Schizotypy and the association with brain function and structure

A thesis submitted to the University of Manchester for the degree of PhD in the Faculty of Medical and Human Sciences

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Introduction: Schizotypy is a personality trait that shares some of the characteristics of clinical disorders such as schizophrenia. Similarities are found in expression of psychotic-like experiences and presence of attenuated negative signs. Furthermore, schizotypal samples are associated with impairments in cognitