associated with a reliance on verbal strategies to complete the task in high schizotypy. This suggestion is supported by the larger involvement of the left hippocampus compared to the right hippocampus in the high schizotypy group.

An alternative interpretation is that the insula is involved in egocentric spatial memory processing due to its association with proprioceptive and vestibular awareness and insula activation has been reported in egocentric, but not allocentric, spatial memory using this task (Parslow et al, 2004). Thus high schizotypes may need to rely on an egocentric representation to a greater extent during retrieval due to inefficient encoding of the distal cues during encoding. This is in line with previous literature suggesting that egocentric spatial memory is spared in schizophrenia whilst allocentric spatial strategies are impaired (Hanlon et al, 2006; Weniger & Irle, 2008). However, although it has been argued that allocentric spatial tasks can be solved by egocentric means, the time and design constraints imposed on subjects during memory retrieval do not favour using egocentric strategies. Another possibility is that participants could use a cue guidance strategy for example remembering a specific cue and the distance from the wall of the pole location and then at retrieval following the outer wall until the cue is located. However, visual observation of the participant's trajectory towards the remembered pole location during memory retrieval suggests this was not the way participants solved the task. Further this is not the most efficient method for completing the task in the given time frame.

Additionally, high schizotypy was associated with increased activation of the anterior cingulate gyrus. Generally, this region is involved in performance monitoring and attention (Carter et al, 1998) and thus increased activation of this region may be related to increased cognitive effort in

high schizotypy and hypervigilance of performance. Nelson et al (2010) have suggested that the role of the anterior insula and the anterior cingulate cortex is in higher level cognitive control and focusing of attentional processes. Greater activation of this region has been observed in schizophrenia (Glahn et al, 2005) suggesting a greater monitoring of cognitive operations in patients with schizophrenia. Further, alterations in cingulate gyrus function have been observed on a virtual Morris Water Maze (Sava & Yurgelan-Todd, 2008).

7.5.4   Methodological considerations

Only limitations specific to this task will be discussed in this section. Limitations relating to broader issues in this thesis will be discussed in the final discussion chapter.

An advantage of using this task is that the arena conditions can be modified to measure egocentric and allocentric spatial memory. To do this start positions can be varied between encoding and retrieval conditions and between trials (allocentric) or kept the same (egocentric). I chose the former as I was specifically interested in allocentric spatial memory and based on previous literature stating that allocentric but not egocentric spatial learning and memory is impaired in schizophrenia (Weniger & Irle 2008). However there is a paucity of research looking at specific spatial memory strategies in schizotypy and schizophrenia and it would have been beneficial to include the egocentric version of this task for comparison in high schizotypy. Consideration however had to be given to the length of time subjects were kept in the MR scanner and addition or extension of a task would not have been practically feasible. Additionally, the study would have benefited from recording participant's chosen strategy for completing the task by asking them verbally post scanning. As mentioned in the discussion it is unlikely that subjects were using an egocentric strategy due to the recruitment of neural networks that underlie allocentric spatial memory however recording their chosen strategy would allow us to both rule out this possibility or to account for it within the analysis.

The use of a block design with 30 seconds per block for encoding and retrieval may have reduced the BOLD signal in the hippocampal-parahippocampal region and obscured performance across groups. During encoding subjects have to locate a clearly visible pole within 30 seconds and this is quite easy to do. Subjects therefore may not have been encoding for the whole of the 30 seconds of the encoding condition if they reached the pole before the end of the block which may have reduced BOLD signal activation. However, one could argue that if a participant reached the pole early they could still be encoding the pole location by focusing on the patterns in the immediate vicinity of the pole. The opposite problem arises for the retrieval condition. Subjects have 30 seconds to navigate from a different start position to where they estimate the pole was located during encoding. It could be argued that 30 seconds is not sufficient time to retrieve the location from memory, navigate to the chosen location and be accurate in terms of both distance and angle. Subjects who performed poorly, as indexed by larger deviation between true and estimated pole location, may not necessarily have had poorer allocentric spatial memory but may have failed to reach the exact location in 30 seconds. This may have obscured any true performance differences between the groups in terms of allocentric spatial learning and memory.

7.5.5 Conclusions

Overall the results suggest that high schizotypes recruit the hippocampal-parahippocampal region in a different way to control subjects with lower recruitment of the right hippocampal region during encoding and bilateral increased activation during retrieval in the absence of a measured difference in performance. Furthermore, whilst hippocampal activation is associated with better performance in controls this relationship is absent in high schizotypes suggesting inefficient recruitment of this region. At retrieval, hyperactivation of this region is associated with worse performance suggesting its recruitment in high schizotypes is aberrant. Retrieval is

also associated with increased activation of the insula and ACC in high schizotypes suggesting that this group find the task cognitively challenging and recruit regions associated with vigilance, attention and cognitive control.   Hyperactivation of these regions in high schizotypes might therefore reflect an increase in cognitive effort and performance monitoring in order to maintain performance in the task.

Chapter 8: Functional Imaging Results – Platform Task

8.1   Introduction

As discussed in Chapter 4 several researchers have designed virtual reality radial arm mazes for use in humans. These typically mimic the animal radial arm maze by starting subjects on a central platform with 8 arms radiating out from the centre. Surrounding the maze are environmental cues. Typically, four out of eight arms are baited with rewards that the participant is instructed to collect. Errors are defined by whether subjects return to previously successful arms or arms never baited. In the human case, the arms can be mimicked in virtual reality of target locations can be clustered around a central starting point. The allocentric demand for both the animal and the human is generated by the need to use external cues to orientate themselves keep track of which arms have been visited, an egocentric strategy not sufficient provided the task is set up in the right manner.

In this chapter a variant of a human radial arm maze termed the Platform Task designed by Robin Morris, David Parslow and Elena Antonova at the Institute of Psychiatry will be introduced. As with other tasks of allocentric spatial memory this task has been associated with activation of the hippocampus and parahippocampal gyrus, parietal and occipital cortex, prefrontal, thalamic, striatal and motor cortices (unpublished data). The decision to include this task as a measure of allocentric spatial memory in this thesis is that it is ideal for titrating difficulty levels as the number of target locations (here termed platforms, hence the name of the task) can be increased from 4 through to 8 platforms. Thus, BOLD activation and cognitive performance can be ascertained as spatial memory load increases and differences between the groups can be investigated under easy and challenging conditions. Additionally, there is a

common misconception that the Morris Water Maze and Radial Arm Maze are interchangeable measures of allocentric spatial memory but researchers have begun to suggest that these may in fact be tapping different aspects of spatial cognition (Astur et al, 2005). In this study, the researchers compared performance of males and females on three tasks of spatial memory: a virtual Morris Water Maze, a virtual Radial Arm Maze and a mental rotation task. Apart from a correlation between the measures obtained on the virtual MWM and mental rotation ability there were no correlations between performance measures on any of the tasks. The authors suggest that the two tasks of spatial memory do not assess spatial cognition in the same manner even when controlling for motivation, stress and motor demands and therefore that there are different procedural demands of the task that elicit different forms of spatial cognition. Thus an additional reason for including the platform as a second measure of allocentric spatial memory is to assess the sensitivity of these tasks to differences in cognition and brain function in healthy volunteers with schizotypal traits. Ultimately, this may provide information for future researchers seeking to choose appropriate tests of allocentric spatial memory.

8.2   Specific Hypothesis

Specific hypotheses explored using this task was as follows:

1.   Based on previous studies of allocentric spatial learning and memory in schizophrenia individuals high in schizotypal traits will perform worse of this task compared to the control group.

2.   The control group will demonstrate a pattern of activation in line with previous studies of spatial learning and memory using human analogues of the radial arm maze including activation of the hippocampus and parahippocampal gyrus.

3.   As performance on the allocentric spatial memory component of the Platform Task is thought to rely on activation of the hippocampus and parahippocampus, BOLD activation in these regions will be negatively correlated with performance (as BOLD activation increases there will be a decrease in number of errors made).

4.   High schizotypy will be associated with a different pattern of brain activation specifically reduced activation of the hippocampus and parahippocampal gyrus compared to control subjects.

5.   In line with Siever & Davis (2004) model of schizotypal personality disorder (see Chapter 3), high schizotypy will be associated with increased activation of prefrontal regions compared to control subjects

6.   A different pattern of BOLD activation will be found in high schizotypy as memory load increases.

8.3   Methods

8.3.1   Subjects

Forty two subjects overall completed the studies in this thesis.

Thirty eight subjects were included in the analysis of this task. Two subjects were unable to complete the task within the scanner due to hardware difficulties and two subjects did not complete all eight platforms.

Screening procedures, inclusion and exclusion criteria, schizotypy group allocation and selection of subjects is discussed in Chapter 5. Image acquisition is reported in Chapter 5, section 5.4.2.

8.3.2   Task Design

<u>Programming</u>

The task was programmed in virtual reality (VR) format by Third Dimension (Dorset, United Kingdom) using Superscape VR software (Superscape, Hampshire, UK). Images were displayed via a projector onto a Perspex screen at the foot of the scanning table. For navigating around the VR environment, the participant used a Magnetic Resonance Imaging (MR) compatible tracker ball.

<u>Design of the task</u>

In the Platform Task, the participant is started in the centre of an array of yellow platforms. On the periphery of the platform area are landmarks (e.g. a castle, trees, a fire truck, and a windmill), randomly arranged outside of the circular perimeter of the central area.   These landmarks are presented in Figure 36. The task is set up such that in the first search the participant has to try different location until they find a target ('baited') location. Once this has been accomplished the target location moves to another location and the original location is no longer designated a target within that trial. Once the second search is successful, the target location moves and again the successful location is excluded as a location. This continues until all the locations have been used as targets. Hence the aim of the task is, using a series of searches to visit each of the platforms once during each trial, using the landmarks to identify platforms already visited. An example of a trial presented from the participant's viewpoint is given in Figures 37. Subjects move about the virtual environment using an MR compatible tracker ball and can move to the left or the right. Movement forward towards a platform is accomplished by using the trackerball to place the cursor over the platform and clicking on the tracker ball button. This effectively selects the platform. An example of selection of a platform is presented in Figures 38. Once a platform is selected, the participant is informed of whether

their choice is correct by a green tick appearing on the screen. An incorrect response is signalled by a red cross appearing on the screen. Feedback responses are presented in Figure 39 and 40. Once a platform is selected the participant is physically moved to that platform, so altering their viewpoint each time. This is to encourage an allocentric spatial memory strategy to be used. Difficulty is titrated by varying the number of platforms from 4 to 6 to 8 and subjects complete three sets of four platform trials, three sets of six platform trials and 3 sets of 8 platform trials. A trial ends when all platforms have been visited. Between each set of trials subjects are presented with a 10 second blank screen (rest) followed by a coloured screen (visual control) and then a second 10 second blank screen (rest). In Figure 41, an example of four, six and eight platforms as shown from an aerial perspective is provided.

Note that the design of this task differs from the animal procedure; in the latter all the locations are initially baited and the exclusion of a target occurs when the bait is removed by the animal. The human analogue was designed in the particular fashion to help avoid the development of specific strategies to get round the cognitive mapping demand, for example, simply selecting proximal locations. Furthermore, to disrupt stimulus-response strategies on each search it was designated that only certain platforms can only be visited, and these are coloured yellow. Platforms that are coloured red are blocked and cannot be selected. The blocking varies between trials in a pseudorandom fashion.

Figure 36 Collection of items used to make up the scenery in the Platform Task.
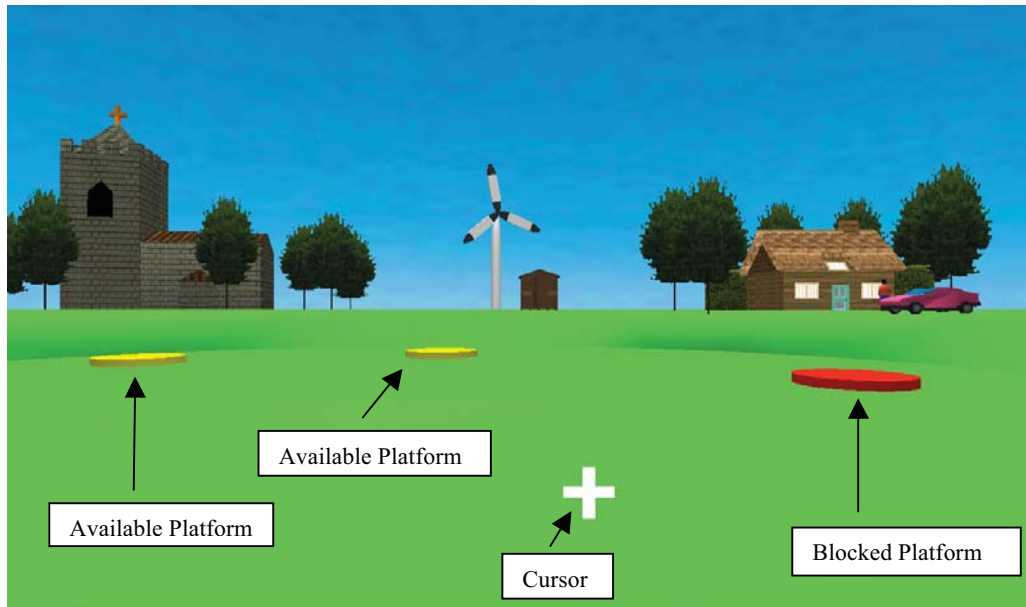
Figure 37 Example of a trial from the perspective of the viewer demonstrating platform options (yellow platforms can be selected whereas red platforms are blocked).
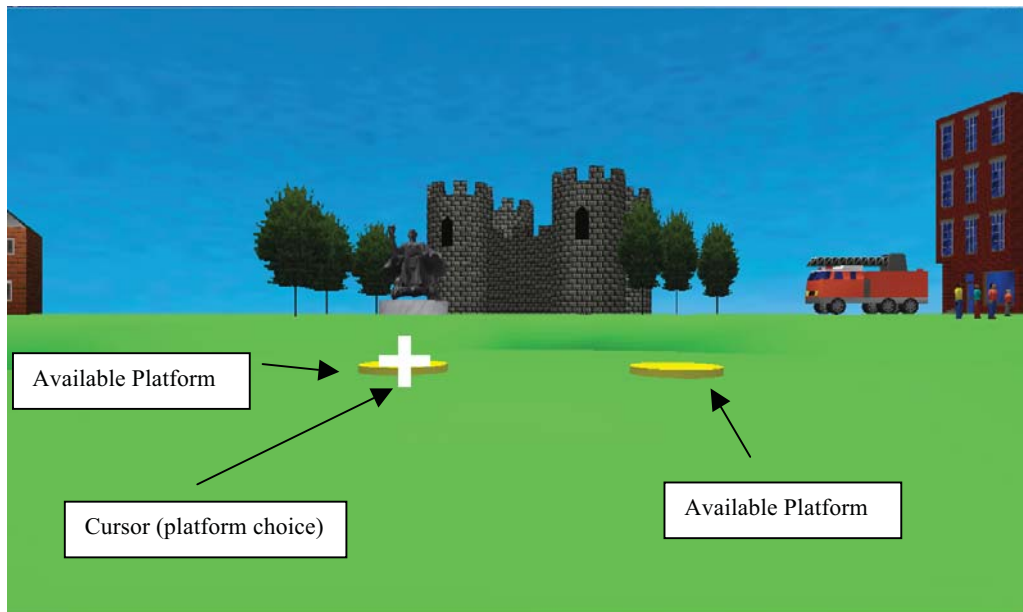
Figure 38 Example of a trial from the perspective of the viewer demonstrating a potential platform decision. To select a platform the subject places the cursor over the platform and presses a button on the trackerball to indicate selection.

Figure 39 Feedback on a correct selection of a platform.
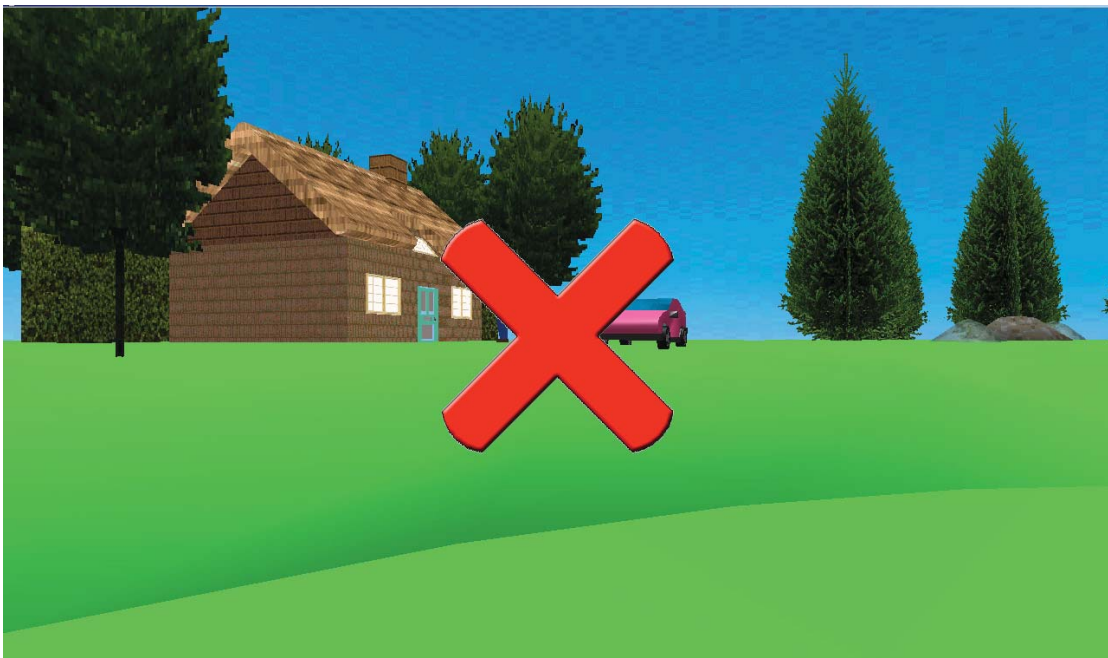
Figure 40 Feedback on an incorrect selection of a platform
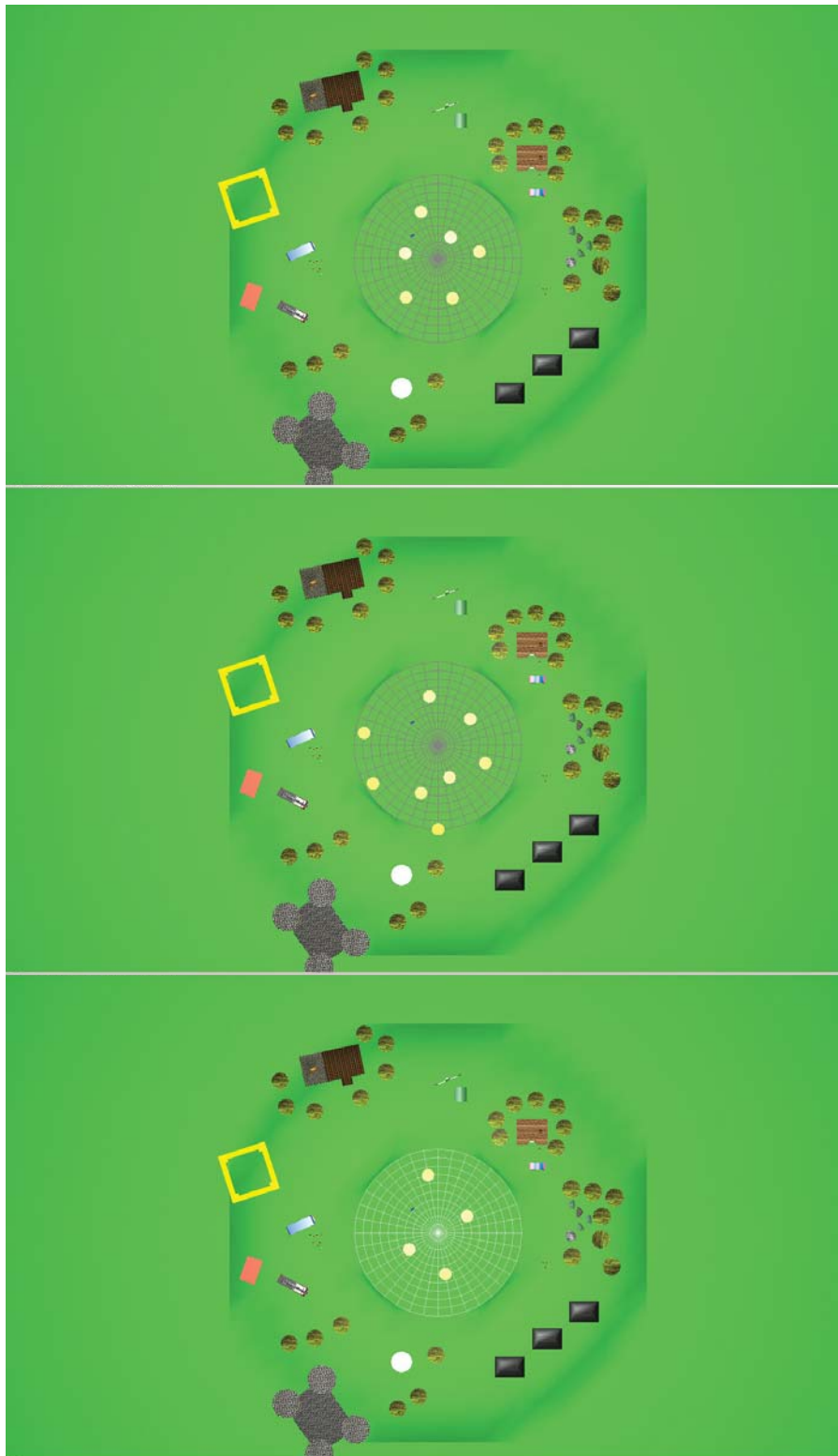
Figure 41 Aerial perspective demonstrating the layout of the platforms for 4, 6 and 8 platform trials.

8.3.3 Procedure

Subjects received one training session of the screening day with a full run through of the task inside the mock scanner. This was to ensure that subjects were familiar with the VR environment, the hardware used to navigate the environment and the scanning environment. In addition on the testing day, prior to being in the actual scanner, subjects received another practice session. As subjects were tested anywhere between 1 and 6 weeks after the screening visit, a second practice session ensured that they had not forgotten the requirements of the task.

8.3.4 Data Analysis

8.3.4.1 Behavioural Data

Dependent variables are time to complete each set of trials, between search errors and within search errors. A between search error is recorded when a participant returns to a platform that was previously tried and correct. A within search error is recorded when a participant return to a platform that was previously tried and was incorrect.

As there were three levels of difficulty (4 platforms, 6 platforms and 8 platform trials) a repeated measures ANOVA was used to investigate accuracy and reaction time across the within subject variable difficulty and the between subjects variable schizotypy group.

8.3.4.2 Functional Imaging Data

Preprocessing of the functional images

Preprocessing steps were the same for all tasks and are presented in Chapter 5.

Model Specification

Model specification is as outlined methods chapter 5.

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First Level Analysis

A mini-block design was chosen to analyse the data from the Platform Task which consisted of combining the trials for each level into on column, so generating three columns, the four, six and eight platform levels. The onset and durations were entered for each condition (4 platforms, 6 platforms, 8 platforms, rest, control and errors) and for each subject; all variables were modelled by convolving the onset of each block with the hemodynamic response function. No temporal derivatives or interactions between trials were required. Six rotational and translational movement parameters generated by the realignment procedure for each subject were entered as regressors (nuisance covariates). Following estimation of the statistical model, contrast images were generated for each task comparison and for each subject. Contrasts were 4 platform > rest condition, 6 platform > rest condition and 8 platform > rest condition. Whilst there are numerous contrasts that could be investigated, these were chosen as suitable for addressing the hypothesis set out in section 8.2.

A second design matrix was created with the platform levels collapsed into one column of the design matrix and a parametric modulation added. The effect of adding a parametric modulation design is to investigate BOLD activation (and deactivation) as difficulty linearly increases.

Second Level Analysis

Contrast images were analysed using a one sample t-test to show the main effect of task in each group and a two sample t-test was used to test between groups differences in BOLD activation.

fMRI statistical inference

Statistical inference was set as outlined in section 5.5.3.3 of the Chapter 5.

Small Volume Correction (SVC)

ROIs were defined and administered as outlined in sections 5.5.3.4

Performance correlations

Performance correlations were performed as set out in Chapter 7 (section 7.4.4.3).

8.4   Results

8.4.1   Demographics

Gender and ethnicity were evaluated using chi-square. Age had a non-normal distribution (Control Group: $W = .778$, df = 18, $p = 0.001$; High Group: $W = .849$, df = 20, $p = 0.005$). Transformation did not significantly improve the distribution therefore the non-parametric Mann Whitney test was performed. The variable education had three missing values therefore a series mean calculation was performed to replace these values.   The new education variable was normally distributed (Control group: $W = .942$, df = 18, $p = .313$; High schizotypy group: $W = .960$, df = 20, $p = .083$). IQ (NART-R score) was also normally distributed (Control group: $W = .960$, df 18, $p = .599$; High schizotypy group: $W = .945$, df = 20, $p = .298$). Education and IQ were investigated using independent t-tests. Schizotypy groups did not differ on age, gender, IQ, years in education or ethnicity (data presented in Table 29).

Table 29 Demographic variables by schizotypy group

	Control Group	High Schizotypy	Statistical Test
Age Range	24.17 (6.04) 19 – 42	23.35 (4.97) 18 – 37	U = 169.500, p = .762
Gender (Ratio M:F)	8:10	9:11	χ2 = 0.001, df =1, p = .615
Ethnicity (N) White Black Asian	 14 0 4	 15 2 3	 χ2 = 2.078, df = 2, p = .354
Education	15.28 (1.52)	15.77 (1.44)	t = -1.032, df = 36, p = .390
NART-R Score	116.29 (4.10)	116.74 (4.00)	t = -.347, df = 36, p = .730

Data represents means (SD) unless otherwise stated.

8.4.2 Schizotypy Scores

Schizotypy scores were determined by total score on the SPQ. Allocation to the average schizotypy group included scores 21-36 and allocation to the high group included scores of 43 and above.

Total SPQ score was not normally distributed (Control group: W = .888, df = 18, p = 0.035; High schizotypy group: W = .875, df = 20, p = 0.015). Therefore a non-parametric Mann Whitney test was performed. The SPQ subscale cognitive perceptual was normally distributed (Control group: W = .911, df = 18, p = .090; High schizotypy group: W = .971, df = 20, p = .774) as was interpersonal (Control group: W = .978, df = 18, p = .923; High schizotypy group: W = .967, df = 20, p = .681) and independent t-tests were used to investigate group differences. Disorganised was not normally distributed (Control group = .975, df = 18, p = .886; High schizotypy group = .890, df = 20, p = .027) therefore a non-parametric Mann Whitney test was performed.

Table 30 Schizotypal personality scores in each group

	Control Group	High Schizotypy Group	Statistical Test
SPQ Total Range	26.94 (5.16) 21-36	48.35 (4.93) 43-58	$U = 360.00$, $p < 0.001$
Cognitive Perceptual Range	10.05 (7.09) 1-29	20.05 (5.16) 10-29	$t = -4.998$, $df = 36$, $p < 0.001$
Interpersonal Range	11.94 (4.47) 4-22	21.60 (5.78 8-31	$t = -5.708$, $df = 36$, $p < 0.001$
Disorganised Range	8.72 (2.98) 4-15	12.85 (2.90) 6-16	$U = 302.50$, $p < 0.001$

Data represents means (SD) unless otherwise stated.

8.4.3   Behavioural Results

Mauchly's test of sphericity was significant and as such these results are presented with a Greenhouse-Geisser correction. Means and standard deviations are reported in Table 31.

Accuracy

Between Search Errors

A two factor group (control and high schizotypy) x difficulty (4 platform, 6 platform and 8 platform) repeated measures ANOVA revealed a significant main effect of difficulty ($F_{(1.64, 58.90)} = 65.74$, $p < 0.001$) but no effect of group ($F_{(1, 36)} = 0.715$, $p = .430$). There was no significant interaction between group and difficulty level ($F_{(1.64, 58.90)} = .1.388$, $p = .256$).

Within search errors

A two factor group (control and high schizotypy) x difficulty (4 platform, 6 platform and 8 platform) repeated measures ANOVA revealed a significant main effect of difficulty ($F_{(1.17, 42.21)} = 7.13$, $p = 0.002$) but no effect of group ($F_{(1, 36)} = 0.356$, $p = .554$). There was no significant interaction between group and schizotypy ($F_{(1,36, 42.22)} = 0.674$, $p = .439$).

Reaction Time

A two factor group (control and high schizotypy) x difficulty (4 platform, 6 platform and 8 platform) repeated measures ANOVA revealed a significant main effect of difficulty ($F_{(1.43, 51.34)}$ = 333.53, p < 0.001) but no effect of group ($F_{(1, 36)}$ = 0.244, p = .624). There was no significant interaction between difficulty and group ($F = _{(1.43, 51.34)}$ = 0.003, p = .986).

Table 31 Means and standard deviations for performance on the Platform Task

	Average Schizotypy	High Schizotypy
Between Search Errors: 4 platforms	0.28 (0.37)	0.32 (0.28)
Between Search Errors: 6 platforms	0.93 (1.23)	0.85 (0.75)
Between Search Errors: 8 platforms	2.87 (1.61)	2.30 (1.40)
Within Search Errors: 4 platforms	0	0
Within Search Errors: 6 platforms	0.15 (0.28)	0
Within Search Errors: 8 platforms	0.28 (0.67)	0.30 (0.49)
Mean Time: 4 platforms	43.11 (8.26)	45.84 (12.90)
Mean Time: 6 platforms	68.79 (16.36)	71.45 (20.18)
Mean Time: 8 platforms	111.67 (25.31)	114.74 (28.68)

Data represents means (SD) unless otherwise stated.

8.4.4   Functional Imaging Results

8.4.4.1 Group Maps

8.4.4.1.1   Control Group

Four Platforms

Activation was observed during four platform trials compared to rest in the control group in the bilateral precuneus, left inferior occipital gyrus, left superior parietal lobule, bilateral thalamus, bilateral occipital gyrus, right claustrum, right medial frontal gyrus and right inferior frontal gyrus, left caudate, left cerebellum and right parahippocampus.

Table 32 Significant activations during four platform trials compared to rest in the control group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x,y,z
Precuneus (R)	7	702	6.24	28 -74 41
Inferior Occipital Gyrus (L)	18	238	5.98	-26 -89 1
Superior Parietal Lobule (L)	7	717	5.97	-30 -51 60
Thalamus (L)		390	5.89	-10 -21 10
Middle Occipital Gyrus (R)	18	187	5.70	28 -93 6
Inferior Occipital Gyrus (L)	9	111	5.56	-40 -76 0
Thalamus (R)		142	5.52	16 -23 10
Precuneus (L)	7	223	5.46	-16 68 44
Claustrum (R)		23	5.31	-30 16 3
Medial Frontal Gyrus (R)	6	49	5.25	28 -3 52
Parahippocampus (R)	36	26	5.15	26 -39 -10
Inferior Frontal Gyrus (R)	9	12	5.14	57 11 25
Caudate (L)		37	5.12	-12 -8 21
Cerebellum (L)		10	5.08	-28 -40 -22
Inferior Occipital Gyrus (R)	19	9	4.89	42 -72 -1

All regions are reported $p < 0.05$ FWE corrected. L = left hemisphere, R = right hemisphere.
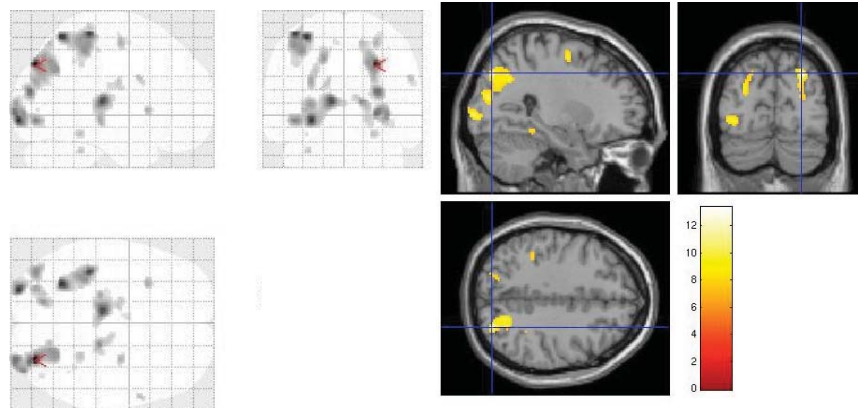
Figure 42 Significant activations during four platform trials compared to rest in the control group

Additionally, lowering the threshold to a less conservative $p < 0.001$ uncorrected revealed additional activations in the right middle and left inferior frontal gyrus, left insula, left temporal gyrus, right cerebellum and right medial frontal gyrus in the control group.

Table 33 Significant activations during four platform trials compared to rest in the control group.

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x,y,z
Right Cerebellum (R)		425	4.30	8 -61 -24
Temporal Gyrus (L)	41	132	4.28	-53 -17 14
Middle Frontal Gyrus (R)	9	162	4.12	46 32 28
Parietal Lobe (R)	43	4	3.26	65 -7 21
Middle Frontal Gyrus (R	9	5	3.22	34 44 33
Inferior Frontal Gyrus (L)	9	4	3.20	-36 21 -13
Medial Frontal Gyrus (R)	6	1	3.12	12 -20 -11
Insula (L)	13	1	3.10	-32 26 15

All regions reported at $p < 0.001$ uncorrected. L = left hemisphere, R = right hemisphere.
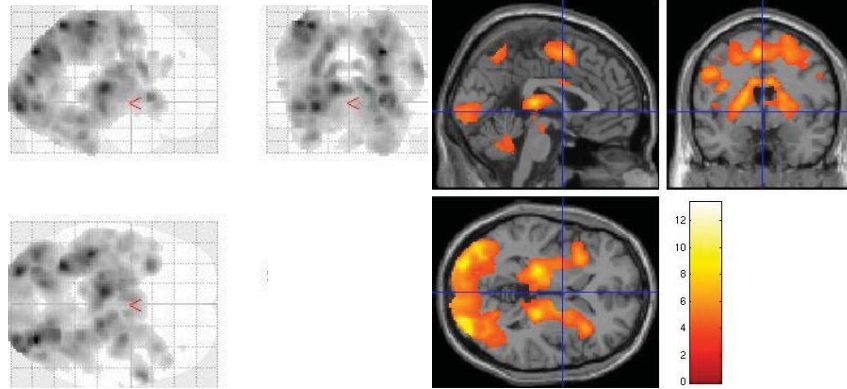
Figure 43 Uncorrected activations during four platform trials compared to rest in the control group.

Small volume correction revealed significant bilateral activation of the hippocampus and parahippocampal gyrus during four platform trials compared to rest in the control group.

Table 34 Significant hippocampal activation in the four platform trials compared to rest in the control group.

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x, y and z
Hippocampus (R)		228	4.67	22 -24 -8
Hippocampus (L)		185	4.63	-22 -24 -6

All regions reported p < 0.05 small volume corrected. L = left hemisphere, R = right hemisphere.

Figure 44 Hippocampal activations during four platforms contrasted to rest in the control group (small volume corrected).

Table 35 Significant activations in the parahippocampal gyrus during four platform trials compared to rest in the control group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x, y and z
Parahippocampus (R)	36	309	4.90	26 -37 -8
Parahippocampus (L)	36	99	4.68	-30 -38 -14

All regions reported p < 0.05 small volume corrected. L = left hemisphere, R = right hemisphere.
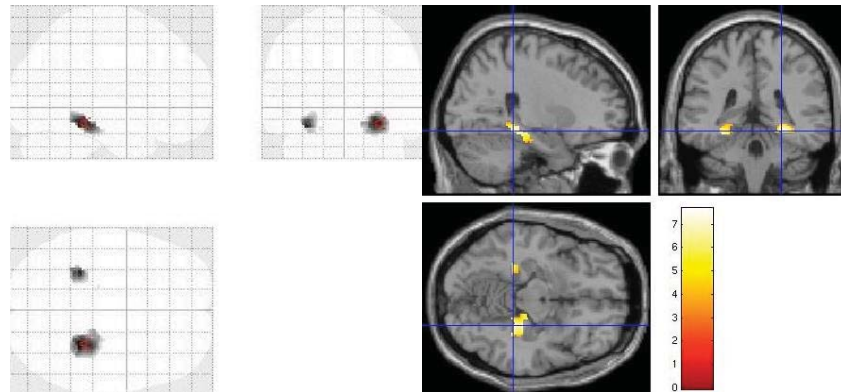
Figure 45 Parahippocampal activations during four platforms contrasted to rest in the control group (small volume corrected)

Six Platforms

Activations were observed in the 6 platform trials compared to rest in the control group in left middle occipital gyrus, left parietal lobe and left inferior parietal lobule.

Table 36 Significant activations during 6 platform trials compared to rest in the control group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x,y,z
Middle Occipital Gyrus (L)	18	13	4.94	-24 -93 3
Parietal Lobe (L)	5	27	4.91	-34 -42 56
Inferior Parietal Lobule	40	11	4.91	-40 -34 52

All regions reported at p < 0.05 FWE corrected. L = left hemisphere, R = right hemisphere.

Figure 46 Significant activations during six platform trials compared to rest in the control group.

Lowering the threshold to a less conservative uncorrected p < 0.001 revealed additional activations in the right medial and inferior frontal gyrus, right hippocampus, right striatum, left medial frontal gyrus/anterior frontal polar region and right inferior frontal gyrus in the control group when comparing 6 platform trials to rest in the control group.

Table 37 Uncorrected activations during 6 platform trials compared to rest in the control group.

Region	BA Equivalent	Cluster Size	Z score	Maximum coordinates x,y,z
Medial Frontal Gyrus (R)	6	734	4.17	24 -1 50
Inferior Frontal Gyrus (R)	9	412	4.10	55 9 29
Middle Frontal Gyrus (R)	46	216	3.97	46 30 24
Parahippocampus (R)	28	10	3.65	14 -15 -23
Basal Ganglia (R)	Putamen	121	3.47	24 6 5
Frontal Pole (L)	10	8	3.45	-40 42 18
Inferior Frontal Gyrus (R)	47	44	3.34	36 23 -1

All regions reported at p < 0.001 uncorrected. L = left hemisphere, R = right hemisphere.
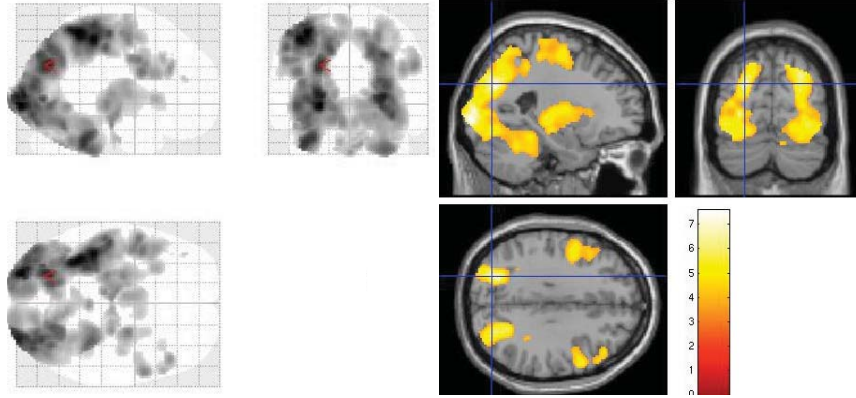
Figure 47 Uncorrected activations during six platform trials compared to rest in the control group.

Applying a small volume correction using the WFUpickatlas (details provided in Chapter 5) revealed bilateral hippocampal activation in the control group during six platform trials compared to rest.

Table 38 Significant activations in the hippocampus during the 6 platform condition compared to rest in the control group (small volume corrected)

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates
Hippocampus (L)		51	3.58	-22 -22 -7
Hippocampus (R)		32	3.44	28 -28 -9

All regions are reported p < 0.05 small volume corrected. L = left hemisphere, R = right hemisphere.

Figure 48 Significant hippocampal activations during six platform trials compared to rest in the control group (small volume corrected)

Table 39 Significant activations in the parahippocampal gyrus during 6 platform trials compared to rest in the control group (small volume corrected)

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates
Parahippocampus (L)	36	53	3.93	-28 -37 -10
Parahippocampus (R)	36	96	3.58	28 -37 -8

All regions are reported p < 0.05 small volume corrected. L = left hemisphere, R = right hemisphere.

Figure 49 Significant parahippocampal activations during six platform trials compared to rest in the control group (small volume corrected)

Eight Platforms

Activations were observed during 8 platform trials compared to rest in the control group in the right middle occipital gyrus and cuneus, family wise error corrected for multiple comparisons.

Table 40 Significant activations during 8 platform trials compared to rest in the control group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x,y,z
Middle Occipital Gyrus (R)	19	13	4.94	44 -80 2
Middle Occipital Gyrus (R)	19	8	4.87	34 -91 8
Cuneus (R)	19	2	4.81	26 -79 21
Middle Occipital Gyrus (R)	19	1	4.78	30 -81 19

All regions reported p < 0.05 FWE corrected. L = left hemisphere, R = right hemisphere.
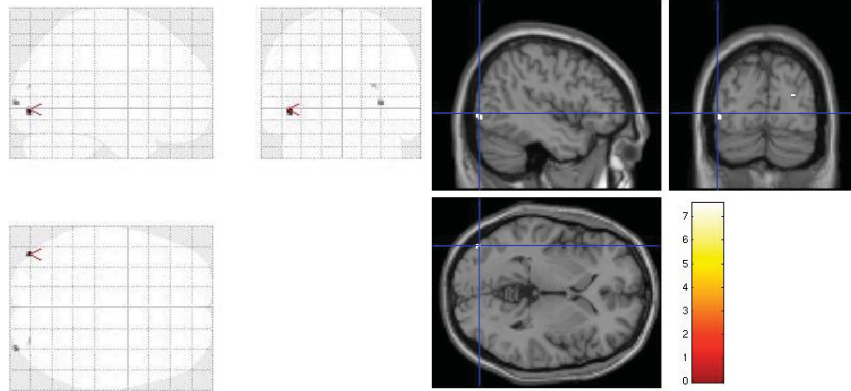
Figure 50 Significant activations during eight platform trials compared to rest in the control group

Lowering the threshold to a less conservative uncorrected level of p < 0.001 revealed activation in the left middle occipital gyrus, right middle frontal gyrus, left lentiform nucleus, left inferior and medial frontal gyrus, right superior frontal gyrus, right insula, right fusiform gyrus and right cerebellum in the control group during eight platform trials compared to rest.

Table 41 Uncorrected activations in the 8 platform trials compared to rest in the control group.

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x,y,z
Middle Frontal Gyrus (R)	46	513	4.28	50 32 26
Lentiform Nucleus (L)	Lateral Globus Pallidus	1927	4.25	-22 -13 3
Inferior Frontal Gyrus (L)	9	452	4.11	-53 5 31
Superior Frontal Gyrus (R)	6	992	3.93	24 3 66
Medial Frontal Gyrus (L)	6	492	3.85	-8 -21 47
Insula (R)	13	161	3.60	34 21 -1
Cerebellum (R)		14	3.37	8 -56 -26
Fusiform Gyrus (R)	37	41	3.25	48 -53 -7

All regions are reported at the p < 0.001 uncorrected. L = left hemisphere, R = right hemisphere.
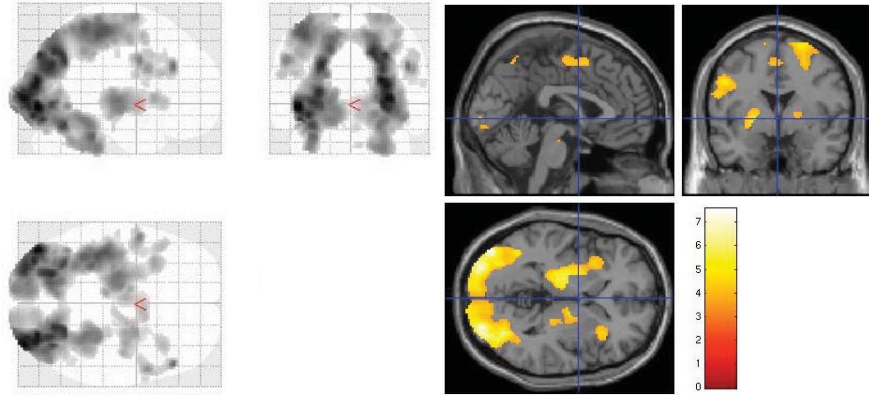
Figure 51 Uncorrected activations during eight platform trials compared to rest in the control group

Applying a small volume correction using the WFUpickatlas (see methods section for details) revealed significant bilateral activation of the hippocampus and parahippocampal gyrus during eight platform trials compared to rest in the control group.

Table 42 Significant activations of the hippocampus during 8 platform trials compared to rest in the control group (small volume corrected)

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x, y, z
Hippocampus (L)		16	3.68	-22 -22 -7
Hippocampus (R)		12	3.45	24 -24 -6

All regions are reported p < 0.05 small volume corrected. L = left hemisphere, R = right hemisphere.
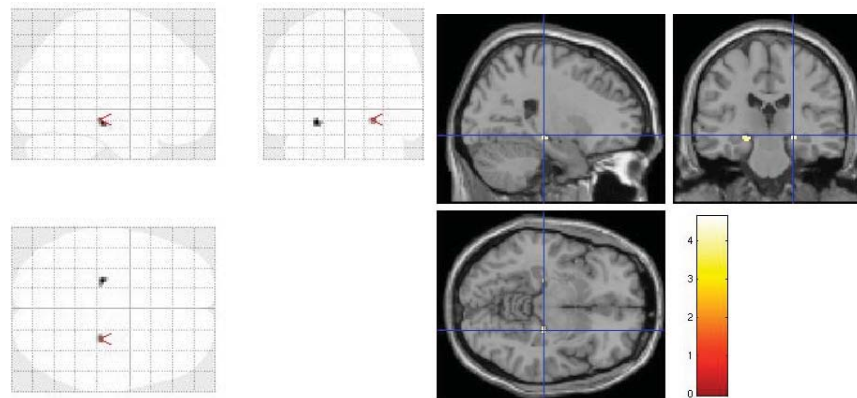
Figure 52 Significant hippocampal activations during eight platform trials compared to rest in average schizotypy (small volume corrected)

Table 43 Significant activations in the parahippocampus during eight platform trials compared to rest in the control group (small volume corrected)

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x,y,z
Parahippocampus (R)	36	72	3.90	26 -37 -8
Parahippocampus (L)	19	7	3.53	-32 -43 -6

All regions are reported p < 0.05 small volume corrected. L = left hemisphere, R = right hemisphere.
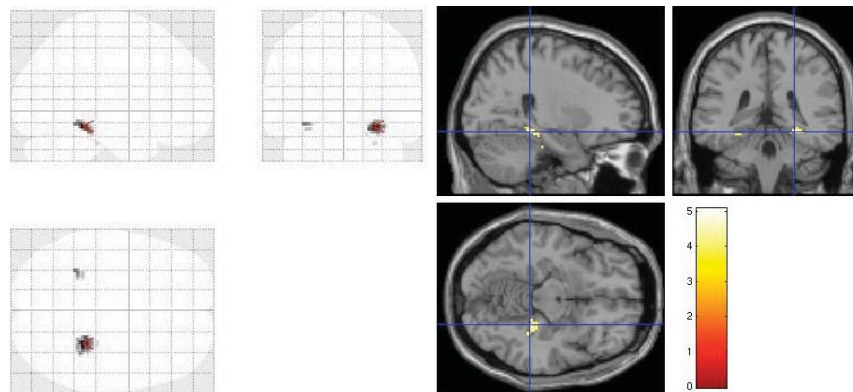
Figure 53 Significant hippocampal activations during eight platform trials compared to rest in average schizotypy (small volume corrected)

8.4.4.1.2   High Schizotypy

<u>Four Platforms</u>

Activation was observed in the 4 platform condition compared to rest in the high schizotypy group in the bilateral cerebellum, left occipital gyrus, right middle frontal gyrus, bilateral inferior frontal gyrus, left precuneus and right superior parietal lobule, left thalamus and left superior temporal gyrus, family wise error corrected for multiple comparisons

Table 44 Significant activations during four platform trials contrasted to rest in the high schizotypy group.

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x,y,z
Cerebellum (R)		4097	6.65	38 -42 -30
Inferior Occipital Gyrus (L)	18	986	6.64	-26 -91 -4
Middle Frontal Gyrus (R)	6	818	6.63	30 -3 52
Cerebellum (L)		503	6.60	-26 -44 -20
Parietal Lobe (L)	3	3592	6.47	-42 -25 53
Middle Frontal Gyrus (R)	9	106	6.09	44 33 30
Inferior Frontal Gyrus (R)	9	128	5.91	59 9 27
Inferior Frontal Gyrus (L)	9	199	5.81	-46 7 22
Precuneus (L)	19	201	5.78	-22 -78 41
Thalamus (L)		329	5.69	-20 -20 -2
Superior Parietal Lobule (R)	7	1116	5.68	18 -67 55
Cerebellum (L)		130	5.59	-6 -74 -11
Superior Frontal Gyrus (L)	6	288	5.49	-2 6 46
Cerebellum (L)	113	113	5.44	-28 -72 -12

All regions reported at the $p < 0.05$ FWE corrected level. L = left hemisphere, R = right hemisphere.
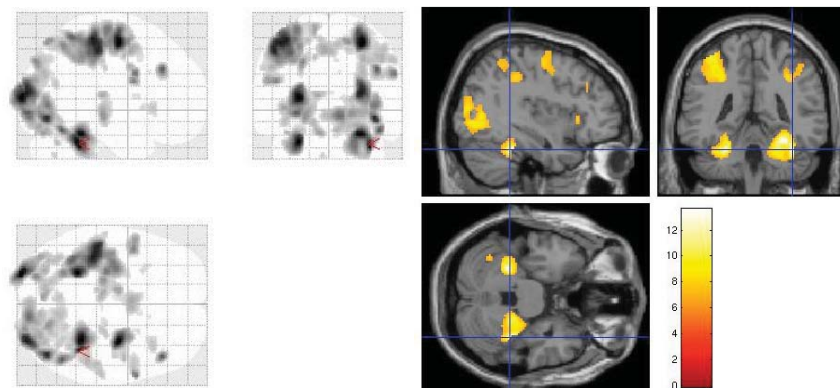
Figure 54 Significant activations during four platform trials compared to rest in the high schizotypy group

Lowering the threshold to a less conservative level of $p < 0.001$ uncorrected revealed additional activations in the left insula, right middle frontal gyrus, right caudate and right middle frontal gyrus in the high schizotypy group during 4 platforms compared to rest.

Table 45 Uncorrected activations during 4 platform trials compared to rest in the high schizotypy group.

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x,y,z
Insula (L)	13	91	3.75	-46 -21 14
Middle Frontal Gyrus (L)	10	63	3.66	-30 41 11
Caudate (R)		9	3.32	18 1 26
Middle Frontal Gyrus (R)	9	13	3.27	-34 33 32
Cingulate Gyrus (R)	24	1	3.10	10 1 29
Cingulate Gyrus (L)	24	1	3.09	-10 15 25

All regions are reported at the p < 0.001 uncorrected level. L = left hemisphere, R = right hemisphere.
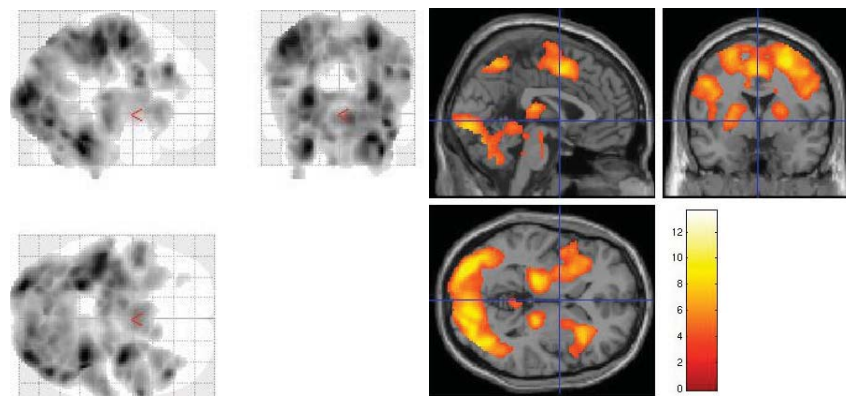
Figure 55 Uncorrected activations during four platform trials compared to rest in the high schizotypy group

Applying a small volume correction using the WFUpickatlas (see methods section for details) revealed bilateral hippocampal and parahippocampal activation during 4 platform trials compared to rest in the high schizotypy group.

Table 46 Significant hippocampal activations during four platform trials compared to rest in the high schizotypy group (small volume corrected)

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x,y,z
Hippocampus (R)		165	5.11	24 -20 -9
Hippocampus (L)		139	4.87	-22 -22 -10

All regions are reported p < 0.05 small volume corrected. L = left hemisphere, R = right hemisphere.
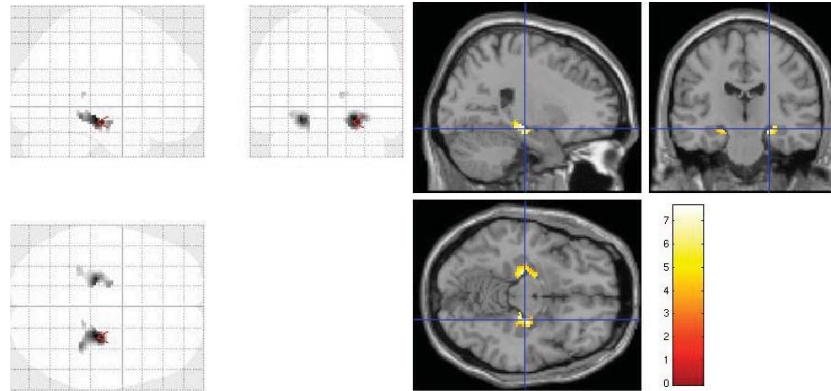
Figure 56 Significant hippocampal activations during four platform trials compared to rest in the high schizotypy group (small volume corrected)

Table 47 Significant activations in the parahippocampus during 4 platforms contrasted to rest in the high schizotypy group (small volume corrected)

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates
Parahippocampus (R)	36	417	5.36	30 -37 -8
Parahippocampus (L)	36	175	4.63	-26 -37 -10

All regions are reported p < 0.05 small volume corrected. L = left hemisphere, R = right hemisphere.
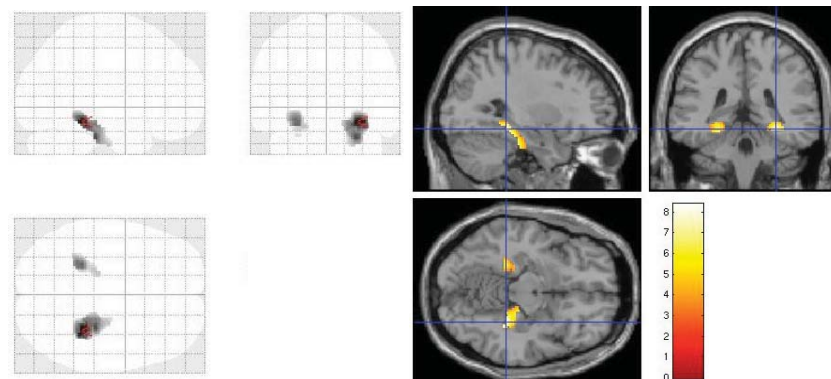
Figure 57 Significant parahippocampal activations during four platform trials compared to rest in the high schizotypy group (small volume corrected)

Six Platforms

Activations were observed in bilateral middle occipital gyrus, bilateral medial frontal gyrus,

bilateral cerebellum, bilateral precuneus and bilateral fusiform gyrus in the high schizotypy

group when contrasting four platform trials to rest, corrected for multiple comparisons.

Table 48 Significant activations during six platform trials compared to rest in the high schizotypy group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x, y and z
Middle Occipital Gyrus	18	649	5.70	-24 92 21
Precuneus	7	190	5.59	-22 -82 40
Middle Occipital Gyrus	19	1310	5.57	28 -91 16
Middle Frontal Gyrus	6	370	5.53	30 -3 50
Cerebellum		106	5.36	-4 -65 -25
Cerebellum		193	5.32	26 -40 -15
Middle Frontal Gyrus	6	929	5.25	-26 -5 46
Fusiform Gyrus	19	37	5.25	-28 -74 -11
Cerebellum		129	5.18	-32 -46 -21
Superior Parietal Lobule	7	136	5.10	16 -67 55
Middle Frontal Gyrus	9	19	5.09	44 32 28
Cerebellum		18	4.99	32 -61 -10
Fusiform Gyrus	37	9	4.95	48 -59 -7
Medial Frontal Gyrus	6	10	4.94	-8 6 49
Inferior Frontal Gyrus	19	20	4.93	40 -72 -1
Parietal Lobe	2	6	4.86	50 -23 47

All regions reported at p < 0.05 FWE corrected. L = left hemisphere, R = right hemisphere.
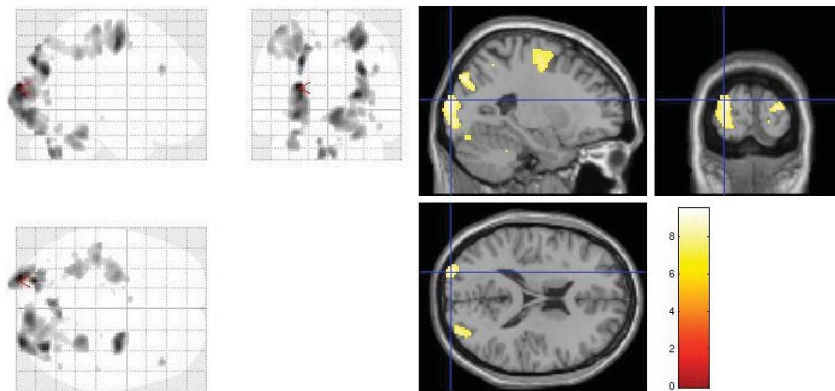
Figure 58 Significant activations during six platform trials compared to rest in high schizotypy

Lowering the threshold to p < 0.001 uncorrected revealed activation in the bilateral frontal gyrus and bilateral cingulate gyrus in the high schizotypy group when comparing six platform trials to rest, corrected for multiple comparisons

Table 49 Uncorrected activations during the 6 platform trials compared to rest in the high schizotypy group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x, y, z
Insula	13	473	4.60	28 27 2
Middle Frontal Gyrus	10	69	3.72	34 44 18
Middle Frontal Gyrus	10	64	3.53	-30 39 11
Cingulate Gyrus	32	16	3.48	10 21 30
Middle Frontal Gyrus	9	16	3.45	-36 33 33
Cingulate Gyrus	32	16	3.40	26 42 10

All regions reported at p < 0.001 uncorrected. L = left hemisphere, R = right hemisphere.
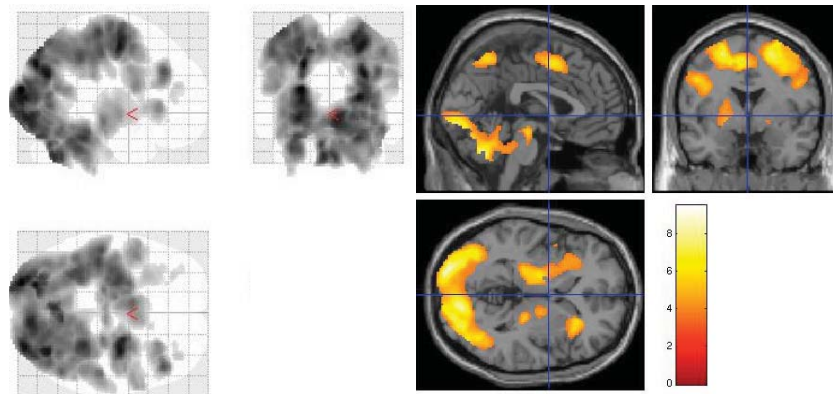
Figure 59 Uncorrected activations during six platform trials compared to rest in high schizotypy

Applying a small volume correction using WFUpickatlas (see methods section) revealed bilateral hippocampal activation during 6 platform trials compared to rest in the high schizotypy group (presented in Table 50 and Figure 60).

Table 50 Significant hippocampal activations during 6 platform trials compared to rest in the high schizotypy group (small volume corrected)

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x,y,z
Hippocampus (R)		119	4.65	24 -22 -7
Hippocampus (L)		75	4.10	-18 -24 -7

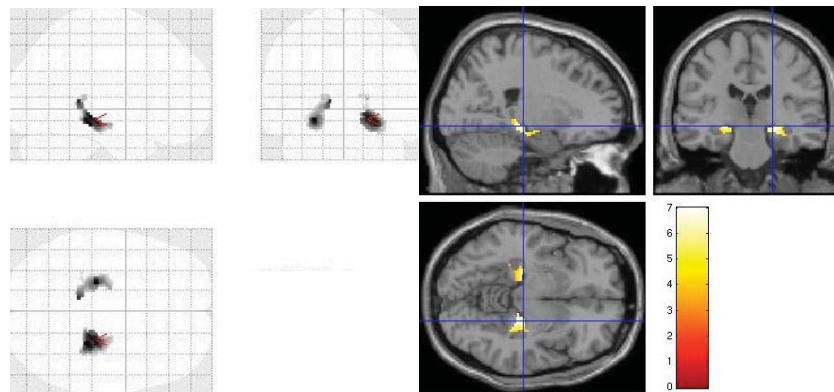All regions are reported p < 0.05 small volume corrected. L = left hemisphere, R = right hemisphere.
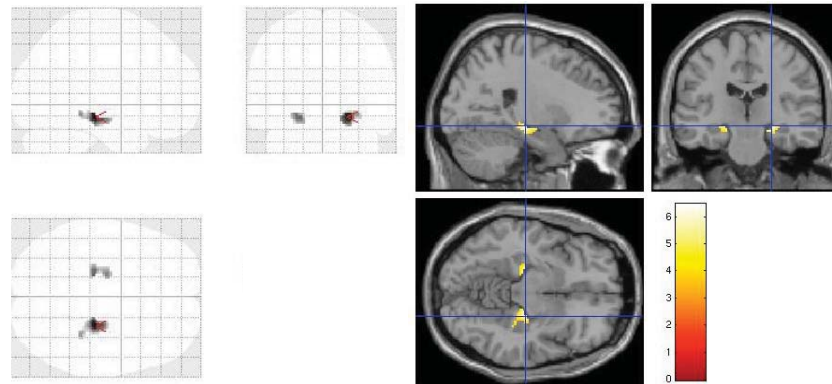
Figure 60 Significant hippocampal activations during six platform trials compared to rest in the high schizotypy group (small volume corrected)

Small volume correction revealed significant activations in the parahippocampus during six platform trials compared to rest in the high schizotypy group which are shown in Table 51 and Figure 61.

Table 51 Significant activations in the parahippocampus during 6 platform trials compared to rest in the high schizotypy group (small volume corrected)

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x,y,z
Parahippocampus (R)	36	312	4.86	30 -37 -8
Parahippocampus (L)	36	83	4.06	-26 -37 -10

All regions are reported small volume corrected. L = left hemisphere, R = right hemisphere.
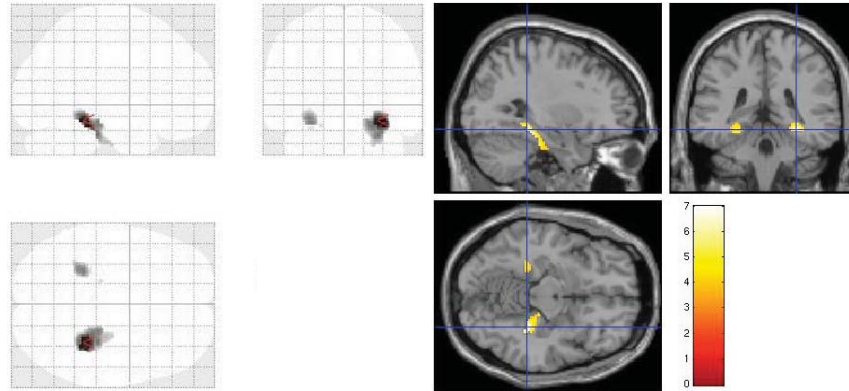
Figure 61 Significant parahippocampal activations during six platform trials compared to rest in the high schizotypy group (small volume corrected)

Eight Platforms

Activation was observed during the 8 platform trials compared to rest in the high schizotypy group in bilateral middle occipital gyrus, bilateral precuneus, left fusiform gyrus, bilateral medial frontal gyrus, left inferior parietal lobule, bilateral cerebellum and right parahippocampus, family wise error corrected for multiple comparisons.

Table 52 Significant activations during 8 platform trials compared to rest in the high schizotypy group

Region	BA Equivalent	Cluster Size	Z Score	Maximum Coordinates x,y,z
Middle Occipital Gyrus (R)	19	1739	5.78	30 -87 15
Precuneus (L)	19	134	5.63	-24 -81 43
Middle Occipital Gyrus (L)	19	662	5.53	-28 -90 18
Temporal Lobe (L)	37	131	5.51	-30 -47 -14
Medial Frontal Gyrus (R)	6	238	5.50	26 -5 48
Inferior Parietal Lobule (L)	40	1008	5.42	-48 -29 49
Cerebellum		44	5.36	-4 -67 -19
Precuneus (R)	7	76	5.26	16 -65 55
Fusiform Gyrus (L)	37	87	5.13	-40 -59 -7
Medial Frontal Gyrus (L)	6	55	5.04	-6 6 48
Parietal Lobe (R)	2	2	4.85	51 -21 47
Parahippocampus (R)	28	4	4.84	24 -20 -7
Cerebellum (R)		1	4.79	2 -61 -24

All regions reported at the p < 0.05 FWE corrected level. L = left hemisphere, R = right hemisphere.
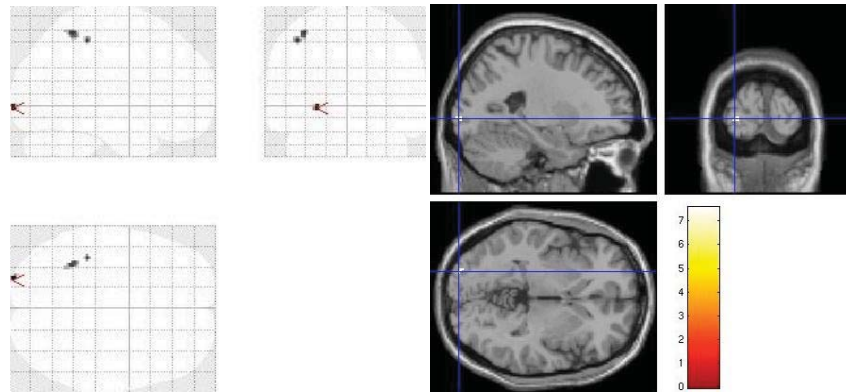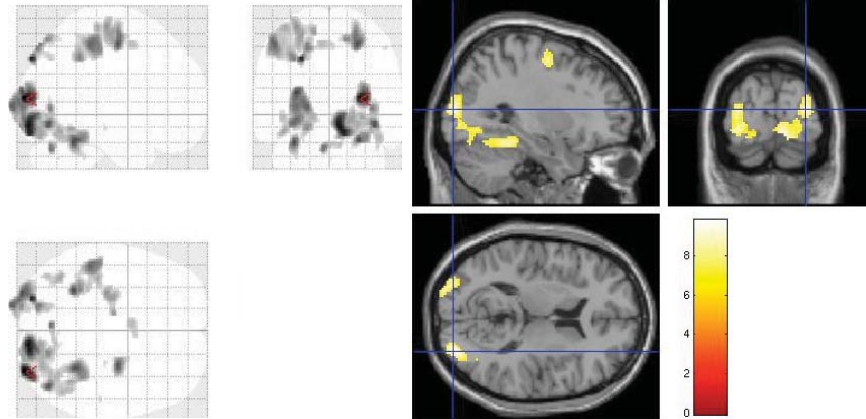
Figure 62 Significant activations during the eight platform trials compared to rest in the high schizotypy group

Lowering the threshold to a less conservative p < 0.001 uncorrected revealed activations in the right middle frontal gyrus, left thalamus, right caudate, right insula and left inferior frontal gyrus in the high schizotypy group during eight platform trials compared to rest.

Table 53 Uncorrected activations during the 8 platform trials compared to rest in the high schizotypy group.

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates
Middle Frontal Gyrus (R)	46	510	4.73	42 34 24
Thalamus (L)		1124	4.62	-20 -21 -2
Caudate (R)		83	4.30	16 -12 26
Insula (R)	13	236	4.29	26 27 2
Inferior Frontal Gyrus (L)	9	248	3.73	-44 7 24

All regions reported at p < 0.001 uncorrected. L = left hemisphere, R = right hemisphere.
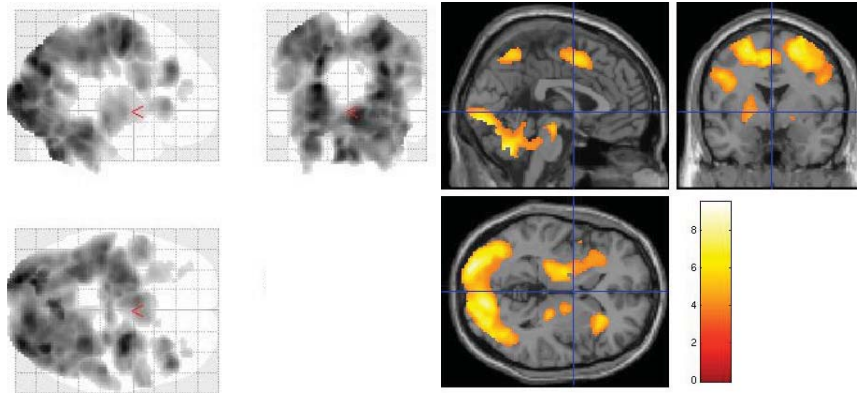
Figure 63Uncorrected activations during eight platform trials compared to rest in the high schizotypy group

Applying a small volume correction revealed bilateral activation of the hippocampus and parahippocampal gyrus in eight platform trials compared to rest in the high schizotypy group.
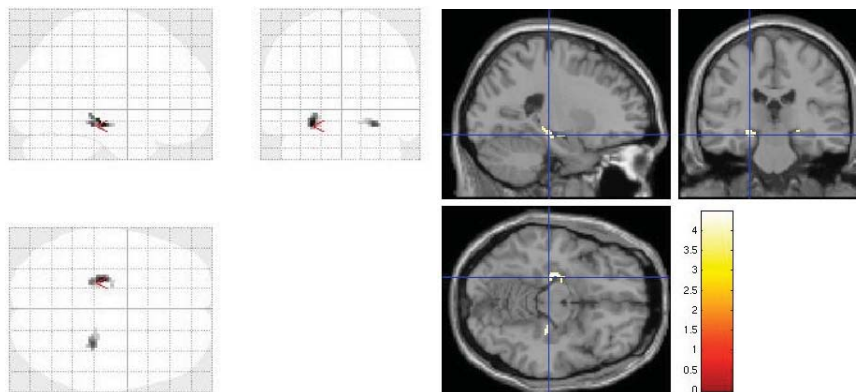
Table 54 Significant hippocampal activations during 8 platform trials compared to rest in the high schizotypy group (small volume corrected)

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates
Hippocampus (R)		94	4.76	26 -20 -9
Hippocampus (L)		37	3.86	-22 -24 -6

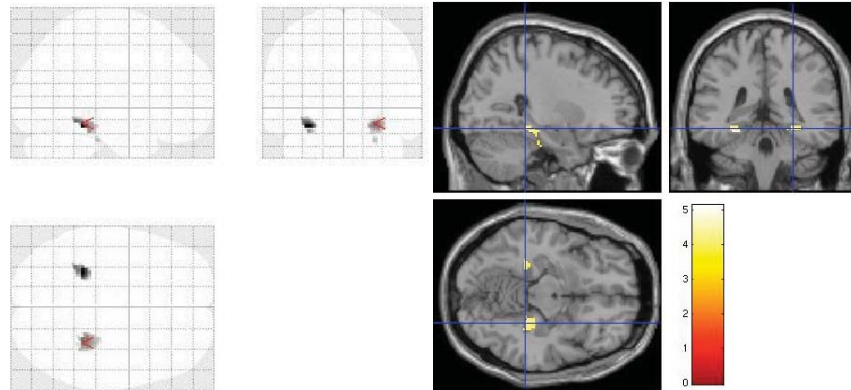All regions are reported p < 0.05 small volume corrected. L = left hemisphere, R = right hemisphere.

Table 55 Significant parahippocampal activations during 8 platform trials compared to rest in the high schizotypy group (small volume corrected)

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates
Parahippocampus (R)	36	249	4.97	32 -37 -7
Parahippocampus (L)	36	69	4.34	-26 -37 -10

All regions are reported p < 0.05 small volume corrected. L = left hemisphere, R = right hemisphere.
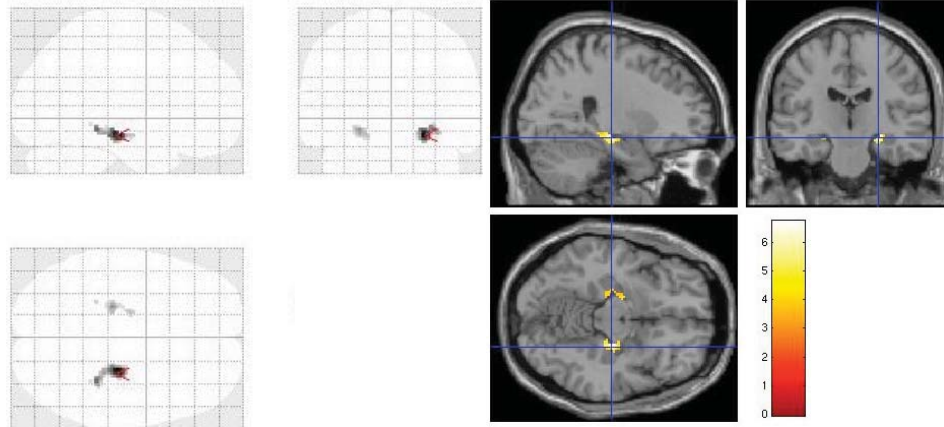
Figure 64 Significant hippocampal activations during eight platform trials compared to rest in the high schizotypy group (small volume corrected)
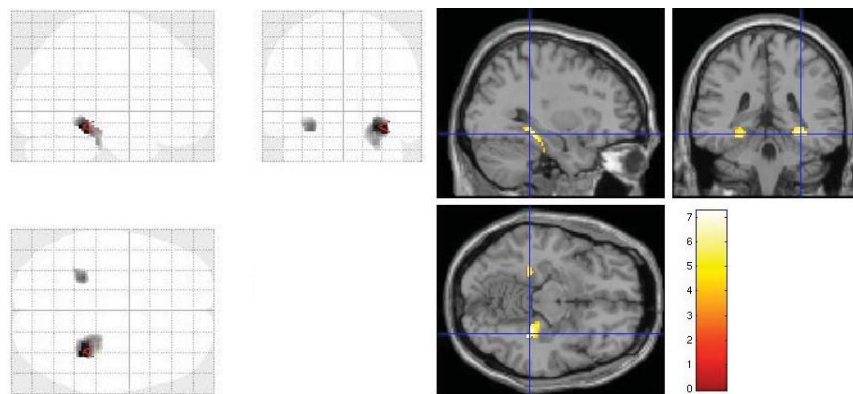
Figure 65 Significant parahippocampal activations during eight platform trials compared to rest in the high schizotypy group (small volume corrected)

8.4.4.2 Group Differences

There were no significant differences in functional activation between the two groups corrected for multiple comparisons. Lowering the threshold to p < 0.001 uncorrected revealed functional differences in the superior frontal gyrus and parietal lobes.

Contrasting four platform trials to rest revealed decreased activation in the right superior frontal gyrus (BA9) and increased activation bilaterally in the parietal lobes (BA3/BA40) in the high schizotypy group compared to the control group.

Table 56 Regions of differential activation between the control and high schizotypy groups during four platform trials compared to rest

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x,y,z
Decreased activation in high schizotypy compared to controls				
Superior Frontal Gyrus (R)	9	10	3.44	18 44 35
Increased activation in high schizotypy compared to controls				
Parietal Lobe (L)	3	14	3.60	-61 -16 32
Parietal Lobe (R)	40	6	3.37	59 -27 51

All regions are reported at the $p < 0.001$ uncorrected level. L = left hemisphere, R = right hemisphere.
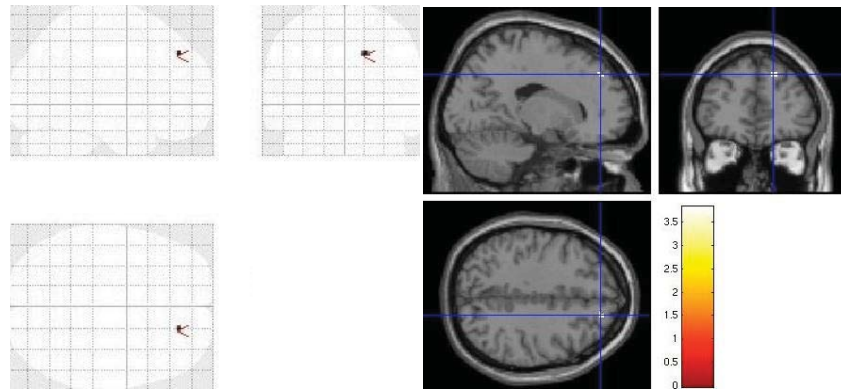
Figure 66 Decreased activation in the superior frontal gyrus in high schizotypy compared to controls during eight platform trials
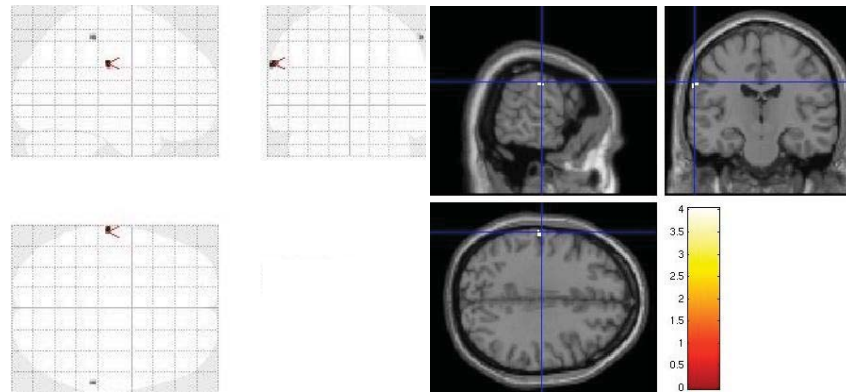
Figure 67 Increased activation of the parietal lobes in high schizotypy compared to controls during four platform trials

No significant differences in functional activation were observed when contrasting six back to rest. Contrasting eight platform trials to rest revealed decreased activation of the right cuneus and increased activation bilaterally of the anterior cingulate gyrus in high schizotypy compared to controls.

Table 57 Regions of differential activation between the control and high schizotypy groups during eight platform trials compared to rest

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates (x, y, z)
Decreased activation in high schizotypy compared to control subjects				
Cuneus (R)	19	16	3.39	6 -90 28
Increased activation in high schizotypy compared to control subjects				
Cingulate Gyrus (L)	24	45	3.64	-18 -16 36
Cingulate Gyrus (R)	24	11	3.32	16 -4 38

All regions are reported p <0.001 uncorrected. L = left hemisphere, R = right hemisphere.
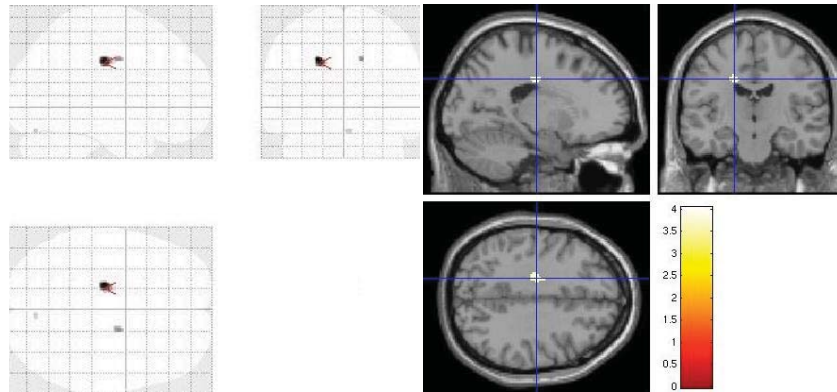
Figure 68 Increased activation in the anterior cingulate cortex bilaterally in high schizotypy compared to controls during 8 platform trials compared to rest

8.4.4.3   Parametric Modulation

A parametric modulation analysis was used to investigate increases and decreases in functional activation as spatial memory load increases.

<u>Control Group</u>

No significant increases in activation were observed as spatial memory load increased in either the control or the high schizotypy group. Lowering the threshold to $p < 0.001$ uncorrected, still did not reveal increases in activation as memory load increased.

Several brain regions demonstrated decreased activation as spatial memory load increased in the control group (see Table 58) including the right anterior cingulate gyrus, bilateral insula, and bilateral middle frontal gyrus, left superior temporal gyrus, bilateral parietal regions, left cerebellum and left cuneus.

Table 58 Brain areas with increased and decreased activation as spatial memory load increases from 4 to 8 platforms in the control group

Regions	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x, y, z
Regions with increased activation with increasing spatial memory load				
None				
Regions with decreased activation with increasing spatial memory load				
Anterior Cingulate (R)	24	8956	5.17	6 1 29
Inferior Parietal Lobule (L)	40	222	4.37	-36 -53 34
Insula (L)	13	432	4.10	-51 -21 14
Insula (R)	13	292	3.99	42 -28 18
Lingual Gyrus (R)	17	168	3.92	2 -89 3
Precentral Gyrus (R)	4	184	3.83	32 -25 53
Postcentral Gyrus (L)	3	128	3.80	-26 -34 55
Cingulate Gyrus (R)	32	21	3.79	10 21 28
Parietal Lobe (R)	39	212	3.67	36 -64 38
Superior Temporal Gyrus (L)	40	27	3.66	-51 -44 21
Precentral Gyrus (L)	4	45	3.58	-53 -10 34
Middle Frontal Gyrus (R)	46	19	3.56	48 43 7
Postcentral Gyrus (L)	2	28	3.55	-38 -30 29
Middle Frontal Gyrus (R)	8	26	3.50	46 10 42
Middle Frontal Gyrus (L)	9	29	3.48	-32 27 35
Cerebellum (R)		40	3.48	2 -66 -8
Cuneus (L)	19	40	3.44	-16 -84 30
Cuneus (L)	18	14	3.43	-16 -79 21

All regions reported $p < 0.001$ uncorrected. L = left hemisphere. R = right hemisphere

High Schizotypy

No increases in brain activation were observed as spatial memory load increased in average schizotypes at a threshold of $p < 0.001$ uncorrected. Several brain regions demonstrated decreased activation as spatial memory load increased in the high schizotypy group including bilateral superior temporal gyrus, right hippocampus, right parahippocampus, left cuneus, left lingual gyrus, left middle frontal gyrus, left fusiform gyrus and right inferior parietal lobe. These results are presented in Table 59.

Table 59 Brain areas with increased and decreased activation as spatial memory load increases from 4 to 8 platforms in the high schizotypy group

Regions	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x, y and z
Regions with increased activation with increasing spatial memory load				
None				
Regions with decreased activation with increasing spatial memory load				
Superior Temporal Gyrus (L)	22	710	5.35	-46 -37 2
Hippocampus (R)		36	4.23	32 -18 -10
Cuneus (L)	19	47	3.94	-14 -88 6
Cerebellum (L)		38	3.85	-2 -38 -32
Parahippocampus (R)	35	19	3.79	24 -17 -29
Cerebellum (L)		58	3.74	-40 -59 -21
Superior Frontal Gyrus (R)	6	73	3.68	0 11 58
Lingual Gyrus (R)	19	102	3.64	18 -41 -1
Superior Temporal Gyrus (R)	38	19	3.59	46 15 -13
Superior Temporal Gyrus (R)	22	42	3.45	48 -42 8
Cerebellum (L)		11	3.39	-8 -49 -6
Middle Frontal Gyrus (L)	6	11	3.37	-48 4 44
Inferior Parietal Lobule (R)	40	11	3.35	40 -47 41
Fusiform Gyrus (L)	37	30	3.35	-24 -55 -9

All regions are reported $p < 0.001$ uncorrected. L = left hemisphere, R = right hemisphere.

8.4.4.4   Performance Correlations

8.4.4.4.1   Relationship between hippocampal function and performance

As the left and right hippocampus is thought to be involved in allocentric spatial memory and performance on spatial navigation tasks (see Chapter 4) the relationship between activation of this region and performance was investigated. Previous studies have highlighted that the relationship between activation of the hippocampus and performance of these tasks is different in patients with schizophrenia compared to controls (Folley et al, 2010).

In order to investigate the relationship between hippocampal functioning and performance in controls and high schizotypes, correlational analysis was performed using the beta estimates derived from the individual group maps using independently derived ROIs (see methods above and in previous chapter).

No correlations between hippocampal activity and performance (between search errors or time to complete trials) were observed in either controls or high schizotypy groups for four or eight platforms. Few subjects made within search errors so this dependent variable was not included in this analysis.

At six platforms a negative relationship emerged between hippocampal activity and between search errors (r = .416, df 18, p = 0.043, one tailed) in average schizotypes indicating better performance (fewer errors made) is associated with greater hippocampal BOLD signal (see Figure 71). There was no relationship between hippocampal activity at six platforms and performance in high schizotypy (r = .164, df = 20, p = .245, one tailed).
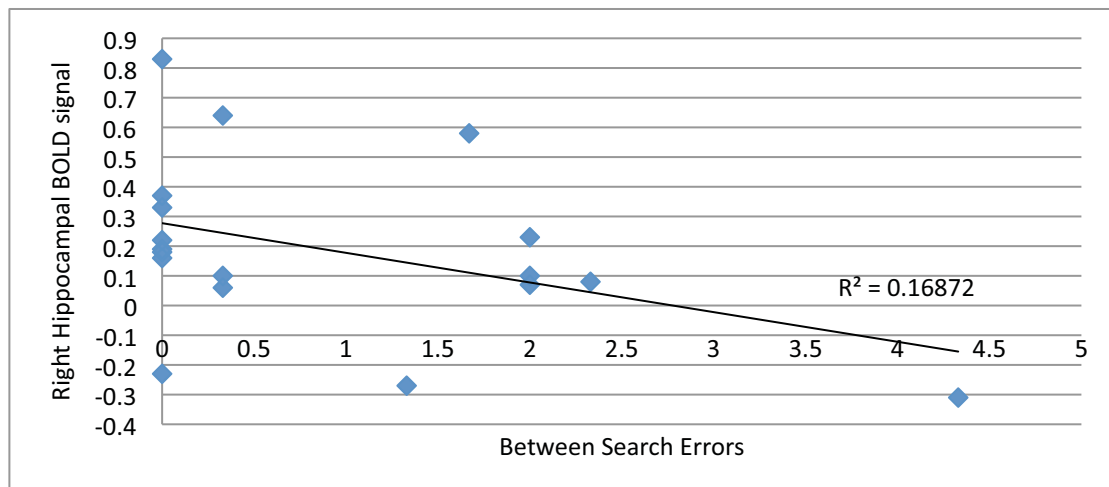
Figure 69 The relationship between performance (between search errors) and right hippocampal BOLD signal in the control group

8.5 Discussion

8.5.1 Summary of results

There were no behavioural differences between groups on reaction time or accuracy in four, six or eight platform trials. Subjects made very few within or between search errors on the task regardless of schizotypy group. Functional imaging revealed a pattern of activation consistent with a spatial memory network including activation of the hippocampus and parahippocampal gyrus, parietal lobes, prefrontal cortex, cingulate gyrus, striatum and thalamus. No differences were observed in the hippocampus or parahippocampal gyrus, however high schizotypy was associated with lower activation of the right superior frontal gyrus (BA9) and increased activation of the parietal lobes bilaterally (BA3 and BA40) during four platform trials. During eight platform trials, high schizotypy was associated with increased activation of the anterior cingulate gyrus bilaterally. However, none of these activation differences survived correction for multiple comparisons. Investigations into the relationship between performance and hippocampal activation revealed a significant relationship between hippocampal activation and between search errors during six platforms in the control group. The direction of the correlation indicated that increased hippocampal activation is associated with fewer between search errors. This relationship was absent in high schizotypy. Further, no relationship between hippocampal activation and performance was observed at four or eight platforms in either group. The association between six platforms and behaviour may reflect the increased task demands at this level compared to four platform trials but six platform trials are less demanding than eight platforms when performance begins to break down. No regions demonstrated increased activation as spatial memory load increased but decreases were observed. The average group demonstrated deactivations in the right anterior cingulate, left inferior parietal lobule, bilateral insula, bilateral middle frontal gyrus, left superior temporal gyrus bilateral precentral and

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postcentral gyrus, left lingual gyrus, right cerebellum and bilateral cuneus. The high group meanwhile had decreased activation of the bilateral superior temporal gyrus, right hippocampus, right parahippocampus, left cuneus, right superior frontal gyrus, left middle frontal gyrus, right inferior frontal gyrus and left fusiform gyrus.

8.5.2   Behavioural Data

There were no behavioural differences between groups on reaction time or accuracy. The accuracy of both groups was good with few within or between search errors made across platform trials. However, to date there is no published literature using this task. Further studies will be necessary to determine what the average level of performance is on this task across different populations.

As with the Arena Task discussed in the preceding chapter subjects were extensively trained on this task and this may have masked cognitive difficulties in the high schizotypy group as well as the fact that the high schizotypes were free from confounding factors such as lower IQ, lower educational status and substance and alcohol use. This is advantageous for assessing functional differences in the absence of performance confounds and allows us to assess if functional compensation in neural regions may lessen the cognitive deficits observed in this group.

8.5.3   Task related activations across groups

Functional MRI revealed BOLD activation consistent with performance on a VR radial arm maze including activation of the parietal cortex, premotor and motor cortices, medial prefrontal cortex (Iaria et al, 2003) inferior and superior frontal gyrus and fusiform gyrus (Astur et al, 2005). We also observed hippocampal and parahippocampal activation in both groups. This is in contrast to what Astur et al (2005) who reported deactivation of the anterior cingulate, hippocampus and parahippocampus during a VR radial arm maze. This likely reflects the

different task design; the platform task is designed to control strategy use (see introduction and methods of this chapter) and encourage allocentric spatial processing. Without experimental control of strategy use a lack of hippocampal/parahippocampal activation may reflect an increased use of stimulus response strategies. This is what is observed in the Iaria and colleagues studies (Iaria et al, 2003; Bohbot et al, 2004) whereby subjects can choose either strategy and this is related to the degree to which they recruit the hippocampus or caudate nucleus. Marsh (2010) also imposed constraints on strategy use and observed parahippocampal activation. Caudate activity was also observed during performance and this has been linked to stimulus response strategies on VR radial arm mazes (e.g. Iaria et al, 2003) which may suggest that some subjects used a non-spatial strategy in performing the platform task. However, the caudate nucleus has also been observed as active in rewarded spatial learning trials (Marsh et al, 2010) suggesting that caudate activity in this task could be related to reception of feedback as platforms are selected. In support of this explanation increased activation of the striatum generally (Ullsperger & Cramon, 2003) and caudate specifically (Tricomi, 2006) has been associated with positive and negative feedback. Alternatively, it may be inevitable that all subjects will activate a spatial network of regions associated with both allocentric and egocentric spatial memory as the demands of the task may require allocentric representations to be recoded into an egocentric frame of reference in order to navigate the environment successfully. It has also been demonstrated that speed of navigation is related to caudate activity in spatial memory tasks perhaps reflecting a neural substrate of reconciling spatial information with efficient movement towards a goal (Maguire et al, 1998).

8.5.4   Group comparisons

There were no significant differences in BOLD activation between the two groups at $p < 0.05$ corrected for multiple comparisons. Dropping the threshold to $p < 0.001$ uncorrected revealed

small group differences at 4 platform trials and 8 platform trials. Controls had increased activation in the dorsolateral prefrontal cortex during 4 platform trials compared to high schizotypes whilst high schizotypes had increased activation in the parietal lobes compared to average schizotypes. The dorsolateral prefrontal cortex has been linked to selecting appropriate strategies in spatial memory tasks and its lower activation in high schizotypy may reflect less consideration regarding adoption of a particular strategy. High schizotypes may, instead of deliberating on which strategy/frame of reference to use, immediately adopt a particular strategy. Increased activation in the parietal lobes in high schizotypes may reflect an early attempt to adopt an egocentric spatial strategy perhaps by counting platforms or trying to code the platforms in regard to their bodily position. Four platform trials are relatively easy and thus an egocentric spatial strategy may be sufficient to complete these trials. However, both groups evinced strong hippocampal activation at 4 platforms suggesting that an allocentric spatial reference frame was used at this early trial stage.

Differences were also observed at the 8 platform stage but again these differences did not survive correction for multiple comparisons. High schizotypes had increased activation of the anterior cingulate gyrus bilaterally compared to average schizotypes. This suggests increased cognitive effort and cognitive control in high schizotypes as the task becomes more challenging. Further, it suggests that high schizotypes are responding more to the conflict between platform choices and exerting a high degree of performance monitoring to complete the task. Although no significant differences were found in reaction time, the data suggests that high schizotypes took longer to complete each set of trials; this may be the result of taking longer to deliberate between conflicting platform choices. Alternatively, the anterior cingulate cortex may be hyperactive due to its role in suppressing competing information from earlier trials or earlier platform choices. If this information cannot be inhibited successfully, remembering platform choices during a trial may be confused with earlier platform trials and thus more errors will be

made. The anterior cingulate gyrus may be working harder to inhibit this information in high schizotypes; in line with this hypothesis schizotypy has been associated with impairments in inhibition (see introductory chapter 2). In the Astur et al (2005) study on the neural correlates of radial arm maze performance a deactivation of the anterior cingulate gyrus was observed. We also observed a deactivation of the anterior cingulate gyrus as spatial memory load increased in the control group but not the high group. Although no increase in anterior cingulate function was observed linearly with increasing memory load; increased activation of this region was observed in high schizotypy at 8 platforms.

No differences were observed between average and high schizotypy in the medial temporal lobes as hypothesised. Both groups activated the hippocampus and parahippocampal gyrus at all three levels of the task consistent with an allocentric spatial memory task. This may be due to the overall memory component of this task. In the Arena Task presented earlier, schizotypy groups differed in activation of the hippocampus at encoding and retrieval with a complex pattern of hypo- and hyperactivation. A spatial memory task such as the platform may not elicit group differences in hippocampal recruitment as the fine-grained distinctions between memory processes for example encoding, maintenance and retrieval are not delineated. Rather than being across the board dysfunctional it would appear that the hippocampus is aberrantly recruited by high schizotypes during encoding and retrieval processes; this may be obscured by a memory task that does not examine the underlying sub-components of spatial memory. Of interest however, hippocampal activation was associated with better performance on the six platform levels of the task in controls but not in the high schizotypy group. This was also demonstrated in the Arena Task where there was a decoupling between task relevant activation of the hippocampus and performance.

8.5.4   Methodological considerations

Whilst every effort was taken to ensure that subjects were restricted to adoption of an allocentric spatial memory strategy subjects could have used a variety of strategies to complete this task. Although strong activation was observed in the hippocampus and parahippocampal gyrus in this task across groups, parietal and caudate nuclei activity was also observed and increased activation of the parietal cortex bilaterally in high schizotypy. Caudate nuclei activity has been associated with the adoption of non-spatial strategies in previous radial arm mazes when subjects can adopt either a spatial or non-spatial strategy to complete the task. However, unlike the tasks used in those studies we have imposed constraints in the task design that encourage subjects to adopt an allocentric spatial strategy to complete the task. Although this does not completely rule out a participant adopting a particular strategy, we would expect this to be reflected in poorer performance such as longer times to complete each set of trials or an increase in errors made. This study would have been greatly strengthened by verbally recording participant's choice of strategy post scanning. This would have answered questions about the potential choice of strategy and could have been included in the analysis. This could be addressed by comparing functional activation between groups on an egocentric and allocentric version of the same task; thus elucidating the neural correlates that underpin spatial memory generally, those that are specific to either type of spatial reference type and how these might differ in schizotypy.

Further, although FWE correction for multiple comparisons was applied to the imaging analysis conducted on this task, which controls the number of false positives present in the SPM maps, several analyses were conducted on the same experiment as there are three levels of the task and the analyses was performed in two groups. It is therefore not strictly true to describe each analysis as upholding the FWE whole brain correction and thus results must be viewed with this in mind.

8.5.5 Conclusions

To conclude, this study validated the Platform task as a measure of allocentric spatial memory and activated the hippocampus and parahippocampal gyrus, frontal regions, parietal cortex, occipital lobe, striatum and motor cortex; regions known to be involved in spatial learning and memory. Small group differences were observed in the dorso-lateral prefrontal cortex, parietal lobes and anterior cingulate but these did not reach statistical significance when corrected for multiple comparisons. Neither of the two allocentric spatial memory tasks used so far has elicited group differences in behavioural measures. As allocentric spatial memory tasks have not been explored to date in schizotypal personality the n-back task was included as a measure of general cognitive ability and attentional capacity. These results will now be reported in chapter 9.

Chapter 9: Functional Imaging Results – N-back Task

In this chapter, experimental results will be presented obtained using the N-back task. In Chapter 2 and 3, attention, executive function and working memory in schizophrenia and schizotypal personality were discussed therefore this chapter will focus mainly on the current results and previous literature on the N-back.

9.1   Introduction

To recap, working memory is described in several ways: as a cognitive system for the temporary storage and manipulation of remembered information (e.g. Heckers, 2001) and more specifically as the process by which a remembered stimulus is held "online" to guide behaviour in the absence of external cues or prompts (Goldman-Rakic, 1995). It is generally agreed that it comprises a fundamental set of processes and is an integral component of many cognitive operations, from complex decision making to selective attention (Owen, McMillan, Laird, & Bullmore, 2005).

The N-back task has become synonymous with working memory function and is commonly employed to investigate the neural basis of working memory processes. Typically, it involves monitoring a series of letters or numbers and responding whenever a stimuli is presented that is the same as one presented *n* previously, where *n* is a prespecified integer, using 1, 2 or 3 (Owen, et al., 2005). It taps cognitive processes associated with monitoring, updating and manipulation of information. Load is varied ranging from 1 back to 3 back with some researchers employing parametric designs and some comparing any or all of these conditions against 0 back (a condition that does not require working memory and is a measure of attention). Stimuli can be varied and typically is verbal (e.g. letters or words) or non-verbal (e.g. faces, shapes, pictures).

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For the rest of this review the focus will be on results using the verbal stimulus as this type of stimulus was employed in this thesis.

A meta-analysis by Owen et al (2005) has demonstrated that the N-back robustly activates a network of regions including bilateral and medial posterior parietal cortex (BA7/40), bilateral premotor cortex (BA6/8), dorsal cingulate/medial premotor cortex including supplementary motor area (SMA), bilateral frontal pole (BA10), bilateral dorsolateral prefrontal cortex (BA9/46), bilateral mid-ventrolateral prefrontal cortex or frontal operculum (BA45/47), medial and lateral cerebellum and thalamus. The dorsolateral prefrontal cortex has been implicated in numerous cognitive functions that are relevant to the N-back task, amongst others, including monitoring and manipulation of information within working memory (e.g. Owen, 1997) response selection (e.g. Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000) and implementation of strategies to facilitate organisation of material before encoding (e.g. Fletcher, Shallice, & Dolan, 1998). The mid-ventrolateral prefrontal cortex (BA45/47) meanwhile is involved in the selection, comparison and judgement of stimuli held in short and long term memory (e.g. Petrides, 1994) and the parietal lobes are thought to be involved in the storage of WM contents (e.g. Jonides et al., 1998)

Functional MRI of working memory processes using the N-back in schizophrenia have identified both hypo-activation (e.g. Callicott, et al., 1998) and hyper-activation (e.g. Callicott, et al., 2003) of the prefrontal cortex. This has been explained by a model whereby the relationship of fMRI activation with WM load is represented by overlapping inverted U-curves, with the patient's curve shifted to reflect lower capacity thus providing points of both hyper and hypo-frontality. Thus, an individual's activation is likely to be low when task difficulty is low and that individual's capacity are maximal; when task difficulty increases, activation declines as capacity is exceeded. Studies have begun to suggest that working memory in schizophrenia is

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characterised not by task related hypo- and hyper-activations but by a failure of deactivation. For example, Nejad et al (2011)report a failure to deactivate temporo-parietal regions in patients with schizophrenia compared to controls as load increases on a verbal N-back task comparing 2-back to 1-back and 0-back. The differences observed in deactivation were observed in the absence of performance differences between groups and differences in task related activations. Further, as verbal working memory relies on the interaction between frontal articulatory networks and posterior language areas it is possible that, rather than magnitude of activation, frontal cortical abnormalities are manifested in terms of functional connectivity between frontal and posterior language areas.

Individuals with schizotypal personality have also demonstrated cognitive impairments on the N-back test and this has been associated with positive schizotypy (Schmidt & Honey, 2009) disorganised schizotypy traits (Kerns & Becker, 2008), and negative schizotypy (Smyrnis et al, 2007). Few studies have investigated working memory using functional imaging and the N-back task in schizotypal personality. A functional MRI study of the 2-back version of the N-back in low schizotypes, high schizotypes (as defined by scores on the OLIFE) and patients with schizophrenia revealed BOLD activation in high schizotypes intermediate between controls and patients(Haworth, 2003). This suggests that at the cognitive and neural level, the N-back is a robust task for distinguishing between controls and schizotypes.

The N-back task was included in this thesis as a measure of general cognitive ability, attentional resources and functional activation. The N-back has a robust pattern of activation and is sensitive to subtle cognitive impairments. Thus, inclusion of this task serves as an ancillary task to assess the sensitivity of the allocentric spatial memory tasks to differentiating between the groups at the cognitive and neural level. Further, studies have suggested that successful performance in patients with schizophrenia is associated with compensatory functional

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activation of alternative brain regions and/or hyperactivation of task relevant brain regions (Callicott et al, 2003; Manoach et al, 2000). Schizotypy may also be associated with compensatory mechanisms of neural activation which may serve to lessen the impact of psychotic trait expression. Investigation of schizotypal performance on the N-back task during fMRI is used to investigate this hypothesis.

9.2   Specific Hypothesis

Specific hypotheses explored using this task were as follows:

1.   Based on previous studies of working memory in schizophrenia and in schizotypal personality individuals high in schizotypal traits will perform worse on this task compared to controls.

2.   The control group will demonstrate a pattern of activation in line with previous studies of spatial learning and memory using the N-back task including activation of the DLPFC (BA9/46), premotor (BA6) mid-ventral prefrontal cortex (BA45/47), ventrolateral prefrontal cortex (BA44), anterior frontal polar region (BA10) and posterior parietal regions (BA7/40).

3.   As performance on the N-back is thought to rely on activation of the dorsolateral prefrontal cortex, BOLD activation in this region will be associated with better performance.

4.   High schizotypy will be associated with a different level of activation in the prefrontal cortex (dorsolateral prefrontal cortex (BA9/46), middle frontal gyrus/frontal pole region (BA10), mid-ventral prefrontal cortex (BA45/47) and the anterior cingulate gyrus (BA24/32) compared to controls. Specifically lower activation of the dorsolateral prefrontal cortex will be observed in high schizotypy and increased activation of BA10.

6.   High schizotypy will be associated with a different pattern of activation as a function of working memory load with increased activation observed during trials of low working memory load and decreased activation observed during trials with a higher working memory load reflecting a shifted inverted U shaped curve.

7.   There will be a difference between low and high performers in activation of the dorsolateral prefrontal cortex (BA9/46) and this pattern will be different in high schizotypy compared to controls.

9.3 Methods

9.3.1 Subjects

40 subjects were included in the full analysis of this task. One participant was excluded due to unrecorded behavioural data and one participant was excluded due to being an extreme outlier on the behaviour measures. Demographics and schizotypy scores for this group are reported in the results section of this chapter.

Screening procedures, inclusion and exclusion criteria, schizotypy group allocation and selection of subjects are as discussed in Chapter 5.

9.3.2 Task Design

Black letters are presented on a white background in a prespecified sequence. Four sets of trials are presented; 0-back, 1-back, 2-back and 3-back and each set is repeated 3 times. During 0-back subjects need to respond each time they see a letter X presented on the screen. During 1-back subjects need to respond each time they see a letter that is identical to a letter presented 1 letter back. During 2-back subjects need to respond to each time they see a letter that is identical to one presented 2 letters back. During 3-back subjects need to respond each time they see a letter than is identical to one presented 3 letters back. Responses are made by pressing a button on a joystick. A joystick rather than a standard button box was used because an MR compatible joystick was used for the navigation task and it was felt that it was better to continue to use that than to interrupt the scanning session to change hardware. Subjects were told at the beginning of each set of trials which condition was about to start. See illustration in Figure 70 for N-back set up.
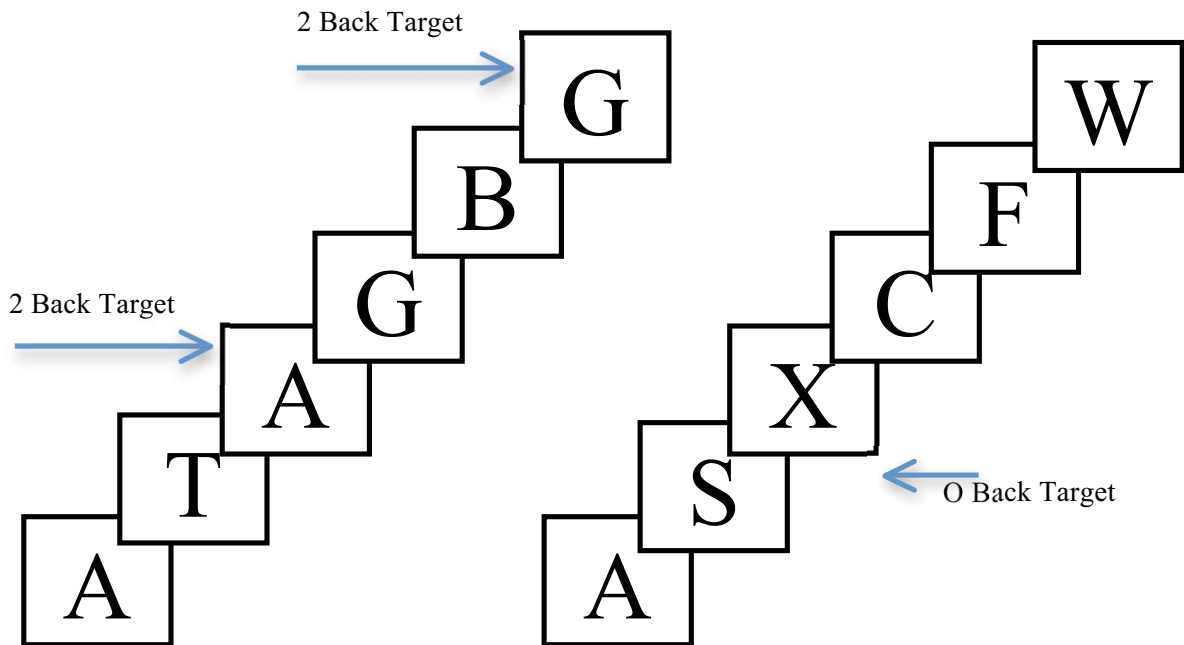
Figure 70 Visual illustration of the N-back task using a 2-back trial and 0-back trial as examples.

9.3.3   Data Analysis

9.3.3.1 Behavioural Data

Behavioural measures derived from the N-back task are number and percentage of correct responses, errors of commission and omission, correct rejections and latency of errors and correct responses.   Errors of commission are when subjects respond to a letter when it is an incorrect target (i.e. they make a response when they shouldn't) and errors of omission are when subjects fail to respond to a correct target letter (i.e. they don't respond when they should). Correct rejections are incorrect letters that are rejected as correct and is calculated as number of letters minus errors of commission.

A repeated measures ANOVA was employed with 1-back, 2-back and 3-back as within subject variables and schizotypy group as a between subjects factor. 0-back was added into the model as

a covariate of attention. SPSS 18 was used to analyse the behavioural data and significance defined as $p < 0.05$. A repeated measure ANOVA is a parametric test that rests on the assumption of normality, sphericity and independence of the distribution. However, a non-parametric equivalent for repeated measures across 2 or more groups does not exist. Several researchers have suggested that repeated measure ANOVA is robust to small violations of these assumptions (Glass, Peckman & Sanders, 1972; Lix, Keselman & Keselman, 1996). Thus if a non-normal distribution is observed and transformation of the variables does not appreciably change the distribution than a repeated measure ANOVA will still be employed.

9.3.3.2 Functional Imaging Data

<u>Preprocessing of the functional images</u>

Preprocessing steps were the same for all tasks and are presented in Chapter 5.

<u>Model Specification</u>

As per section 5.5.3.2 of the general methods section.

First Level Analysis

The onset and durations were entered for each condition (0-back, 1-back, 2-back, 3-back, responses and instructions) and for each subject; all variables were modelled by convolving the onset of each block with the hemodynamic response function. No temporal derivatives or interactions between trials were required. Six rotational and translational movement parameters generated by the realignment procedure for each subject were entered as regressors (nuisance covariates). Following estimation of the statistical model, contrast images were generated for each task comparison and for each subject. Contrasts were 1-back > 0-back, 2-back > 0-back, 3-back > 0-back and all back > 0-back.

A second design matrix was constructed to investigate the effect of working memory load on BOLD activation. All trials (1-back, 2-back and 3-back) were collapsed into a single column of the design matrix and a parametric modulation added to model the linear increase in working memory load.

Second Level Analysis

Contrast images were analysed using a one sample t-test to show the main effect of task in each group and a two sample t-test was used to test between groups differences in BOLD activation.

fMRI statistical inference

Statistical inference is discussed in section 5.5.3.2.

Small Volume Correction (SVC)

Based on previous studies of working memory using the N-back in humans *a priori* region of interest was the dorsolateral prefrontal cortex (BA9/46) and parietal cortex (BA40/7). Based on

previous studies of schizophrenia and schizotypal personality additional *a priori* regions of interest are the anterior cingulate cortex (BA24) and frontal-pole area (BA10). ROIs performed as discussed in 5.5.3.3.

Performance correlations

Performance correlation methods are as outlined in section Chapter 5 and Chapter 7.

9.4 Results

9.4.1 Demographics

Gender and ethnicity were evaluated using chi-square. Age had a non-normal distribution (Control Group: W = .824, df = 19, p = 0.003; High Group: W = .873, df = 21, p = 0.011). Transformation did not significantly improve the distribution therefore the non-parametric Mann Whitney test was performed. The variable education had three missing values therefore a series mean calculation was performed to replace these values. The new education variable was normally distributed (Control group: W = .928, df = 19, p = .161; High group: W = .918, df = 21, p = .77). IQ (NART-R score) was also normally distributed (Control group: W = .958, df 19, p = .530; High group: .959, df = 21, p = .492). Education and IQ were investigated using independent t-tests. Schizotypy groups did not differ on age, gender, IQ, years in education or ethnicity (data presented in Table 60)

Table 60 Demographics by schizotypy group

	Control Group	High Schizotypy Group	Statistical Test
Age	25.42 (6.82)	23.47 (4.96)	U = 171.00, p = .438
Range	19-42	18-37	
Gender (Ratio M:F)	8:10	11:11	χ^2= .123, df = 1, p = .761
Ethnicity (N) White Black Asian	15 0 4	15 3 3	χ^2 = 3.05, df = 2, p = .304
Education	15.54 (1.85)	15.55 (1.75)	t = -.131, df = 38, p = .896
NART-R IQ Score	116.04 (4.42)	116.49 (4.07)	t = -.342, df = 38, p = .734

Data represents means (SD) unless otherwise stated.

9.4.2 Schizotypy Scores

Schizotypy scores were determined by total score on the SPQ. Allocation to the control group included scores 21-36 and allocation to the high group included scores of 43 and above.

Total SPQ score was not normally distributed (Control group: W = .841, df = 19, p = 0.005; High Schizotypy group: W = .866, df = 21, p = 0.008). Therefore a non-parametric Mann Whitney test was performed. The SPQ subscale cognitive perceptual was not normally distributed (Control group: W = .872, df = 19, p = .015; High schizotypy group: W = .973, df = 21, p = .792). The subscale interpersonal was normally distributed (Control group: W = .977, df = 19, p = .901; High schizotypy group: W = 961, df =21, p = .536) as was disorganised (Control group = .974, df = 19, p = .850; High schizotypy group = .910, df = 21, p = .056) therefore independent t-tests were used.

Table 61 Schizotypy scores in each group

	Control group	High Schizotypy Group	Statistical Test
SPQ Total	25.89 (4.66)	48.14 (4.90)	U = 399.00, p < 0.001
Range	21-35	43-58	
Cognitive Perceptual	9.26 (6.72)	19.81 (5.15)	U = 357.50, p < 0.001
Range	1-29	10-29	
Interpersonal	11.21 (4.95)	21.76 (5.68)	t = -6.231, df = 38, p < 0.001
Range	1-22	8-31	
Disorganised	8.57 (3.34)	12.71 (2.90)	t = -4.192, df = 38, p < 0.001
Range	3-15	6-16	

Data reported in means (SD) unless otherwise stated.

9.4.3 Behavioural Results

Outliers were assessed at the Attention and 1-back level where results should be near maximal.

Dependent measures reported are correct responses, errors of commission, and latency of correct responses and errors of commission. Percentage errors and errors of omission are alternative measures of correct responses and are not reported. Correct rejections are also not reported as these are alternative measures of errors of commission.

Data was not normally distributed. Transformation of the non-normal variables did not normalise the distribution. There is no non-parametric equivalent of repeated measures ANOVA for the analysis of two groups. Several researchers have suggested that repeated measures ANOVA is robust to small deviations from normality (Glass, Peckham, & Sanders, 1972; Lix, Keselman, & Keselman, 1996). In the absence of a suitable alternative, repeated measure ANOVA was performed. To ensure the results did not appreciably change using a non-parametric statistic, dependent variables were assessed at each individual level of difficulty using a Mann Whitney test and reported if significantly different.

Correct Responses

A two factor (group: controls [average] and high schizotypy) x three factor (difficulty: 1-back, 2-back and 3-back) repeated measures ANOVA revealed no significant main effect of difficulty on correct responses ($F_{(1.48, 54.8)}$ = 0.84, p = .406). There was no significant main effect of schizotypy group on correct responses ($F_{(1, 37)}$ = 3.96, p = 0.054). There was no significant interaction between schizotypy group and difficulty level ($F_{(1.48, 54.8)}$ = 0.45, p = .579).

Errors of Commission

A two factor (group: controls [average scores] and high schizotypy) x three factor (difficulty: 1-back, 2- back and 3-back) repeated measures ANOVA revealed a significant main effect of difficulty ($F_{(1.16, 42.82)}$ = 11.94, p < 0.001) and a significant interaction between difficulty and schizotypy group ($F_{(1.16, 42.82)}$ = 6.85, p < 0.05). There was a significant effect of schizotypy group on errors of commission ($F_{(1, 37)}$ = 5.72, p < 0.05).

Reaction Time

A two factor (group: controls [average scores] and high schizotypy) x three factor (difficulty: 1-back, 2- back and 3-back) repeated measures ANOVA revealed no significant main effect of difficulty ($F_{(1.65, 61.40)}$ = 1.14, p = .318) and no significant main effect of group ($F_{(1, 37)}$ = .0083, p = .775). There was no significant interaction between difficulty and schizotypy group. ($F_{(1.65, 61.40)}$ = 0.21, p = .771).

Table 62 Performance measures on the N-back task across schizotypy groups reported as means (SDs)

	Control Group	High Schizotypy Group
Correct Responses 1-back	8.84 (0.50)	9.0 (0)
Correct Responses 2-back	8.53 (0.84)	8.80 (0.60)
Correct Responses 3-back	7.26 (1.04)	7.71 (0.90)
Errors of Commission 1- back	0	0.05(0.22)
Errors of Commission 2- back	0.05(0.23)	0
Errors of Commission 3- back	0.63(0.90)	0.10(0.30)
Reaction Time 1-back	458.97(73.52)	413.09 (67.47)
Reaction Time 2-back	522.64(89.79)	453.50(82.01)
Reaction Time 3-Back	595.85(172.63)	515.53 (101.62)

9.4.4　Functional Imaging Results

9.4.4.1　Group Maps

9.4.4.1.1 Control Group

No activations were observed for the contrast 1-back > 0-back in the control group.

<u>2 Back Condition</u>

Activation was observed in the bilateral inferior parietal lobes (BA40) and right middle frontal gyrus (BA8) during 2-back compared to 0-back at an FWE corrected level of $p < 0.05$ (presented in Table 63 and Figure 71). Lowering the threshold to a less conservative $p < 0.001$ uncorrected revealed activations in the bilateral superior and middle frontal gyrus (BA6), right middle frontal gyrus/anterior frontal pole (BA10), inferior frontal gyrus (BA9), inferior frontal gyrus (BA47) and cerebellum in the control group (see Table 64 and Figure 72)

Table 63 Significant activations during 2-back compared to 0-back in the control group.

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x, y, z
Inferior Parietal Lobule (R)	40	432	5.82	44 -41 41
Inferior Parietal Lobule (L)	40	102	5.27	-32 -50 39
Middle Frontal Gyrus (R)	8	20	5.30	54 10 38

All activations reported p < 0.05 FWE corrected. L = left hemisphere, R = right hemisphere.
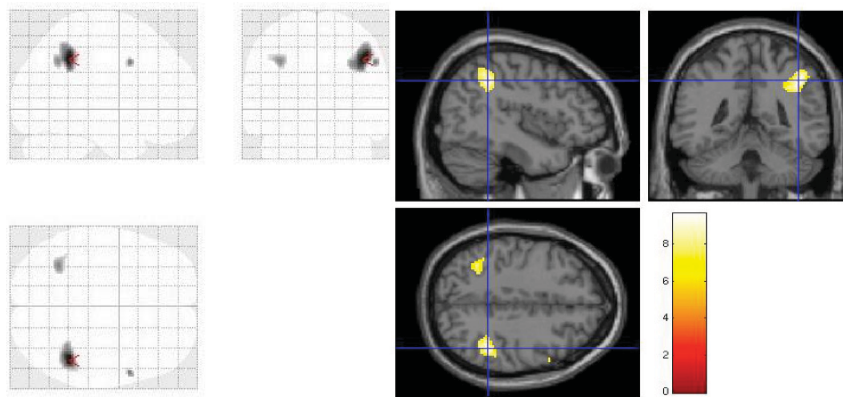
Figure 71 Significant activation contrasting 2-back to 0-back in the control group

Table 64 Uncorrected level activations during 2-back compared to 0-back in the control group.

Region	BA Equivalent	Cluster size	Z score	Maximum Coordinates x, y, z
Superior Frontal Gyrus (L)	6	385	4.60	-4 5 57
Inferior Frontal Gyrus (L)	9	1054	4.06	-42 10 24
Middle Frontal Gyrus (R)	6	427	3.78	32 1 52
Middle Frontal Gyrus (L)	6	126	3.78	-26 -1 57
Middle Frontal Gyrus (R)	10	51	3.74	36 51 3
Left Cerebellum (L)		8	3.43	-32 -60 -29
Inferior Frontal Gyrus (R)	47	2	3.16	34 21 -3

All activations reported at p < 0.001 uncorrected level. L = left hemisphere, R = right hemisphere.
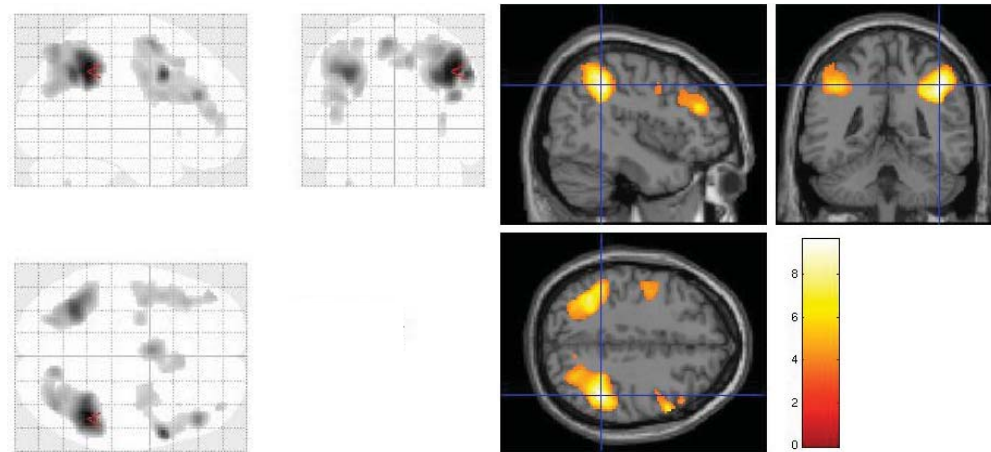
Figure 72 Uncorrected level activations contrasting 2-back to 0-back in the control group.

<u>3 Back Condition</u>

Activation was observed in the right inferior parietal lobule (BA40) in control group during 3-back compared to 0-back at a FWE corrected level of p < 0.05 (presented in Table 65 and Figure 73).

Table 65 Significant activations during the 3-back compared to 0-back in the control group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x, y, z
Inferior Parietal Lobule (R)	40	51	5.06	42 -41 39

All regions reported p < 0.05 FWE corrected. R = right hemisphere.
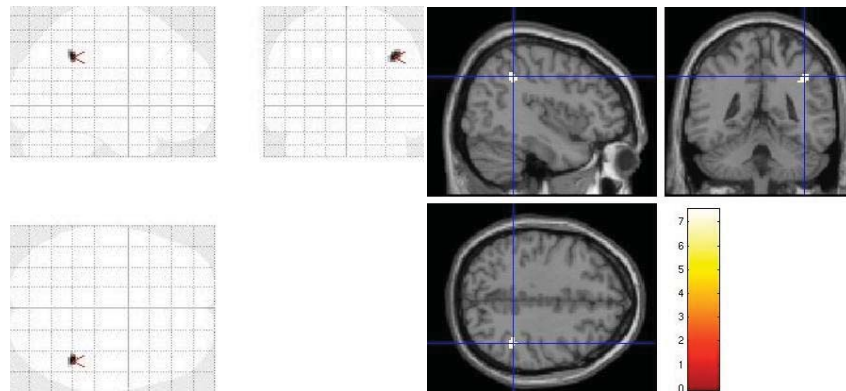
Figure 73 Significant activations during 3-back compared to 0-back in the control group

Lowering the threshold to p < 0.001 uncorrected revealed additional activations in the right middle frontal gyrus (BA6), right middle frontal gyrus (BA9), left middle frontal gyrus (BA46), superior parietal lobule (BA7), left cerebellum and inferior frontal gyrus (BA47) in the control group, presented in Table 66 and Figure 74).

Table 66 Uncorrected level activations during the 3-back compared to 0-back in the control group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x, y , z
Middle Frontal Gyrus (R)	6	327	4.31	28 2 64
Middle Frontal Gyrus (R)	9	372	4.11	44 31 30
Superior Parietal Lobule (L)	7	614	3.98	-30 -49 39
Superior Frontal Gyrus (L)	6	63	3.95	-4 5 57
Cerebellum (L)		30	3.82	-32 -58 -40
Superior Frontal Gyrus (L)	6	50	3.59	-26 -3 57
Precentral Gyrus (L)	6	15	3.28	-40 0 33
Middle Frontal Gyrus (R)	6	26	3.26	46 6 40
Middle Frontal Gyrus (L)	46	2	3.15	-42 21 25
Inferior Frontal Gyrus (R)	47	1	3.09	34 24 -2

All activations reported at p < 0.001 uncorrected level. L = left hemisphere, R = right hemisphere.
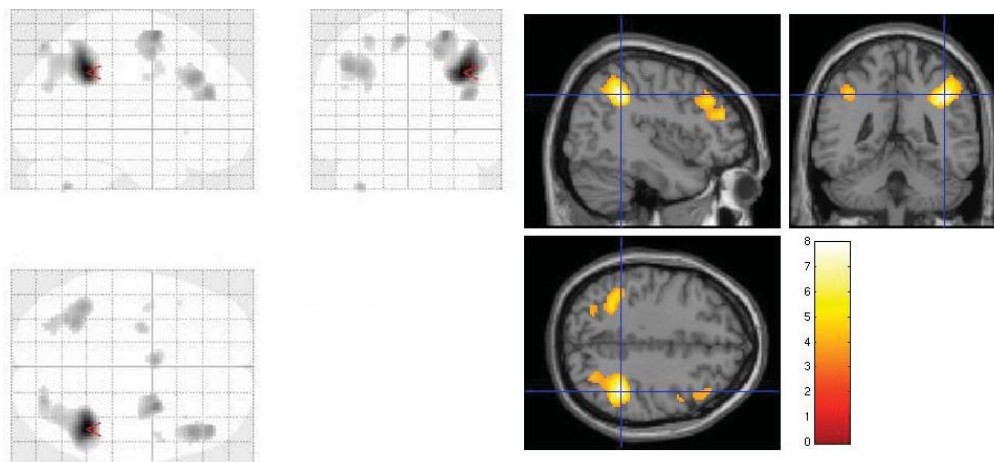
Figure 74 Uncorrected level activations contrasting 3-back to 0-back in the control group

9.4.4.1.2 High Schizotypy

No activations were observed contrasting 1-back > 0-back in the high schizotypy group.

<u>2-back Condition</u>

Activation was observed during 2-back compared to 0-back in the right parietal lobe (BA7) in the high schizotypy group at an FWE corrected level of p <0.05 (presented in Table 67 and Figure 75).

Table 67 Significant activations during 2-back condition compared to 0-back in the high schizotypy group

Region	BA Equivalent	Cluster Size	Z score	Coordinates
Parietal Lobe (R)	7	60	5.20	16 -63 51

All regions reported p < 0.05 FWE corrected. L = left hemisphere ; R = right hemisphere.
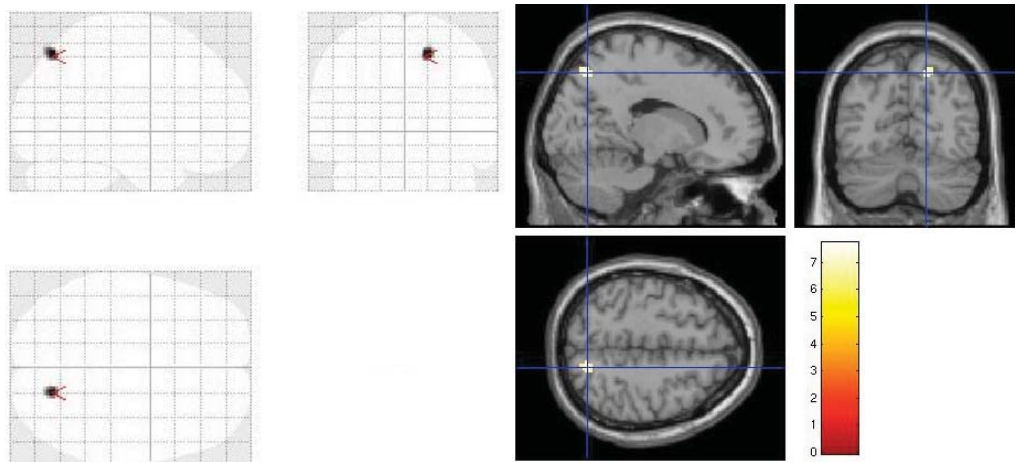
Figure 75 Significant activations contrasting 2-back to 0-back in the high schizotypy group.

Lowering the threshold to p < 0.001 uncorrected revealed additional activations in the bilateral middle frontal gyrus (BA6), left parietal lobe (BA7), and middle frontal gyrus (BA9) in the high schizotypy group, presented in Table 68 and Figure 76.

Table 68 Uncorrected level activations during 2-back compared to 0-back in the high schizotypy group

Region	BA Equivalent	Cluster Size	Z score	Coordinates
Middle Frontal Gyrus	6	208	4.29	-26 1 53
Parietal Lobe	7	700	3.94	-26 -54 43
Middle Frontal Gyrus	6	146	3.89	32 3 59
Middle Frontal Gyrus	9	74	3.55	44 32 30
Parietal Lobe	7	15	3.20	32 -72 32

All regions are reported at the p < 0.001 uncorrected level. L = left hemisphere, R = right hemisphere.
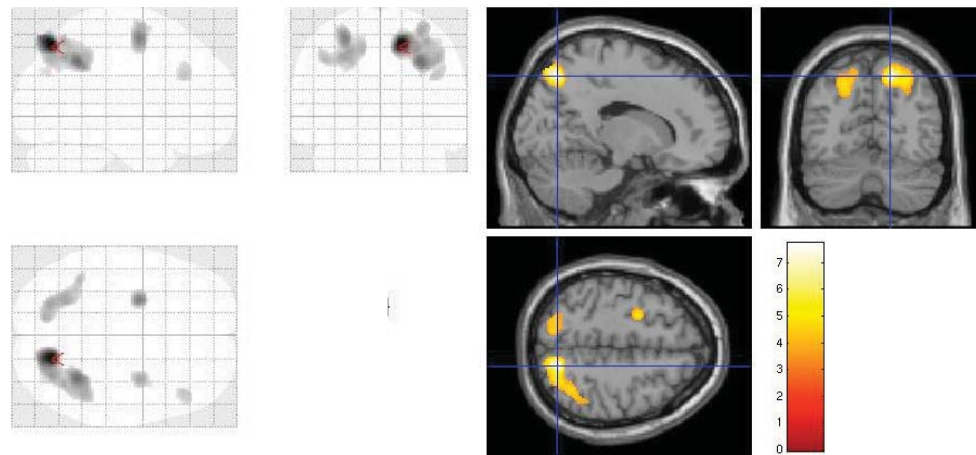
Figure 76 Uncorrected level activations contrasting 2-back to 0-back in the high schizotypy group

Activations were observed during 3-back compared to 0-back in right middle frontal gyrus (BA6), right parietal lobe (BA7) and right middle frontal gyrus (BA9) in the high schizotypy group (see Table 69 and Figure 77).

Table 69 Significant activations during 3-back compared to 0-back in the high schizotypy group

Region	BA Equivalent	Cluster Size	Z score	Coordinates
Middle Frontal Gyrus	6	70	5.12	32 3 59
Parietal Lobe	7	44	5.02	16 -76 56
Middle Frontal Gyrus	9	27	4.81	48 35 30

All activations reported $p < 0.05$ FWE corrected. L = left hemisphere, R = right hemisphere.
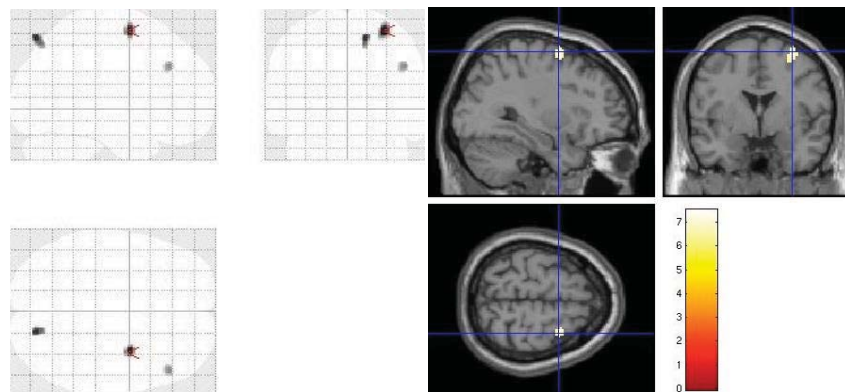
Figure 77 Significant activations during 3-back compared to 0-back in the high schizotypy group

Lowering the threshold to $p < 0.001$ uncorrected revealed additional activations in the left inferior parietal lobule (BA40), right medial frontal gyrus (BA8), left middle frontal gyrus (BA9), right inferior frontal gyrus (BA47) and right middle frontal gyrus (BA10) (see Table 70 and Figure 78).

Table 70 Uncorrected level activations during 3-back compared to 0-back in high schizotypy

Region	BA Equivalent	Cluster Size	Z score	Coordinates
Inferior Parietal Lobule	40	812	4.42	-38 -48 43
Middle Frontal Gyrus	6	369	4.31	-28 5 53
Medial Frontal Gyrus	8	268	3.86	4 20 43
Middle Frontal Gyrus	9	108	3.60	-48 31 32
Inferior Frontal Gyrus	47	77	3.55	32 35 -2
Middle Frontal Gyrus	10	18	3.39	36 44 18
Superior Frontal Gyrus	10	1	3.13	-34 55 16
Middle Frontal Gyrus	10	1	3.09	-36 53 18

All activations are reported at the $p < 0.001$ uncorrected level. L = left hemisphere, R = right hemisphere.
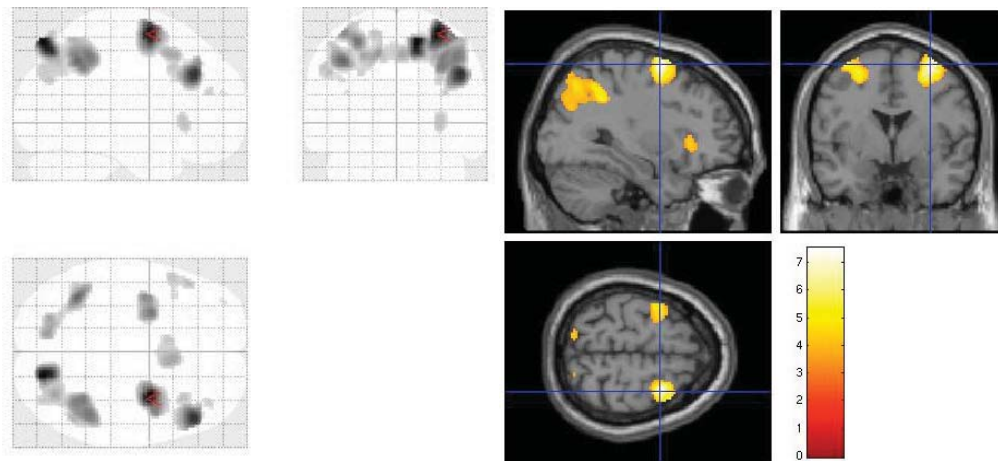
Figure 78 Uncorrected level activations contrasting 3-back to 0-back in the high schizotypy group

9.4.4.2 Group Differences

There were no differences in BOLD activation in any region using contrasts 1-back > 0-back and 3-back > 0-back. However, when contrasting 2-back to 0-back two areas of decreased activation in high schizotypy were observed. These brain regions were identified as left insula (BA13) and left dorsolateral prefrontal cortex (BA46), presented in Table 71 and Figure 79..

Table 71 Differences in BOLD activation between controls and high schizotypes contrasting 2-back to 0-back

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x, y, z
Controls > High Schizotypes				
Insula (L)	13	19	3.70	-30 -30 24
Middle Frontal Gyrus (L)	46	7	3.25	-36 30 20
High Schizotypes > Controls				
None				

All regions reported p < 0.001 uncorrected. L = left hemisphere, R = right hemisphere.
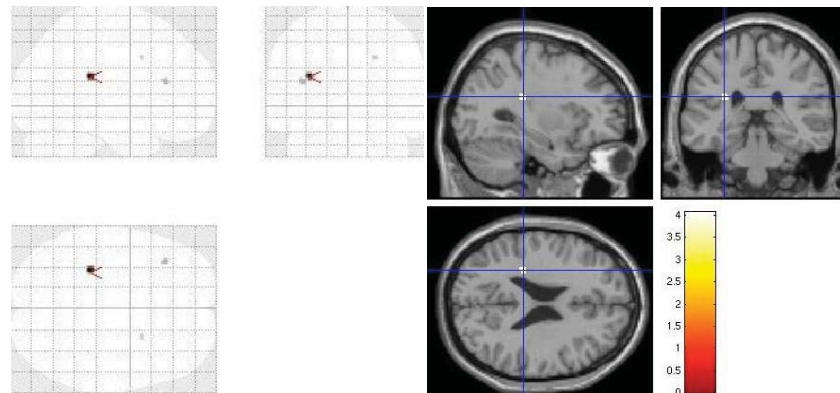
Figure 79 Decreased activation of the left insula and left dorsolateral prefrontal cortex in the high schizotypy group contrasting 2-back to 0-back

9.4.4.3 Effect of load and schizotypy

In order to investigate the effects of load a second design matrix was constructed with all conditions collapsed into an additional single column and a parametric modulation added to measure activation against the linear increase in working memory load (1-back, 2-back and 3-back).

Control Group

Increasing working memory load was associated with increased activation in the right middle frontal gyrus (BA9), bilateral inferior frontal gyrus (BA44/47) left precuneus (BA7), left parietal lobe (BA39), right middle frontal gyrus (BA10), left insula (BA13) and superior and middle frontal gyrus (BA6) in average schizotypy. These results are presented in Table 72.

Table 72 Activations associated with increasing working memory load in the control group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x, y, z
Middle Frontal Gyrus (R)	9	731	4.69	46 33 32
Inferior Frontal Gyrus (L)	44	865	4.59	-53 7 16
Superior Frontal Gyrus (L)	6	672	4.42	-8 7 57
Middle Frontal Gyrus (R)	9	1277	4.37	42 43 39
Precuneus (L)	7	329	4.11	-16 -66 40
Parietal lobe (L)	39	332	4.03	-28 -49 34
Middle Frontal Gyrus (L)	6	124	3.76	-26 4 48
Middle Frontal Gyrus (L)	10	93	3.72	-34 47 16
Insula (L)	13	57	3.61	-30 20 8
Middle Frontal Gyrus (R)	8	60	3.58	26 9 35
Inferior Frontal Gyrus (R)	47	12	3.23	36 25 0
Precentral Gyrus (L)	6	5	3.17	-48 -4 41

All regions reported $p < 0.001$ uncorrected. L = left hemisphere; R = right hemisphere.

Increasing working memory load was also associated with decreased activation in the left posterior cingulate (BA23), right insula (BA13), left cerebellum, left middle temporal gyrus (BA39), right middle temporal gyrus (BA21), cingulate gyrus (BA32) left medial frontal gyrus

(BA10) and right medial frontal gyrus (BA11), left parahippocampus (BA36) and left cuneus (BA19). These results are presented in Table 73.

Table 73 Deactivations associated with increasing working memory load in the control group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x, y, z
Posterior Cingulate (L)	23	1262	4.77	-4 -55 19
Insula (R)	13	275	3.77	44 -13 15
Cerebellum (L)		46	3.73	-8 -52 4
Middle Temporal Gyrus (L)	39	53	3.70	-51 -69 26
Medial Frontal Gyrus (L)	10	16	3.59	-14 36 50
Medial Frontal Gyrus (R)	11	161	3.57	4 52 -13
Middle Temporal Gyrus (R)	21	23	3.57	38 -12 -13
Cingulate Gyrus (L)	32	17	3.50	-2 35 -7
Middle Temporal Gyrus (R)	42	5	3.23	67 -29 7
Parahippocampus (L)	36	3	3.14	-28 -39 -10
Cuneus (L)	19	1	3.10	-18 -98 22

All regions reported p < 0.001 uncorrected. L = left hemisphere; R = right hemisphere.

High Schizotypy

Increasing working memory load was associated with increased activation in the right inferior parietal lobe (BA40), bilateral middle frontal gyrus (BA6), inferior frontal gyrus (BA47), left superior frontal gyrus (BA10) and right middle frontal gyrus (BA10) in the high schizotypy group. The results are reported in Table 74.

Table 74 Activations associated with increasing working memory load in the high schizotypy group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x, y, z
Inferior Parietal Lobe (R)	40	6582	5.93	50 -54 47
Middle Frontal Gyrus (R)	6	3064	5.40	28 5 55
Middle Frontal Gyrus (L)	6	2412	4.97	-28 5 59
Inferior Frontal Gyrus (R)	47	228	4.51	32 25 -3
Superior Frontal Gyrus (L)	10	210	4.09	-34 55 16

Middle Frontal Gyrus (R)	10	9	3.64	20 -56 -4

All regions reported $p < 0.001$ uncorrected. L = left hemisphere; R = right hemisphere.

Increasing working memory load was associated with decreased activation in the right cuneus (BA19), superior frontal gyrus (BA9), left hippocampus, right amygdala, left posterior cingulate (BA30), bilateral middle temporal gyrus (BA21), left parietal lobe (BA5), right superior temporal gyrus (BA6), right fusiform gyrus (BA37), and right inferior frontal gyrus (BA45) in the high schizotypy group. These results are reported in Table 75.

Table 75 Deactivations associated with increasing working memory load in the high schizotypy group

Region	BA Equivalent	Cluster Size	Z score	Maximum Coordinates x, y, z
Cuneus (L)	19	2357	5.66	18 -92 29
Superior Frontal Gyrus (L)	9	2818	4.86	-8 60 28
Parahippocampus (R)	Amygdala	2715	4.82	24 -1 -18
Posterior Cingulate (L)	30	1534	4.73	-10 -52 15
Temporal Lobe (R)	21	58	4.53	48 6 -36
Parahippocampus (L)	Hippocampus	2991	4.49	-28 -33 -8
Parietal Lobe (L)	5	529	4.16	-22 -43 70
Superior Frontal Gyrus (R)	6	1326	3.84	10 -16 63
Middle Temporal Gyrus (L)	21	37	3.83	-46 6 -36
Fusiform Gyrus (R)	37	480	3.72	40 -45 -16
Middle Temporal Gyrus (L)	39	83	3.64	-36 -73 9
Middle Temporal Gyrus (R)	21	38	3.57	51 1 -17
Inferior Frontal Gyrus (R)	45	8	3.51	55 33 4
Middle Temporal Gyrus (L)	39	30	3.48	-44 -71 18

All regions reported $p < 0.001$ uncorrected. L = left hemisphere; R = right hemisphere.

9.5   Discussion

9.5.1   Summary of results

Both groups activated brain regions associated with performance of the N-back including the dorsolateral prefrontal cortex (BA9/46), mid ventral prefrontal cortex (BA47), middle frontal gyrus/premotor regions (BA6), middle frontal gyrus/anterior frontal pole (BA10), posterior parietal lobe (BA7/40) and cerebellum at 3-back and at 2-back. This is consistent with previous literature using a verbal N-back as presented in a recent meta-analysis (Owen et al, 2005). No regions were more activated at 1-back compared to 0-back in either group and this plausibly reflects the near perfect performance across groups at this level. As working memory load increased so did neural activation in the middle frontal gyrus (BA9), inferior frontal gyrus (BA44) mid ventral prefrontal cortex (BA47), middle frontal gyrus/premotor regions (BA6), middle frontal gyrus/anterior pole region (BA10) and parietal lobe (BA39/40). As working memory load increased deactivations were observed in the cingulate gyrus (BA23/30), middle temporal gyrus (BA21/39) and parahippocampus (BA36). No differences were observed between the two groups as a function of working memory load.

Decreased activation of the left insula and left middle frontal gyrus (dorsolateral prefrontal cortex) was observed during 2-back trials compared to 0-back in high schizotypy but these differences were small and did not reach significance when corrected for multiple comparisons. No differences were observed in BOLD activation between the groups at 1-back or 3-back.

9.5.2   Behavioural Data

No differences were observed on any of the cognitive measures of accuracy or reaction time. Across all three conditions (0-back, 1-back, 2-back and 3-back) very few errors were made by either group; performance in this sample was considerably higher than that reported in the literature. There was a non-significant trend for the high schizotypy group to perform better on this task than average schizotypes; however the near perfect performance of nearly all subjects means that one person scoring 8/9 in the average schizotypy group presents as worst

performance in the average group. As can be seen in Table 64, there is very little difference between the group means for any of the dependent variables. However, there was a modest effect on errors of commission with the control group making slightly more errors. Several studies have observed lower performance in schizotypal subjects on the N-back task (Kerns & Becker, 2008; Schmidt & Honey, 2009; Smyrnis et al, 2007) however these studies have all related worse performance to one of the symptom profiles of schizotypy i.e. positive or negative schizotypy rather than using a total schizotypy syndrome score as is used in this thesis. Other studies have also reported no differences when comparing low and high schizotypy groups in performance of the 2-back version of the N-back task (Haworth, 2003, thesis).

It is likely that practice effects had a significant impact on the exceptional performance observed across groups. Both groups were trained at the screening and testing visit offline before performance in the scanner. Further, subjects who volunteered for this study may have volunteered for many research studies before (volunteer bias) and the N-back is a commonly employed cognitive measure. Thus, subjects may have been exposed to this task on numerous previous occasions.

9.5.4 Group comparisons

Decreased activation of the left insula and left dorsolateral prefrontal cortex was observed in high schizotypy relative to controls at the $p < 0.001$ uncorrected level. Of interest, we observed this lower activation in the absence of any performance differences between the two groups. However, differences were small and did not reach significance when corrected for multiple comparisons. We did not observe an increase in activation of BA10 or other supplementary frontal regions (i.e. BA47) in high schizotypy as predicted from the schizotypal personality literature at the threshold of $p < 0.001$ uncorrected for any of the levels of working memory load.

The lack of strong functional differences between the two groups may reflect the lack of difficulty associated with the task in either group. It has been suggested that reduced activation of prefrontal regions emerges under conditions of reduced cognitive capacity; the task used in this thesis may not have been difficult enough to elicit activation differences in our high functioning sample. The lack of functional and cognitive differences may also reflect a relative sparing of cognitive functions dependent upon the prefrontal and parietal regions in high schizotypy. This is difficult to reconcile with the numerous studies indicating impaired cognition in schizotypy using tasks of executive functioning such as the WCST, tasks of attention such as the CPT and tasks of working memory such as the N-back or delayed match to sample for example (see Chapter 2). However, little is known to date about the underlying factors that contribute to compensatory functional activity and it may be the case that additional factors besides a high expression of schizotypal personality traits differentiate the negative from positive cognitive findings. To this end of course, the number of negative schizotypy and cognition studies is unknown as they are unlikely to be published, at least to the same extent, as those with positive findings.

9.5.4   Methodological considerations

Other studies have demonstrated that there is a different activation pattern between low and high performers on this task and that this differs between patients and controls. This hypothesis could not be tested with the current data because of the high level of performance of all subjects. A larger variance in performance in both groups would have allowed investigation into these performance/activation differences in schizotypal personality. Additionally, previous behavioural studies using the N-back have taken the approach of using the individual trait dimensions (e.g. positive schizotypy). This may be more informative than using an overall schizotypy group design for certain aspects of cognition.

9.5.5 Conclusions

We included this task as a general measure of cognitive ability and attention to assess if a well standardised measure of cognition and functional activation could differentiate between the groups. No differences were observed in any of the cognitive measures and performance was near optimal for the majority of subjects regardless of schizotypy group. Task related activations were in line with previous literature for both schizotypy groups and although there was a decrease in activation of the left insula and left dorsolateral prefrontal cortex in high schizotypy, these differences were small and non-significant when corrected for multiple comparisons.

Chapter 10: Overall Discussion

I will begin by summarising the results presented in this thesis before discussing each in turn and then in reference to previous literature.

10.1 Summary of Results

Across tasks there were no behavioural differences observed between average and high schizotypy groups on any of the behavioural measures suggesting that high schizotypy is not associated with deficits in allocentric spatial memory ability.

Structural MRI revealed small group differences where high schizotypy is associated with grey matter volume reductions in right hippocampal, bilateral medial frontal gyri and right middle frontal gyrus. Increased grey matter volume of the left cuneus, left inferior occipital gyrus, left temporal gyrus, left medial frontal gyrus, bilateral superior temporal gyrus, right inferior frontal gyrus, right medial frontal gyrus and right posterior cingulate gyrus was also observed in high schizotypy. White matter volume differences were also observed with decreases for the high schizotypy group of the left fusiform gyrus, right supramarginal gyrus, left parahippocampus, right inferior frontal gyrus and superior temporal gyrus sand increases of the right parahippocampus, right lingual gyrus, right fusiform gyrus, left middle frontal gyrus and left lingual gyrus. However, none of these differences were significant corrected for multiple comparisons and thus run the risk of being contaminated with false positives.

Functional imaging differences revealed differences in BOLD activation of the hippocampus between the two groups when memory encoding and retrieval processes were examined

separately. Decreased activation of the right hippocampus was observed in high schizotypy during memory encoding; conversely increased activation of the left and right hippocampus was observed at memory retrieval. This is in light of comparable performance on the tasks between groups. In terms of this performance, activation of the right hippocampus at encoding was related to better performance in controls whereas no relationship was observed in high schizotypy. At memory retrieval, the increased activation of the right hippocampus in high schizotypy was related to worse performance. In line with previous literature this supports the involvement of the right hippocampus in memory encoding and successful allocentric spatial memory performance whereas it is not required and may even be detrimental to performance at memory retrieval. This may reflect a sustained use of cognitive mapping at memory retrieval in schizotypal personality; in effect the high schizotypes may still be trying to learn or process the environment at a time when they should be able to retrieve it more efficiently from memory.

No hippocampal or parahippocampal differences in BOLD activation were observed during the Platform task. However, whereas hippocampal activity was associated with better performance (fewer errors) in average schizotypy no such relationship was observed in high schizotypy. High schizotypy was associated with lower activation of the dorsolateral prefrontal cortex and increased activation of the parietal lobes during four platform trials but this was not significant corrected for multiple comparisons. During eight platform trials the anterior cingulate gyrus was more active bilaterally in the high schizotypes but did not survive correction for multiple comparisons. Greater activation of the anterior cingulate was also observed during memory retrieval in high schizotypy as well as the left anterior insula in the Arena Task. Taken together this may suggest that schizotypy is associated with hypervigilance of performance, increased cognitive effort and increased attentional resources. It is proposed that this combination may be sufficient to compensate for alterations in hippocampal activity during spatial memory performance and the decoupling between recruitment of task relevant neural circuitry and

performance. The small but none significant volume decreases in the hippocampus were not in the same location as the observed functional differences. The structural differences were located in the hippocampus proper whereas the functional differences were located primarily in the anterior hippocampus extending to the entorhinal cortex (part of the parahippocampal gyrus).

10.2   Allocentric spatial memory ability in high schizotypy

No behavioural differences were observed between average and high schizotypy on any of the tasks used in this thesis. Although high schizotypy has been associated with cognitive deficits in many diverse domains (i.e. working memory, sustained attention, inhibition) in the previous literature (for review see Raine, 2006) it is not wholly surprising that we did not observe them in this thesis. Notably, the amount of training the subjects received may have masked any cognitive differences observed between the two groups. However, analysis of data acquired at training sessions did not reveal a significant difference in performance. The benefits of extensively training subjects on the tasks are many; firstly it allows one to assess functional activation differences in the absence of performance confounds which have rendered many fMRI studies in schizophrenia hard to interpret. Secondly, it ensures that subjects understand a task and any alterations in performance or brain function cannot be attributed to not understanding the task requirements. Finally, it allows for the identification of potential compensatory mechanisms which may render performance normal in high schizotypy but are nonetheless functionally different in either recruitment or degree of activation than that observed in the control group. This latter point may also explain the lack of behavioural differences observed in this study. This is supported by previous literature that has demonstrated that patients with schizophrenia who have comparable performance to controls activate a more diverse network or demonstrate hyperactivation of task relevant circuitry to achieve this performance (Callicott et al, 2003).

An alternative explanation is that the sample recruited in this study was very carefully selected to rule out recreational drug use, smokers, excessive alcohol consumption and co-occurrent psychiatric conditions. This had a significant advantage of allowing assessment of group differences free from confounds associated with schizotypy but it may not be representative of the true schizotypy profile. Schizotypy has been associated with elevated recreational drug use, nicotine and alcohol consumption (Barkus & Murray, 2010; Esterberg, Goulding, McClure-Tone, & Compton, 2009) It would be beneficial to conduct further research into the effects of some of these additional factors on allocentric spatial memory performance to investigate whether any of them predict worse performance on these tasks. This would be informative of the likely environmental factors of schizotypy involved in cognitive impairments of spatial learning and memory.

10.3   Structural MRI investigation

No structural differences were observed at a $p < 0.05$ level corrected for multiple comparisons. Several regions were identified at a $p < 0.001$ level and these will not be discussed further with the exception of the hippocampus which was predicted to be smaller in high schizotypes and which is directly related to the task used in this study. Lower hippocampal volumes have been observed in individuals with positive schizotypal traits (Flaum & Anderson, 1995) and those with clinically defined personality disorder (Dickey et al, 2007). Further, hippocampal volume reductions are observed in chronic and first episode schizophrenia patients (eg. Velakoulis, et al., 1999; Witthaus, et al., 2009), clinical high risk groups (Fusar-Poli, et al., 2011) and relatives of patients with schizophrenia (eg. Seidman, et al., 1999; Seidman, et al., 2002). Thus it would appear that lower hippocampal volumes are associated with psychosis along the continuum ranging from subtle volume changes in healthy volunteers with schizotypal traits through to more pronounced hippocampal changes in schizophrenia. Although the hippocampal volume

changes observed here were not significant volume reductions in this region may be present in those at risk for the disorder, or those who share common genetic or environmental factors, and that onset of psychosis leads to a worsening of these already present structural abnormalities.

We did not observe any differences in grey or white matter volume of the parietal lobes, despite the precuneus being identified as a region increased in schizotypy in the Modinos et al (2010) study. We also observed no differences in recruitment of this region during the Arena Task and increased activation of the parietal lobes during the four platform condition of the Platform task. As spatial memory is thought to rely on activation of the parietal lobes (see introductory chapter) a sparing of this region across tasks may be related to the lack of differences in performance between the two groups, with essential spatial manipulation abilities associated with parietal lobe functioning showing weakness. However, this thesis did not set out to directly test the involvement of the parietal lobe in schizotypal personality and, as such, paradigms or region of interest studies explicitly testing the parietal lobes would be needed to confirm this suggestion.

It should also be noted that the differences observed were not significant corrected for multiple comparisons and are reported at an uncorrected voxel level threshold. Without applying an appropriate correction for multiple comparisons there is an increased risk of false positives contained in the SPM maps. However, reduced hippocampal volume in the high schizotypy group was hypothesised *a priori* based on previous literature in schizotypal personality; this increases our confidence that this is not a chance finding in this analysis.

10.4   Functional MRI findings

The functional imaging results have demonstrated that both the Arena task and the Platform task elicit activation in spatial memory circuitry in line with previous literature (see introductory chapter). This includes activation of the hippocampus and parahippocampal gyrus, prefrontal

cortex, inferior parietal lobes and precuneus, cingulate gyrus, occipital lobes, striatum and thalamic cortices. In healthy controls, activation of the hippocampus is related to better performance on tasks of allocentric spatial memory further confirming its role in successful allocentric spatial memory performance.

Investigation of between group differences revealed a differential activation of the hippocampus in high schizotypy. At encoding, there is a lower activation of the right hippocampus in high schizotypes compared to controls and hippocampal activity at encoding does not correlate with performance. This suggests that activation of the hippocampus is inefficient in high schizotypy and this may be related to poor encoding strategies since encoding of distal cue information is thought to rely on intact hippocampal integrity (Parslow et al, 2004). Impairments in memory encoding have been demonstrated in both schizophrenia (Hall, et al., 2010; Heckers, et al., 1998; Weiss et al., 2003)and in high risk for psychosis groups (Allen et al, 2009). In these studies comparable performance is normally attained using compensatory increased activation of frontal and temporal structures during memory retrieval (Hall et al, 2010). It has been suggested that memory retrieval in schizophrenia is largely spared (Boyer, Phillips, Rousseau, & Ilivitsky, 2007).

In the arena task, the left anterior insula cortex and right anterior cingulate cortex were hyperactive during memory retrieval which suggests greater involvement of the ventral attentional system in high schizotypy. This may be necessary to remain engaged with the task and to monitor performance and allocation of attention during cognitively challenging components of the task. A greater use of this system may arise from a failure to sufficiently encode locations in memory during the encoding condition. A mechanism by which this may arise is that right hippocampal activity during memory retrieval is associated with the degree to which subjects are trying to recall the encoded location of the pole resulting in a consistent

activation of the hippocampus as one navigates through space. As this occurs, increased activity of the cingulate gyrus monitors this activity and ensures errors in distance and angle are corrected. An alternative explanation is that the hippocampal activation at retrieval may be related to sustained cognitive mapping; in effect this means they are still attempting to "learn" the environment.

We did not observe hippocampal or parahippocampal differences between groups on the Platform Task. However, hippocampal activation was related to better performance (fewer errors) in the control group but not in high schizotypy. This suggests that the hippocampal activation in the high schizotypy group may be inefficient. It may also reflect use of, or attempted use of, alternative strategies to complete the task such as a stimulus-response strategy. As the task was designed to favour use of an allocentric strategy the choice of an egocentric strategy would not be the best choice for completing the task. However, if high schizotypy is associated with impairments in allocentric spatial memory, adoption of an egocentric strategy may reflect a long term preference for use of this strategy regardless of the experimental conditions. In line with this hypothesis, increased activation of the insula has been reported using the egocentric version of the Arena task (Parslow et al, 2004) and we also observed an increase in insula activity in high schizotypy on the Arena task. However, use of a non-spatial strategy to complete the tasks used in this thesis is unlikely due to the constraints placed on subjects in the experimental set up. The activation of areas thought to be related to egocentric spatial memory can be plausibly explained in terms of the relationship between egocentric and allocentric spatial memory; it is likely that any task will involve the combined use of egocentric and allocentric frames of reference as egocentric information may form the basis of allocentric spatial maps or conversely allocentric spatial information may be recoded into an egocentric framework for navigating towards a goal (N. Burgess, 2006)

In terms of alternative strategies, it should be noted that one explanation would be a use of a verbal learning and memory strategy to remember the pole (Arena Task) or platforms visited (Platform Task) and this would result in activation of the left hippocampus and anterior insula observed in the Arena Task in this study.

10.5   Comparison to Siever & Davis's model of schizotypal personality

Siever and Davis (2004) proposed a model of schizotypal personality in which impairments in the temporal lobes are indicative of vulnerability to schizophrenia and are present along the schizophrenia spectrum. Differences between schizotypal personality and schizophrenia emerge when investigating the prefrontal regions and schizotypal personality has been shown to be associated with relatively spared prefrontal cortex particularly the anterior frontal polar area, Brodmann area 10. Although the authors developed this model based on the literature available on schizotypal personality disorder, a clinically diagnosed collection of schizotypal traits, they suggest that the model may also apply to healthy volunteers with schizotypal traits. The results obtained in this thesis suggest that the medial temporal lobes, particularly the hippocampus, are also affected in high schizotypy with small grey matter volume decreases observed in the right hippocampus, a differential pattern of BOLD activation in response to task conditions and a decoupling between this region and performance.

In terms of the prefrontal cortex, the picture is not quite as straightforward. We did not observe any significant structural or functional differences between the two groups in any of the prefrontal regions. A small but none significant increase was observed in BA10 which would be predicted by Siever & Davis's (2004) model but this did not survive correction for multiple comparisons. Surprisingly we did not observe any increases in functional activation in this region in the high schizotypy group above the threshold set in this thesis.

Notably what was observed in this thesis was greater activation of the anterior cingulate gyrus bilaterally across allocentric spatial memory tasks as well as no significant volumetric differences in this region. What this suggests is that whilst schizophrenia has been associated with reduced activation and volume of the cingulate gyrus, this area of the frontal-limbic system may be relatively spared in healthy volunteers with schizotypal traits and may work to ameliorate cognitive deficits associated with impairments of the temporal lobes. The cingulate gyrus is associated with "buffering" information between the frontal and temporal lobes and thus sparing of the cingulate gyrus in schizotypal individuals may reduce the impact of frontal-temporal dysfunction within this group (Fletcher et al, 1998).

10.6   Methodological Considerations

Allocation of schizotypy groups

In this thesis I chose to recruit two groups of subjects: average and high schizotypes. As the aim of this thesis was to investigate allocentric spatial memory in high schizotypy I wanted to recruit a control group that was as akin to the normal population as possible rather than an extremely low or no schizotypy group. However these group designs are limited to comparisons between groups and do not lend themselves well to correlational analysis of schizotypal traits. In order to investigate a variable against increasing schizotypal trait expression a full range of scores would need to be recruited and then group analysis could be performed by splitting the sample into the top 10th and 90th percentile or treating the data as a continuous variable. This would require a larger sample to be recruited in order to have sufficient numbers for the group split and would be unreasonable for an imaging study.

The choice not to include a low/no schizotypy group as well as the medium and high schizotypy groups has certain advantages: recruitment of only two groups allowed us to build up a relatively

large sample size in terms of between group comparisons within the confines of a two year study. However, it is acknowledged that a low schizotypy group could be a further development of the study and would allow comparisons along the spectrum of schizotypal traits.   The range of schizotypy scores in the medium range is quite large with 36 being the highest medium score; this may have obscured significant group differences on some of the measures used in this thesis. However, in order to assess the impact of these high SPQ scores within the medium grouping, a sensitivity analysis was performed including average schizotypy scores of 21-30 against those who scored 43 and above.   This did not significantly change the results obtained in this thesis.

Selection of subjects

The selection criteria for the studies in this thesis were strict and both groups were screened for recreational drug, alcohol and nicotine use. Further, the MINI (Sheehan et al, 1998) was used to screen out subjects with mental health concerns. Thus, the sample recruited may not be indicative of the general schizotypy profile as schizotypy is associated with increased use of recreational drug use, alcohol and nicotine use (Barkus & Murray, 2010; Esterberg et al, 2007). Of note, a personal observation in this study is that there is a need to employ clinical tests of recreational drug use and alcohol consumption such as urine testing and alcohol breath tests as several subjects (across schizotypy groups) claimed not to have taken recreational drugs such as cannabis but still failed the drug screening. It should be noted however that inclusion of a clean sample in this thesis allows us to have confidence that the group differences observed are related only to the presence of schizotypal traits and not to the presence of these additional factors. Additionally, using a sample compromised by other factors means that one is less able to isolate the neurocognitive features associated with schizotypy. Another point of diagnostic concern is that we did not rule out the inclusion of adults who may have autistic spectrum traits. Research has suggested that individuals diagnosed with autism spectrum disorders also have high levels of

positive, disorganised and negative schizotypal traits (Barneveld et al., 2011). This could be addressed by using a questionnaire to evaluate autistic traits such as the Autism Questionnaire (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001), which measures the degree to which an individual of normal intelligence might show features of the core autistic spectrum phenotype.

Task Design

Methodological considerations regarding each of these tasks are discussed in the relevant experimental chapters. Across tasks, a concern regarding the use of virtual reality spatial memory tasks inside the MR scanner is that they do elicit more movement than other cognitive tasks. This is most noticeable in the Arena Task where subjects navigate the environment using a MR compatible joystick. For this reason addition of a motor control task to the task design would have been beneficial. Both the Arena and Platform Tasks were designed to measure allocentric spatial memory with necessary constraints placed on the tasks to encourage this type of spatial memory strategy to be used for example by altering the start positions (both Arena and Platform Tasks) and blocking certain platform choices to prevent egocentric strategies such as counting platforms (Platform Task). However, it would have been of interest to verbally record strategies the subjects used after performing the task. This would have allowed investigation of different strategy uses explicitly in schizotypy or allowed for these strategies to have been co-varied for in the analysis. As a caveat, however, verbal reports of strategies do not necessarily imply efficient use of the same strategies and alternative behavioural measurement of strategies is more likely to be informative in this regard. Nevertheless, the tasks are carefully designed to rule out the main strategies that can be used to solve an allocentric task in a non-allocentric fashion so this measurement is not immediately obvious. In relation to this, this thesis focused on investigation of allocentric spatial memory processes in schizotypal personality but it would

have been advantageous to include an egocentric spatial memory task for comparison. This could have been a task that is designed to assess both forms of memory in one run such as the Weniger & Irle (2008) virtual park (allocentric) and maze (egocentric). Alternatively the egocentric version of the arena task could have been used to determine egocentric spatial memory ability in this group (Parslow et al, 2004). This latter suggestion would have allowed neural recruitment common to both egocentric and allocentric spatial memory to be separated from that which differs between the two reference frames and between the two groups. However, an additional task would not have been feasible within the time subjects were inside the MR scanner. Additionally prolonged scanning times increase the chances of subjects becoming disengaged with cognitive tasks and increases movement within the scanner as fatigue and boredom sets in. In hindsight, this thesis may have benefited from including an egocentric as well as an allocentric spatial memory rather than the two allocentric spatial memory tasks as this would have allowed us to acquire more information regarding spatial cognition in these two groups without compromising scan time.

10.7 Future Research

<u>Future Work</u>

In this section I will highlight several ideas for future work generated from this thesis as well as present preliminary results for a new technique obtained during this thesis as a pilot for a future study. This pilot study has not been included in the main body of this thesis as results are both preliminary and are in collaboration with several other researchers.

<u>Future studies in allocentric spatial memory</u>

The results obtained in this thesis suggest that functional differences are observed during allocentric spatial memory performance both in task relevant regions (e.g. hippocampus) and in more general cognitive control brain regions (e.g. anterior cingulate gyrus, insula and prefrontal cortex) in high schizotypy. As suggested in the above section, a follow up study could assess egocentric spatial memory in schizotypy to elucidate the specificity of impairments to allocentric spatial learning and memory as has been suggested in previous literature. As mentioned in the methodological considerations section of this thesis, smaller numbers are recruited in imaging studies than are needed for valid behavioural studies and as such a larger behavioural study on allocentric and egocentric spatial memory performance may be informative. To this end with a larger sample, a more widespread set of scores for each of the personality scales can be recruited and thus can examine the relationship between allocentric spatial memory performance and different domains of schizotypal personality i.e. positive and negative schizotypal traits.

The Platform Task is a newly developed task that has demonstrated robust neural activation in a spatial memory network including the hippocampus, parahippocampal gyrus, parietal lobes, prefrontal cortex, striatum and thalamus. Future studies in healthy volunteers will confirm the robust nature of these activations. This task was piloted in a different sample prior to its use in this study and the same pattern of activation observed. Further, investigations using this task in psychiatric and ageing populations with greater hippocampal atrophy and dysfunction and more severe cognitive impairments would determine whether this task is sensitive to differences between those groups and controls. Both the Arena and Platform Tasks require future studies in diverse populations so that performance and neural activation can be quantified in different samples and, as such, new studies can compare their results to those of previous literature. Of course this is true for all new tasks.

Recently, techniques traditionally used in animals such as electrophysiological recordings have started to be used in humans, albeit in those with clinical conditions like intractable epilepsy. These new recordings from implanted electrodes have located place cells, grid cells and head direction cells in the human medial temporal lobes (Ekstrom, et al., 2003; J. Jacobs, et al., 2010) and this has opened up an exciting new area of research. Allocentric spatial memory tasks that elicit strong hippocampal and parahippocampal activation like the tasks used in this study may be used alongside electrophysiological recordings to ascertain the true nature of medial temporal lobe involvement in these tasks.

Navigational strategies have been linked to differences in basal cortisol levels; with response learners (non-spatial strategies) demonstrating lower basal cortisol levels and poorer memory on a virtual radial arm maze (Bohbot, Gupta, Banner, & Dahmani, 2011). As schizotypal personality has also been related to altered cortisol response(D. D. Weinstein, et al., 1999), future research could assess whether performance of high schizotypes on allocentric spatial memory tasks is modulated by differences in cortisol levels. The hippocampal region is particularly sensitive to the effects of stress hormones and as such investigations into the effects of cortisol levels on hippocampal functioning and how this might differ between controls and schizotypal individuals would further our understanding of the endocrinological biology of schizotypal personality.

<u>Future investigations using the data acquired in this thesis</u>

In the course of my PhD, there has been an explosion in the use of new analysis techniques for the study of structure, function and cognition for example independent components analysis (ICA), machine learning and functional and effective connectivity analysis. These can be applied to analysing the data acquired during this study. The complex pattern of hypo and hyper-activation in schizotypal personality observed in previous literature and in this thesis

suggests that there is an element of compensatory recruitment in schizotypy and as such a neural network approach to analysis of the data may further illuminate the nature of allocentric spatial memory in schizotypal personality. It is conceivable that high schizotypes rely on a different network of brain regions to accomplish tasks than control subjects despite the commonality of some of the areas recruited. This is suggested by Folley et al (2010) who utilised a virtual Morris Water Maze to study allocentric spatial memory in schizophrenia. In this study, five neural networks that underlie spatial memory were identified using ICA. As well as differences observed in individual brain regions using the general linear model, differences were observed in the preferential recruitment of neural networks between patients and controls during different parts of the tasks. Additionally, compensation for lower or aberrant medial temporal lobe activation may manifest itself as a wider recruitment of brain regions in high schizotypy or stronger connectivity between the temporal lobes and other regions. Based on the results obtained in this thesis, the salience/attention network comprising the insular and anterior cingulate cortex warrants further investigation in schizotypal personality. This network could be functionally different in schizotypes without being specific to any one task or cognitive domain as has been shown in schizophrenia (White, Joseph, Francis, & Liddle, 2010)

Both the structural and functional imaging results obtained in this thesis suggest that the hippocampus plays an important role in schizotypal personality. Using machine learning, it is possible to test whether hippocampal structure and/or function can classify an individual as a high schizotype or as a control. Additionally using machine learning it is possible to investigate which one (or a combination) of the collected metrics is best able to classify an individual as a control or as a high schizotype. This is immensely informative in ascertaining which of the many structural, functional and cognitive differences we observe is truly indicative of the schizotypal individual.

<u>Pilot Data</u>

As outlined in the introduction, research has begun to focus on investigation of white matter integrity using diffusion tensor imaging. For the most part this has revealed lower FA in frontal and temporal regions, and the tracts that connect the two, in first episode and chronic schizophrenia patients(Ellison-Wright & Bullmore, 2009; Kyriakopoulos, et al., 2008), high risk for psychosis groups(B. D. Peters, Blaas, et al., 2010), schizotypal personality disorder (Hazlett, et al., 2011; Nakamura, et al., 2005) and psychometrically defined schizotypy(M. T. Nelson, et al., 2011). FA may reflect a number of biological processes but the one most commonly suggested is myelination. However, DTI is not a direct measure of myelin content or integrity. The most direct means of quantifying myelin in vivo is using multicomponent relaxometric imaging (Menon, Rusinko, & Allen, 1992; Stanisz, Kecojevic, Bronskill, & Henkelman, 1999; Webb, Munro, Midha, & Stanisz, 2003). As part of this thesis, myelin data was collected from a subset of subjects using a new technique for the quantification of myelin content termed multicomponent driven equilibrium single pulse observation of T1 and T2 (mcDESPOT)(Deoni, Rutt, Arun, Pierpaoli, & Jones, 2008). Briefly, this technique decomposes the MR signal into discrete contributions from anatomically distinct water compartments on the basis of their relaxation characteristics. In human brain parenchyma, multicomponent relaxometric imaging analysis reliably reveals two water sub-domains: intra and extra-cellular water, and water trapped between the lipid myelin bi-layers. Volume estimates of the myelin-associated water (myelin water fraction; MWF) correlate strongly with histological myelin estimates, providing a non-invasive measure of myelin content (Laule et al., 2006; Webb, et al., 2003)

Imaging data was acquired on a 3T GE signal HDx scanner equipped with an 8 channel head RF array. Whole brain sagittally oriented mcDESPOT data were acquired for each individual with a field of view of (22 x 22 x 16) cm3 and 128 x 128 x 92 imaging matrix. Sequence specific

parameters were as follows: SPGR: echo time (TE)/repetition time (TR) = 1.7/4.3ms; flip angles (α) = {4, 5, 6, 7, 8, 11, 14 and 18}°; receiver bandwidth (BW) = ±32kHz. For SSFP: TE/TR = 1.7ms/3.4ms; α = {10, 16, 21, 27, 33, 40, 50 and 60}°; BW = ±83kHz. SSFP data was acquired with two RF phase cycling increments of 0 and 180° to allow correction for main magnetic field (B_0) inhomogeneities (Deoni, 2009). A reduced resolution (half resolution in Y and Z dimensions) inversion prepared [IR-] SPGR image was also acquired with TE/TR/TI/α = 1.7ms, 4.3ms/ 450ms/5° to correct for transmit flip angle (B_1) errors (Deoni, 2007). Images were linearly co-registered(Jenkinson, Bannister, Brady, & Smith, 2002), non-parenchyma signal removed (S. M. Smith, 2002) and voxel wise myelin content estimates calculated(Deoni, et al., 2008). The voxel wise myelin content maps from all subjects were then non-linearly co-registered to MNI standard space for comparative analysis (Mazziotta et al., 2001). Registration of the myelin maps were accomplished by first non-linearly co-registering the high flip angle T1-weighted SPGR image acquired as part of the mcDESPOT protocol to the MNI template. The calculated transformation matrix was then applied to the participant's myelin content map. Comparison between groups was performed using tract based spatial statistics (TBSS). TBSS incorporates information from the white matter structure, reducing partial volume effects and increasing confidence in comparing corresponding voxels (S. M. Smith et al., 2006). TBSS first creates a skeleton throughout the white matter and then at each point along the skeleton projects the maximum MWF value along a line normal to the path.

To compare the average and high schizotypy subjects, an independent two tailed t-test was performed using Randomise (part of the FMRIB Software Library – www.fmrib.ox.ac.uk/fsl/-). Non-parametric correlations between MWF and SPQ score were performed using skeleton point-wise correlational analysis along the TBSS identified points using Randomise. Cluster-based thresholding was used to control for multiple comparisons.

Data was analysed by Sean Deoni. Results are presented in Figure 80 and 81 and demonstrate increased myelin water fraction in the high schizotypy group at a cluster corrected level of p < 0.05 in left frontal and temporal white matter.
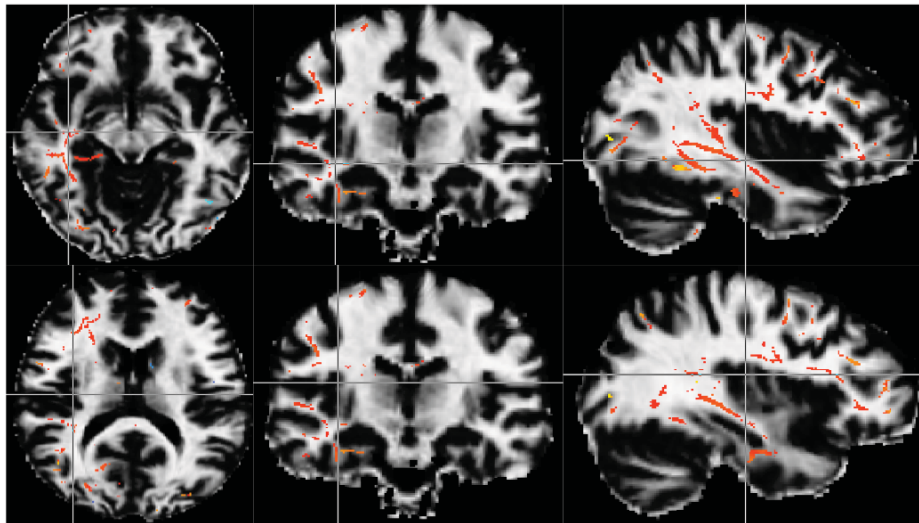
Figure 80 Increased MWF in high schizotypy compared to average schizotypy

(p < 0.05 corrected, red colour scale) Left side of image displays left hemisphere
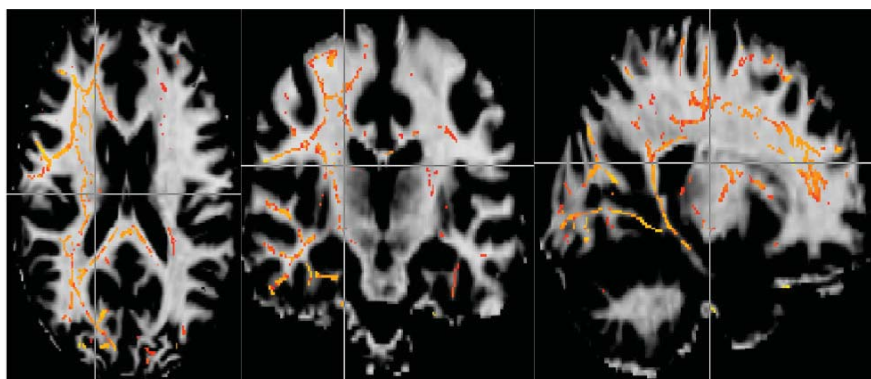
Figure 81 Positive relationship between schizotypy scores and MWF (p <
0.05 corrected, red colour scale) Left side of image displays right hemisphere

The basis for this increase in myelin water fraction is unclear. It could reflect a network of increased axonal connections, as a result or the cause of increased functional connectivity,

reflected in increased myelin water content. Alternatively it could reflect a decompaction of the myelin sheath; the increased intra-wrap space thus reflected in the increased myelin water fraction, which measures the amount of water trapped between the myelin bilayers. The result of an increase in the intra-wrap space between the myelin bilayers is that connectivity will be reduced as conduction velocity will be impaired by the loose weaving of the myelin sheath. The impact of increased myelin water content is that the g-ratio will be affected. The G-ratio is the ratio of the total fibre diameter to the axonal diameter and has an optimal ratio of approximately 0.6. Deviations, either greater or smaller, are likely to affect information processing and ultimately result in impaired cognition. Increases in myelin content suggest a larger total fibre diameter and ultimately this may lead to alterations in neighbouring structures for example smaller grey matter. This preliminary result, on a subset of the larger schizotypy sample, suggests that altered myelin may be a key factor in schizotypal personality and further supports the neurobiological basis of personality traits.

However, this is a new technique which to date has not been used to investigate psychiatric conditions or personality traits in healthy volunteers. Further, the results obtained were lateralised to the left hemisphere and were of *increased* rather than *decreased* myelin content. Thus, these results require replication in a larger sample before firm conclusions can be drawn. This data was collected as pilot data to explore the sensitivity of the technique to differences in myelin content between two schizotypy groups. These preliminary data will now be built upon in a second study where we will run the mcDESPOT sequence again in the same set of schizotypes as validation of the initial results. We will also extend the sample and will be collecting resting state fMRI data, EEG and DTI data with a view to characterising the pattern of brain connectivity in high schizotypy. We will also investigate any alterations found on these metrics against neuropsychological data and cognitive tasks. This will allow investigation into the impact of any observed alterations in connectivity on cognitive ability.

10.8   Conclusions

To conclude, this thesis has demonstrated that in the absence of performance impairments functional differences are observed in the hippocampus, insula and anterior cingulate cortex Subjects with high schizotypy demonstrate an anomalous recruitment (reduced activation during memory encoding and increased activation during memory retrieval) of the hippocampus during allocentric spatial memory and whilst right hippocampal activity during memory encoding correlates with performance in controls this relationship is absent in high schizotypy. Greater activation is observed in the anterior cingulate cortex during allocentric spatial memory performance and this is likely to be related to increased cognitive control and effort in high schizotypes who appear to be hypervigilant of their performance. Right hippocampal volume is smaller in high schizotypy but this was none significant when corrected for multiple comparisons. For the most part, the results provide initial support to suggest the model of schizotypal personality disorder proposed by Siever & Davis (2004) may also apply to healthy volunteers with schizotypal traits. Across methodologies the results presented in this thesis suggest that high schizotypy is associated with structural alterations of the medial temporal lobes specifically the hippocampus and anomalous recruitment of this region during encoding and memory retrieval processes.

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Appendices

Appendix I: Schizotypal Personality Questionnaire Brief (SPQ-B)

Please answer each of the items by circling either Yes or No. Answer all items even if unsure of your answer. When you have finished, check over each one to make sure that you have answered them.

1. People sometimes find me aloof and distant.	Yes	No
2. Have you ever had the sense that some person or force is around you, even though you cannot see anyone?	Yes	No
3. People sometimes comment on my unusual mannerisms and habits.	Yes	No
4. Are you sometimes sure that other people can tell what you are thinking?	Yes	No
5. Have you ever noticed a common event or object that seemed to be a special sign for you?	Yes	No
6. Some people think I am a very bizarre person.	Yes	No
7. I feel I have to be on my guard even with my friends.	Yes	No
8. Some people find me a bit vague and elusive during a conversation.	Yes	No
9. Do you often pick up hidden threats or put-downs from what people say or do?	Yes	No
10. When shopping do you get the feeling that other people are talking notice of you?	Yes	No
11. I feel very uncomfortable in social situations involving unfamiliar people.	Yes	No
12. Have you had experiences with astrology, seeing the future, UFOs, ESP or a sixth sense?	Yes	No
13. I sometimes use words in unusual ways.	Yes	No
14. Have you found that it is best not to let other people know too much about you?	Yes	No
15. I tend to keep in the background on social occasions.	Yes	No
16. Do you ever suddenly distracted by distant sounds that you are not normally aware of?	Yes	No
17. Do you often have to keep an eye out to stop people from taking advantage of you?	Yes	No
18. Do you feel that you are unable to get "close" to other people?	Yes	No
19. I am an odd, unusual person.	Yes	No
20. I find it hard to communicate clearly what I want to say to people.	Yes	No
21. I feel very uneasy talking to people I do not know well.	Yes	No
22. I tend to keep my feelings to myself.	Yes	No

Appendix II: Schizotypal Personality Questionnaire (SPQ)

Please answer each of the items by circling either Yes or No. Answer all items even if unsure of your answer. When you have finished, check over each one to make sure that you have answered them.

1. Do you sometimes feel that things you see on the TV or read in the newspaper have a special meaning for you?	Yes	No
2. I sometimes avoid going to places where there will be many people because I will get anxious.	Yes	No
3. Have you had experiences with the supernatural?	Yes	No
4. Have you often mistaken objects or shadows for people, or noises for a voice?	Yes	No
5. Other people see me as slightly eccentric (odd).	Yes	No
6. I have little interest in getting to know other people.	Yes	No
7. People sometimes find it hard to understand what I am saying.	Yes	No
8. People sometimes find me aloof and distant.	Yes	No
9. I am sure I am being talked about behind my back.	Yes	No
10. I am aware that people notice me when I go out for a meal or to see a film.	Yes	No
11. I get very nervous when I have to make polite conversation.	Yes	No
12. Do you believe in telepathy (mind-reading)?	Yes	No
13. Have you ever had the sense that some person or force is around you, even though you cannot see anyone?	Yes	No
14. People sometimes comment on my unusual mannerisms and habits.	Yes	No
15. I prefer to keep to myself.	Yes	No
16. I sometimes jump quickly from one topic to another when speaking.	Yes	No
17. I am poor at expressing my true feelings by the way I talk and look.	Yes	No
18. Do you often feel that other people have got it in for you?	Yes	No
19. Do some people drop hints about you or say things with a double meaning?	Yes	No
20. Do you ever get nervous when someone is walking behind you?	Yes	No
21. Are you sometimes sure that other people can tell what you are thinking?	Yes	No
22. When you look at a person, or yourself in a mirror, have you ever see the face change right before your eyes?	Yes	No
23. Sometimes other people think I am a little strange?	Yes	No
24. I am mostly quiet when I with other people.	Yes	No
25. I sometimes forget what I am trying to say	Yes	No
26. I rarely laugh and smile.	Yes	No
27. Do you sometimes get concerned that friends or co-workers are not really loyal or trustworthy?	Yes	No
28. Have you ever noticed a common event or object that seemed to be a special sign for you?	Yes	No
29. I get anxious when meeting people for the first time.	Yes	No
30. Do you believe in clairvoyancy (psychic forces, fortune telling)?	Yes	No
31. I often hear a voice speaking my thoughts aloud?	Yes	No
32. Some people think I am a very bizarre person.	Yes	No

33. I find it hard to be emotionally close to other people.	Yes	No
34. I often ramble on too much when speaking.	Yes	No
35. My "non-verbal" communication (smiling and nodding during a conversation) is poor.	Yes	No
36. I feel I have to be on my guard even with my friends.	Yes	No
37. Do you sometimes see special meaning in advertisements, shop windows, or in the way things are arranged around you?	Yes	No
38. Do you often feel nervous when you are in a group of unfamiliar people?	Yes	No
39. Can other people feel your feelings when they are not there?	Yes	No
40. Have you ever seen things invisible to other people?	Yes	No
41. Do you feel that there is no one you are really close to outside of your immediate family or people you can confide in or talk to about personal problems?	Yes	No
42. Some people find me a bit vague and elusive during a conversation.	Yes	No
43. I am poor at returning social courtesies or gestures.	Yes	No
44. Do you often pick up hidden threats or put-downs from what people say or do?	Yes	No
45. When shopping do you get the feeling that other people are talking notice of you?	Yes	No
46. I feel very uncomfortable in social situations involving unfamiliar people.	Yes	No
47. Have you had experiences with astrology, seeing the future, UFOs, ESP or a sixth sense?	Yes	No
48. Do everyday things seem usually large or small?	Yes	No
49. Writing letters to friends is more trouble than it is worth.	Yes	No
50. I sometimes use words in unusual ways.	Yes	No
51. I tend to avoid eye contact when conversing with other people.	Yes	No
52. Have you found that it is best not to let other people know too much about you?	Yes	No
53. When you see people talking to each other, do you often wonder if they are talking about you?	Yes	No
54. I would feel very anxious if I had to give a speech in front of a large group of people.	Yes	No
55. Have you ever felt that you are communicating with another person telepathically (by mind reading)?	Yes	No
56. Does your sense of smell sometimes become unusual strong?	Yes	No
57. I tend to keep in the background on social occasions.	Yes	No
58. Do you tend to wonder off the topic when having a conversation?	Yes	No
59. I often feel that others have it in for me.	Yes	No
60. Do you sometimes feel that other people are watching you?	Yes	No
61. Do you ever suddenly distracted by distant sounds that you are not normally aware of?	Yes	No
62. I attach little importance to having close friends.	Yes	No
63. Do you sometimes feel that people are talking about you?	Yes	No
64. Are you thoughts sometimes so strong that you can almost hear them?	Yes	No
65. Do you often have to keep an eye out to stop people from taking	Yes	No

advantage of you?		
66. Do you feel that you are unable to get "close" to other people?	Yes	No
67. I am an odd, unusual person.	Yes	No
68. I do not have an expressive lively way of speaking.	Yes	No
69. I find it hard to communicate clearly what I want to say to people.	Yes	No
70. I have some eccentric (odd) habits.	Yes	No
71. I feel very uneasy talking to people I do not know well.	Yes	No
72. People occasionally comment that my conversation is confusing.	Yes	No
73. I tend to keep my feelings to myself.	Yes	No
74. People sometimes stare at me because of my odd appearance.	Yes	No

Appendix III   National Adult Reading Test Revised (NART-R) Word list and score sheet

Instructions for NART: These words are pronounced differently to how they read. Please speak each word out loud and clearly so that the experimenter can hear. Please try to pronounce each word as best you can even though some of the words may be quite difficult.

List of words (2nd edition)

CHORD	HIATUS
ACHE	SUBTLE
DEPOT	PROCREATE
AISLE	GIST
BOUQUET	GOUGE
PSALM	SUPERFLUOUS
CAPON	SIMILE
DENY	BANAL
NAUSEA	QUADRUPED
DEBT	CELLIST
COURTEOUS	FACADE
RAREFY	ZEALOT
EQUIVOCAL	DRACHM
NAIVE	AEON
CATACOMB	PLACEBO
GAOLED	ABSTEMIOUS
THYME	DETENTE
HEIR	IDYLL
RADIX	PUERPERAL
ASSIGNATE	AVER
	GAUCHE
	TOPIARY

LEVIATHAN

BEATIFY   SYNCOPE

PRELATE   LABILE

SIDEREAL   CAMPANILE

DEMESNE

WORD	PRONUNCIATION	CORRECT?
CHORD	kord	
ACHE	ayk	
DEPOT	depoh	
AISLE	I1	
BOUQUET	bookay	
PSALM	sahlm	
CAPON	kayp'n	
DENY	denI	
NAUSEA	nawzeea	
DEBT	det	
COURTEOUS	kurtyus	
RAREFY	rayrefI	
EQUIVOCAL	ikwivukal	
NAÏVE	nIeev	
CATACOMB	katucoom	
GAOLED	(jailed)	
THYME	(time)	
HEIR	(air)	
RADIX	raydix	
ASSIGNATE	asignayt	
HIATUS	hIaytus	
SUBTLE	sutl	
PROCREATE	prohkreeayt	
GIST	jist	
GOUGE	gowj	
SUPERFLUOUS	sooperfloous	
SIMILE	similee	
BANAL	bunaal	
QUADRUPED	kwodrooped	
CELLIST	chelist	
FAÇADE	fasaad	
ZEALOT	zelot	
GOUGE	gowj	
SUPERFLUOUS	sooperfloous	
SIMILE	similee	
BANAL	bunaal	
QUADRUPED	kwodrooped	
CELLIST	chelist	
FAÇADE	fasaad	
ZEALOT	zelot	
DRACHM	dram	
AEON	eeon	
PLACEBO	plaseeboh	

ABSTEMIOUS	absteemius	
DÉTENTE	dayt-(aunt)	
IDYLL	adil/idul	
PUERPERAL	pwuerpurul	
AVER	avuur	
GAUCHE	gohsh	
TOPIARY	togpeeuree	
LEVIATHAN	levIuthun	
BEATIFY	beeafifI	
PRELATE	prelit	
SIDEREAL	sIdeeriul	
DEMESNE	(domain)	
SYNCOPE	singkupee	
LABILE	laybIl	
COMPANILE	kampaneeley	

Appendix IV   Mini International Neuropsychiatric Interview (MINI) screening sheet

Screening (and compulsory sections) from the MINI

	Yes	No
A. MAJOR DEPRESSIVE EPISODE A1a) Were you ever depressed or down, most of the day, nearly everyday, for two weeks? IF YES ask:	Yes	No
A1b) For the past two weeks, were you depressed or down, most of the day, nearly every day?	Yes	No
A2a) Were you ever much less interested in most things or much less able to enjoy the things you used to enjoy most of the time, for two weeks? IF YES ask:	Yes	No
A2b) In the past two weeks, were you much less interested in most things or much less able to enjoy the things you used to enjoy most of the time?	Yes	No

	Yes	No
B. SUICIDALITY In the past month did you: B1) Suffer any accident? IF NO TO B1 SKIP TO B2, IF YES, ASK B1a:	Yes	No
B1a) Plan or intend to hurt yourself in that accident either actively or passively (e.g. not avoiding a risk)? IF NO TO B1a, SKIP TO B2: IF YES, ASK B1b:	Yes	No
B1b) Intend to die as a result of this accident?	Yes	No
B2) Feel hopeless?	Yes	No
B3) Think that you would be better off dead or wish you were dead?	Yes	No
B4) Want to harm yourself or to hurt or to injure yourself or have mental images of harming yourself?	Yes	No

B5) Think about suicide?
IF NO TO B5, SKIP TO B7, OTHERWISE:
 	
  Frequency: Intensity:
  Occasionally   Mild
  Often   Moderate
  Very often   Severe
Can you state you will not act on these impulses during this treatment program?
	Yes
	
	Yes
		No
		
		No

B6) Feel unable to control these impulses?	Yes	No
B7) have a suicide plan?	Yes	No
B8) Take any active steps to injure yourself or to prepare for a suicide attempt in which you expected or intended to die?	Yes	No
B9) Deliberately injure yourself without intending to kill yourself?	Yes	No
B10) Attempt suicide? IF NO SKIP TO B11: Hope to be rescued/ survive Expected/ intended to die	Yes	No
In your lifetime: B11) Did you ever make a suicide attempt?	Yes	No

	Yes	No
C. MANIC AND HYPOMANIC EPISODES C1a) Have you ever had a period of time when you were feeling 'up' or 'high' or 'hyper' or so full of energy or full of yourself that you got into trouble, // or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.)	Yes	No

IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN: BY 'UP' OR 'HIGH' OR 'HYPER', CLARIFY AS FOLLOWS: By 'up' or 'high' or 'hyper' I mean: having elated mood; increased energy; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behaviour; phoning or working excessively or spending more money. IF NO, CODE NO TO C1b: IF YES ASK:		
C1b) Are you currently feeling 'up' or 'high' or 'hyper' or full of energy?	Yes	No
C2a) Have you ever been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified? IF NO, CODE NO TO C2b: IF YES ASK:	Yes	No
C2b) Are you currently feeling persistently irritable?	Yes	No

D. PANIC DISORDER D1a) Have you, on more than one occasion, had spells or attacks when you suddenly felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	Yes	No
Db) Did the spells surge to a peak within 10 minutes of starting?	Yes	No

E. AGORAPHOBIA E1) Do you feel anxious or uneasy in places or situations where help might not be available or escape might be difficult, like being in a crowd, standing in a line (queue), when you are alone away from home or alone at home, or when crossing a bridge, or travelling in a bus, train or car or where you might have a panic attack or the panic-like symptoms we just spoke about? IF E1=NO, CIRCLE NO IN E2.	Yes	No
E2) Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?	Yes	No

F. SOCIAL PHOBIA (Social Anxiety Disorder) F1) In the past month, did you have persistent fear and significant anxiety at being watched, being the focus of attention, or of being humiliated or embarrassed? This includes things like speaking in public, eating in public or with others, writing while someone watches or being in social situations.	Yes	No

G. OBSESSIVE-COMPULSIVE DISORDER G1) In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? // (For example, the idea that you were dirty, contaminated or had germs, or fear of contaminating others, or fear of harming someone even though it disturbs or distresses you, or fear you would act on some impulse, or fear or superstitions that you would be responsible for things going wrong, or obsessions with sexual thoughts, images or impulses, or hoarding, collecting, or religious obsessions. (DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)	Yes	No
G4) In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, arranging things or other superstitious rituals?	Yes	No

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H. POSTTRAUMATIC STRESS DISORDER		
H1) Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else? EXAMPLES OF TRAUMATIC EVENTS INCLUDE: SERIOUS ACCIDENTS, SEXUAL OR PHYSICAL ASSAULT, A TERRORIST ATTACK, BEING HELD HOSTAGE, KIDNAPPING, FIRE, DISCOVERING A BODY, WAR, OR NATURAL DISASTER, WITNESSING THE VIOLENT OR SUDDEN DEATH OF SOMEONE CLOSE TO YOU, OR A LIFE THREATENING ILLNESS.	Yes	No
H2) Did you respond with intense fear, helplessness or horror?	Yes	No
H3) during the past month, have you re-experienced the event in a distressing way (such as dreams, intense recollections, flashbacks or physical reactions) or did you have intense distress when you were exposed to a similar event?	Yes	No

I. ALCOHOL DEPENDENCE/ABUSE		
I1) In the past 12 months, have you had 3 or more alcoholic drinks, - within a 3 hour period, - on 3 or more occasions?	Yes	No
I2) In the past 12 months: a) Did you need to drink a lot more in order to get the same effect that you got when you first started drinking or did you get much less effect with continued use of the same amount?	Yes	No
b) When you cut down on drinking did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms (for example, the shakes, sweating or agitation) or to avoid being hungover?	Yes	No
c) During the times when you drank alcohol, did you end up drinking more than you planned when you started?	Yes	No
d) Have you tried to reduce or stop drinking alcohol but failed?	Yes	No
e) On the days that you drank, did you spend substantial time in obtaining alcohol, drinking, or in recovering from the effects of alcohol?	Yes	No
f) Did you spend less time working, enjoying hobbies, or being with others because of your drinking?	Yes	No
g) If your drinking has caused you health or mental health problems did you still keep drinking? ARE 3 OR MORE I2 ANSWERS CODED YES? ASK QUESTION I3.	Yes	No

J: NON-ALCOHOL PSYCHOACTIVE SUBSTANCE USE DISORDERS
Now I am going to show you / read to you a list of street drugs or medicines. J1) In the past 12 months, did you take any of these drugs more than once, to get high, to feel elated, to get "a buzz" or to change your mood? CIRCLE EACH DRUG TAKEN: Stimulants: amphetamines, "speed", crystal meth, "crank", "rush", Dexedrine, Ritalin, diet pills. Cocaine: snorting, IV, freebase, crack, "speedball". Narcotics: heroin, morphine, Dilaudid, opium, Demerol, methadone, Darvon, codeine, Percodan, Vicoden, OxyContin. Hallucinogens: LSD ("acid"), mescaline, peyote, PCP ("Angel dust", "peace pill"), psilocybin, STP, "mushrooms", "ecstasy", MDA, MDMA, or ketamine ("special K"). Inhalants: "glue", ethyl chloride, "rush", nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers"). Cannabis: marijuana, hashish ("hash"), THC, "pot", "grass", "weed", "reefer". Tranquilizers: Quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown, GHB, Roofinol, "Roofies". Miscellaneous: steroids, non-prescription sleep or diet pills. Cough Medicine? Any others?

SPECIFY THE MOST USED DRUG(S):_____

WHICH DRUG(S) CAUSE THE BIGGEST PROBLEM?:_____

K: PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES Now I am going to ask you about unusual experiences that some people have. K1a) Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? NOTE: ASK FOR EXAMPLES TO RULE OUT STALKING.	Yes	No
b) IF YES OR YES BIZARRE: do you currently believe these things?	Yes	No
K2a) Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking?	Yes	No
b) IF YES OR YES BIZARRE: do you currently believe these things?	Yes	No
K3a) Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.	Yes	No
b) IF YES OR YES BIZARRE: do you currently believe these things?	Yes	No
K4a) Have you ever believed that you were being sent special messages through the TV, radio, newspapers, books or magazines or that a person you did not personally know was particularly interested in you?	Yes	No
b) IF YES OR YES BIZARRE: do you currently believe these things?	Yes	No
K5a) Have your relatives or friends ever considered any of your beliefs odd or unusual? INTERVIEWER: ASK FOR EXAMPLES. ONLY CODE YES IF THE EXAMPLES ARE CLEARLY DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS K1 TO K4, FOR EXAMPLE, SOMATIC OR RELIGIOUS DELUSIONS OR DELUSIONS OF GRANDIOSITY, JEALOUSY, GUILT, RUIN OR DESTITUTION, ETC.	Yes	No
b) IF YES OR YES BIZARRE: do they currently consider your beliefs strange?	Yes	No
K6a) Have you ever heard things other people couldn't hear, such as voices? IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behaviour or did you hear two or more voices talking to each other?	Yes Yes	No No
b) IF YES OR YES BIZARRE to K6a: have you heard sounds / voices in the past month? IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behaviour or did you hear two or more voices talking to each other?	Yes Yes	No No
K7) Have you ever had visions when you were awake or have you ever seen things other people couldn't see? CLINICIAN: CHECK TO SEE IF THEY ARE CULTURALLY INAPPROPRIATE.	Yes	No
b) IF YES: have you seen these things in the past month?	Yes	No
CLINICIAN'S JUDGEMENT: K8b) Is the patient currently exhibiting incoherence, disorganized speech, or marked loosening of associations?	Yes	No
K9b) Is the patient currently exhibiting disorganised or catatonic behaviour?	Yes	No
K10b) Are negative symptoms of schizophrenia, e.g. significant affective flattening, poverty of speech (alogia) or inability to initiate or persist in goal-directed activities (avolition), prominent during the interview?	Yes	No
K11a) Are 1 or more <<a>> questions from K1a to K7a coded Yes or Yes Bizarre and is either: MAJOR DEPRESSIVE EPISODE (CURRENT, RECURRENT, PAST)	Yes	No

OR MANIC OR HYPOMANIC EPISODE (CURRENT OR PAST) CODED Yes? If NO to K11a, circle No in both Mood disorder with psychotic features diagnostic boxes and move to K13.		
b) You told me earlier that you had period(s) when you felt (depressed/high/persistently irritable). Were the beliefs and experiences you just described restricted exclusively to times when you were feeling depressed/high/irritable? IF THE PATIENT EVER HAD A PERIOD OF AT LEAST TWO WEEKS OF HAVING THESE BELIEFS OR EXPERIENCES (PSYCHOTIC SYMPTOMS) WHEN THEY WERE NOT DEPRESSED/HIGH/IRRITABLE, CODE NO TO THIS DISORDER. IF ANSWER NO TO THIS DISORDER, ALSO CIRCLE NO TO K12 AND MOVE TO K13.	Yes	No
K12a) Are 1 or more <<b>> questions from K1b to K7b coded Yes or Yes Bizarre and is either: MAJOR DEPRESSIVE EPISODE (CURRENT) OR MANIC OR HYPOMANIC EPISODE (CURRENT) CODED Yes? IF THE ANSWER IS YES TO THIS DISORDER (LIFETIME OR CURRENT) AND K14 AND MOVE TO THE NEXT MODULE.	Yes	No
K13) Are 1 or more <<b>> questions from K1b to K6b coded Yes Bizarre? OR Are 2 or more << b >> questions from K1b to K10b coded Yes (rather than Yes Bizarre)? And did at least two of the psychotic symptoms occur during the same 1 month period?	Yes	No
K14) Is K13 coded Yes? OR Are 1 or more << a >> questions from K1a to K6a, coded Yes Bizarre? OR Are 2 or more << a >> questions from K1a to K7a, coded Yes (rather than Yes Bizarre) AND did at least two of the psychotic symptoms occur during the same 1 month period?	Yes	No

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L: ANOREXIA NERVOSA

L1a) How tall are you?_____

b) What was your lowest weight in the past 3 months?_____

HEIGHT / WEIGHT TABLE CORRESPONDING TO A BMI THRESHOLD OF 17.5 KG/M^2

Height/Weight													
ft/in	4'9	4'10	4'11	5'0	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9
lbs.	81	84	87	89	92	96	99	102	105	108	112	115	118
cm	145	147	150	152	155	158	160	163	165	168	170	173	175
kgs	37	38	39	41	42	43	45	46	48	49	51	52	54

Height/Weight				
ft/in	5'11	6'0	6'1	6'2	6'3
lbs.	125	129	132	136	140
cm	180	183	185	188	191
kgs	57	59	60	62	64

The weight thresholds above are calculated using a body mass index (BMI) equal to or below 17.5 kg/m^2 for the patient's height. This is threshold guideline below which a person is deemed underweight by the DSM-IV and the ICD-10 Diagnostic Criteria for Research for Anc Nervosa.

M: BULIMIA NERVOSA		

M1) In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?	Yes	No
M2) In the last 3 months, did you have eating binges as often as twice a week?	Yes	No

N: GENERALISED ANXIETY DISORDER N1a) Were you excessively anxious or worried about several routine things, over the past 6 months? IN ENGLISH, IF THE PATIENT IS UNCLEAR ABOUT WHAT YOU MEAN PROBE BY ASKING (Do others think that you are a "Worry wart") AND GET EXAMPLES.	Yes	No
b) Are these anxieties and worries present most days? ARE THE PATIENT'S ANXIETY AND WORRIES RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?	Yes Yes	No No

P: ANTISOCIAL PERSONALITY DISORDER Before you were 15 years old, did you: P1a) repeatedly skip school or run away from home overnight?	Yes	No
b) repeatedly lie, cheat, "con" others, or steal?	Yes	No
c) start fights or bully, threaten, or intimidate others?	Yes	No
d) deliberately destroy things or start fires?	Yes	No
e) deliberately hurt animals or people?	Yes	No
f) force someone to have sex with you? ARE 2 OR MORE P1 ANSWERS CODED YES? DO NOT CODE YES TO THE BEHAVIOURS BELOW IF THEY ARE EXCLUSIVELY POLITICALLY OR RELIGIOUSLY MOTIVATED.	Yes Yes	No No
Since you were fifteen have you: P2a) repeatedly behaved in a way that others would consider impossible, like failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself?	Yes	No
b) done things that are illegal even if you didn't get caught (for example, destroying property, shoplifting, stealing, selling drugs, or committing a felony)?	Yes	No
c) been in physical fights repeatedly (including physical fights with your spouse or children)?	Yes	No
d) often lied or "conned" other people to get money or pleasure, or lied for fun?	Yes	No
e) exposed others to danger without caring?	Yes	No
f) felt no guilt after hurting, mistreating, lying to, or stealing from others, or after damaging property? ARE 3 OR MORE P2 QUESTIONS CODED YES?	Yes Yes	No No

Appendix V   Instructions for running the Arena Task

Standardised instructions for the Arena Task

Below are the standardised verbal instructions for the Arena task. These need to be considered alongside the standard operating procedure and a number of practice sessions to be run inside the Paradigm program. At each stage of the demonstration offer general encouragement to the participants and give them sufficient practice on the early sessions so they feel comfortable with firstly using the joystick and then the task - make sure they are comfortable with the task and joystick prior to starting the practice trials.

Verbal Instructions for the Arena Task:

These instructions should be learnt and used verbatim where possible. However, they can be kept alongside the trial versions of the Arena task running on a laptop as reference for the researcher.

If the subject is computer game orientated you can say: "We are using standard instructions to make sure everyone understands what to do. So we will start at a basic level even though things might appear obvious at times".

Describing the joystick

Open the Paradigm program and set to a pole experiment. Follow the basic task set up as per the standardized instructions. Use filename 01_Training_Encoding.htm to describe the task during this section.

In front of you is a space. You will be moving around in it and I will show you how to do this. Just watch to start with and I will take plenty of time to explain what you have to do.

If you watch this – you can see how you can move forward and back in the place using the joystick. (Demonstrate moving forwards and backwards.) Have a go moving forwards and backwards in the place? (subject attempts – use verbal cues such as'that's right – try going forward (or backwards), as necessary).

You can also turn left and right in the place using the joystick. (Demonstrate moving the joystick left and right.) You will be able to move back and forward and move left and right using the joystick. Have a go at moving left and right with the joystick just to get used to moving around. (Or say just have a go for more computer familiar subjects.)

Describing the pole and moving towards the pole

In order to describe this section of the instructions you need to open and set up filename 02_Training_Encoding.htm.

In the place you can see a pole. (Show them the pole in the environment.) You should move forwards towards the pole using the joystick. It can be a little bit to the left or the right and you can use the joystick to move towards it. Watch me do it. (Demonstrate moving to the pole and include some slight movements to the left and right as you do so to demonstrate directional movement.) Now you have a go at moving towards the pole. Does this feel comfortable? At the bottom of the pole there is a base. (Move towards the pole and point to the bottom of the pole.) This is the raised area surrounding the bottom of the pole. You need to move towards the pole and go so you are within the raised area of the base. See how you stop when you get to the raised area. Now would you like to have a go at this? (Start a second trial filename 04_Training_Encoding.htm with the pole and man moved to a different place.) Now as I showed you before use the joystick to move left, right, backwards and forwards so that you move towards the pole. Have a go and move to the pole. Remember to move towards the pole using the most direct route. You can make as many small adjustments either left or right, back or forward in order to get to the pole in the most direct way.

As necessary repeat this practice trial until the subject is confident / competent in terms of moving to the pole. Use filename **** for additional practices on the encoding trials.

Describing the environment

In order to go through these instructions have filename 05_Training_EncodingAndRetrieval.htm open in the Paradigm program.

The idea of the task is to remember where the pole is. So when you go to the pole you have to look around you (Point towards the environment in a sweeping manner.) You have to look at the different patterns on the walls to remember where the pole is. (Demonstrate.) I am moving towards the pole and looking at the patterns on the wall to remember where the pole is. When I next enter this place the pole will not be there but I will need to remember where it is by looking around at the patterns on the wall. So in a moment there will be a break and everything will disappear. There will be a pause and then I will re-enter the place. (Talk this through at the pace of moving towards the pole and entering the rest period.) You can see now this blank screen as it pauses.

Now you can see I have re-entered the place. I have re-entered the place at a different spot to where I started last time. So it will look different – you can see by looking at the walls I am now facing. You can see that the pole has disappeared. (Move around the environment to show them the pole had disappeared.) Remember I was looking around as I was going to the pole last time I was in the place. Now the idea of the task is to go to where the pole was using your memory. You move to where you think the pole was and stop. (Demonstrate doing this.) When I get to where I think the pole was I stop.

Introducing the coloured pictures (take them through the task again with demonstration, but now introduce the coloured pictures; filename 06_Training_EncodingAndRetrieval_Pics.htm)

Now I'll just go through this again once more before you have a go. So I have entered the place where there is a pole….. I am looking around the walls as I move towards the pole. When I get inside the base of the pole I stop and I won't be able to move the joystick anymore.. Now we go to a break in the task where there is a blank screen….. I am now back in the place only this time the pole is not there and I have to remember where is was using the patterns on the wall…. When I have moved to the spot where I think the pole was I just stay in this position….. Now this time there is a further break… so just watch until it finishes… after this you will see a coloured picture…… you don't have to do anything ….. just look at it… now there is another break and it has finished.

First Practice Trial

In order to run the first practice session for the participants have filename 07_Training_EncodingAndRetrieval.htm running in the Paradigm program. Okay now you have seen me do the task a couple of times would you like to have a go now? (Talk them through it. Some short prompts can be used as follows.)

Use prompt, remember at the end you will see the coloured picture and you only have to look at it. Moving to the Pole (encoding)

Push forward to go forward; you can go backwards – pull the joy stick towards you. Push left or right to go in that direction; remember to look at the walls as you do it; move towards the pole; use the shortest route;

Rest

This is where it pauses; wait now for the next bit; there is a blank screen pause and then a colour screen pause.

Retrieval

OK now this is the same place but you have started at a different direction; go to where the pole was; remember to use the patterns on the wall; keep moving until you get to where you think the pole was; When you get to the spot you are happy you just rest there.

At the end of their practice trial say: If they are reasonably fluent say "that was a good start" (and ask if they have any questions; If they are not reasonably fluent in doing the task repeat the demonstration and the practice again. If after this there is indication that the subject is not able to do the task sufficiently well, discontinue at this point.

Training Trials

Proceed to three training trials, using the prompts above as necessary, but fading them out. Please note the three training trials should occur after practice and these should not be repeated. To run the practice trials use filename 08_Training_3xEncodingAndRetrieval.htm

Appendix VI   **Instructions for the Platform Task**

Standardised Instructions for the Platform Task

Below are the standardised verbal instructions for the Platform task. These need to be considered alongside the standard operating procedure and practice sessions to be run inside the Paradigm program. At each stage of the demonstration offer general encouragement to the participants and give sufficient practice on early sessions so they feel comfortable with first using the roller ball and then the task - make sure they are comfortable with the task and roller ball prior to starting the practice trials.

If the subject is computer game orientated you can say: "We are using standard instructions to make sure everyone understands what to do. So we will start at a basic level even though things might appear obvious at times".

Using the roller ball

Initially present participants with a tracker ball which has not been covered in mesh to familiarise them with the equipment.

For this task we are going to use a tracker ball. This is the tracker ball. (Researcher shows the tracker ball to the participant.) The tracker ball has a red ball on the top of it which you use to move around. On the side of the tracker ball here (show the participant the button on the side of the tracker ball) you can see there is a button which you will need to press when I tell you later on. You can have your fingers moving over the ball of the tracker ball and then slide down to press the button. Demonstrate this to the participants and give them to tracker ball to get a feel for how it works.

Now take out the tracker ball to be used inside the scanner with the wire mesh around it.

Because we are using the task inside the brain imaging scanner we have had to place some mesh around the tracker ball so it now looks a little strange. You can see that the tracker ball now has a glove around it. You need to place your hand inside the glove and you can feel the tracker ball underneath your hand just like before. You can feel that the ball moves under your fingers and you can still slide your fingers down to the button on the side.

Let participants play with the tracker ball inside the wire mesh till they are comfortable with moving their hands over the ball and pressing the button.

Open the file Layoutfamiliarisation.htm. In this file participants are presented with the virtual reality environment so they can get used to using the roller ball. There is one platform but it is out of sight so can be ignored.

OK now you are comfortable with the tracker ball and how it feels inside its glove I will talk about the task.

If you look at this computer screen you can see an imaginary space outside. You can see there are trees, buildings and people in the outside space. You will be moving around in it and I will show you how to do this. Just watch to start with and I will take plenty of time to explain what you have to do.

You can look around to see the different objects (demonstrate by pointing out objects); you can also point to things – there is a white marker on the screen to point to things. I can move the marker around to point to things. I use the tracker ball to do this. (Move the cursor around do demonstrate it move around.) You can see if I move quite to the left or right of the screen I can look further around. I can look left and right to see all of the buildings, trees and people. To move to the left I move the pointer to the left side of the screen and to move to the right pointer to the right side of the screen. (Demonstrate pointing left and right.) You can now try the tracker ball. Move the roller ball left and right. Can you see how moving the tracker ball to the left or the right makes you point left and right? You can see the buildings, people and trees all around. (Participant attempts – use verbal cues such as "that's right" –"try going left or right", as necessary).

Moving to a Platform

Once participants are comfortable with the roller ball open file Practice2platforms.htm to show them how to move to a platform. The file will contain only two platforms so participants can feel the sensation of moving towards a platform. Run the session more than once till they are happy with moving towards a platform. The different sessions will have the platform moved out of sight so participants get used to moving to the left or right in order to search for the platforms. In between the different sessions there will be a brief blank screens.

"In the outside space there will platforms (point the platforms), this is a platform. The platform is like a flat saucer. You can see a red and a yellow platform in this outside space. You can use the tracker ball to point to the platform (demonstrate). When a platform is yellow you are able to move to it. However when the platform is red you are not able to move towards it. You can go to the platform by pressing this button (show button). (Researcher moves the cursor over the platform. Demonstrate that only one area of the platform can be selected.) You will swoop towards the platform once you have pressed the button to go towards it. When you get to a platform you are given feedback about whether you have been to this platform before or not. If you have not been to the platform before you will see a green tick to say your selection is correct, if you have been to the platform before and you will see a red cross.

You can see that once you have been to the platform you come back into the space facing the centre of the outside space. You will always end up facing the centre of the outside space after you have moved to the platforms. You can see I am now seeing the outside space from the platform I moved towards. Now I have been to this platform I will move to the other platform which I have not been to yet. You'll notice that the platform is no longer red so I can move towards it.

Now you have seen me move towards a platform I would like you to have a go. Move the tracker ball till the pointer is over the platform. Now when you are ready press the button to move towards the platform. Let's go through this a few times so can get really used to it. You might need to look around to find the platform. When it is not immediately in view cue them to go far left and far right.

Multiple platforms

Open filename Practice4platform.htm which will have a series of four platform environments.

Now you are used to the tracker ball I'll talk you through the aim of this task. As you can see here (point to the platforms on the screen) rather than having two platforms you will normally have several. You need to take a look around and remember where the platforms are in relation to the trees, buildings and people in the outside space. To complete the task well you need to go onto each platform only once. You need to keep in mind which platforms you have visited. You need to keep in mind which platforms you still need to go to as well. To do this look at the buildings, people and trees which are near to each platform. (Show them around the environment and point out what is around the platforms.) As before, you can see that not all the platforms are yellow so you need to go to the yellow platforms. (Move around the platforms talking participants through it. Saying things like: "You can see I am moving to this platform", "Now I remember I have been to this one before so I will go over to this next one".)

Now that you have seen me move around this outside space with a number of platforms I would like you to have a go. We can through this as many times as you like so ask any questions you would like to. Use the tracker ball to move the pointer left and right to take a look at the buildings, trees and people which are around the platforms. Try to fix in your mind where the platforms are by what is around them. Now when you are ready choose which of the yellow platforms you would like to move towards using the pointer. That's right now press the button on the side to go towards it. You can see that once you have been told you have gone to the right platform with the tick you go back into the outside space standing on the platform and facing the middle of the outside space. From here you need to look around and select another yellow platform to go to. Also keep in mind that you can't go to the red platforms.

Talk participants all the way through the four platforms through to the end of the block.

When you have gone to all the platforms two pictures will appear on the screen. One is a blank screen. The other is a swirly picture of different colours. You can see the blank screen now. And if we wait awhile the coloured image will also appear. Each time these images appear it means you have gone to all the platforms in one outside space. When the images disappear and you re-enter the outside space you will be

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in a different space and the platforms will be in a different place. You need to look around the outside space again to see where the platforms are. As before you need to choose a platform to go to. Once you have seen the tick to say you went to a correct platform look around the space again to choose another yellow platform to go to again. Remember to look around at the buildings, trees and people which are around the platforms so you can fix in your mind which platforms you have been to and which ones you need to go to.

Talk participants through the remainder of the four platforms. Give them prompts as and when they need them. Encourage them to look around the environment and verbalise the features of the environment which are around each platform. It may be an idea to get them to talk you through their thought processes as they are completing the task. There will be five different versions of the four platform block to take participants through so they will have plenty of practice. If participants need more practice it can be run again.

Open filename practice6platform.htmto give participants practice on the six platform blocks.

OK. Now you have had go on getting around four platforms we will look at the next level where there are six platforms to work your way around. As before some of the platforms will be yellow and some will be red. You will only be able to go to the yellow platforms. You need to look around at the buildings, trees and people to fix where the platforms are in your mind. Move through the platforms as before and I can talk you through things where you need me to. It might be a good idea for you to talk aloud as you are doing the task to recall what you did when you were working your around the four platforms.

Now you have had a practice of the different numbers of platforms I would like you to do a run through of the full task on your own. Take it at your own pace and use what you have previously learnt to recall where the platforms are.

Open filename Cog2DryRunplatform.htm leave participants to work their way through the multiple levels.

Appendix VII   **Instructions for administering the N-back**

N-back Standardised Instructions

Instructions to be learnt and verbally administered to participants. However they can be used as a reference to researchers when going through a practice run of the task. Instructions for the researcher will be written in italics and instructions to be learnt to be said to participants will be written in normal text.

We will now explain to you another memory task. In this task you are going to see letters coming up on the screen. They will be in the middle of the screen and printed in black. All you need to do is keep in mind the letters you see.

Run Powerpoint presentation nBack1

In this presentation you can see just a stream of letters. You can see that the majority of letters are different from one another but that there were two which were the same following one another. In this case, it was the letter L that was repeated.

Open up presentation Nback1_5

Let's look at another example. You can see how the letters come up on the screen one after another. In this example you can see that the letter "E" is shown twice.

Indicate the two E slides in Powerpoint presentation nBack1_5. Illustrate the presentations with button presses on the joystick.

You will have kept in mind the first E you saw and recognise the second one as a repetition. Here you had to keep in mind only the previous letter which you have seen. This is called "One Back" What we would like you to do is tell us that you recognise that you have seen the same letter twice in a row. We would like you to respond by pressing this button on the joystick. You will be given the opportunity to do this later on. So when you have been told that you are doing "One Back" you need to keep an eye out for two letters which are the same and appear one after the other. Now we will have a look at some more examples.

Repeat one back pointing it out and increasing rate – nback1_4 (4 seconds on screen) nBack1_3 (3 seconds on screen) and nBack1_2 (2 seconds on screen)

Give prompts during the additional presentations for them to attend to the letters on the screen and point out when they would need to respond.

Nback 1 presentations – nBack1 (first presentation shown) nBack1_5 (five seconds on screen), nBack1_4 (4 seconds on screen), nBack1_3 (3 seconds on screen), nBack1_2 (2 seconds on screen)

Run nBack2_5 presentation

The task has several levels. Now that you have practiced "One Back" let's try a slightly more difficult level. Now you will see another stream of letters. Again they will be in the middle of the screen, printed in black. Again we would like you to keep in mind the letters that you see. This time you can see that one letter is repeated but separated by a different letter. Point to the two separated repeated letters. In this example you can see that the letter A appears twice separated by one different letter.

What we would like you to do is tell us that you recognise that you have seen this letter before and that the letter appeared before the last letter presented. We would like you to respond by pressing this button on the joystick. This is called "Two Back". When you are told that you are doing "two back" you need to keep an eye out for two of the same letters separated by one different letter. Now we will look at some more examples.

Repeat one back pointing it out and increasing rate – nback2_4 (4 seconds on screen) nBack2_3 (3 seconds on screen) and nBack2_2 (2 seconds on screen)

Give prompts during the additional presentations for them to attend to the letters on the screen and point out when they would need to respond.

Nback2 presentations – nBack2_5 (5 seconds), nBack2_4 (4 seconds), nBack2_3 (3 seconds), nBack2_2 (2 seconds)

Run nBack3_5 presentation once participant is comfortable with the nBack2 presentations.

Well done.

Finally there will be a section called "Is it X?" Again you will be shown a stream of letters and we would like you to keep in mind the letters that you see. We would like you to tell us when you see the letter X. We would like you to respond by pressing this button on the joystick. When you are told you are doing "Is it X?" you need to keep an eye out for the letter X. Let's have a look at an example of "Is it X?"

Repeat one back pointing it out and increasing rate – nback3_4 (4 seconds on screen) nBack3_3 (3 seconds on screen) and nBack3_2 (2 seconds on screen)

Give prompts during the additional presentations for them to attend to the letters on the screen and point out when they would need to respond.

nBackX presentations – nBackX_5 (5 seconds) nBackX_4 (4 seconds) nBackX_3(3 seconds) nBackX_2 (2 seconds)

All the things you have just done you will do in the full task but not necessarily in this order. A screen will come up to let you know whether it is "one back", "two back", "three back" or "Is it X?" There will be a practice run first. I can tell you what to do again if you have forgotten as well, as we go along. We can go through it slowly until you are used to it. Do you have any questions?

Load up practice run. If necessary prompt participant by reiterating the instructions for each level as they do it and providing feedback. If participant is still unable to grasp the instructions or struggles to make correct responses return to the Powerpoint presentations.

Once participants are familiar with the task run through the Long Playlist for the nback as a final practice run. To be done on the screening day and also just before they go into the scanner.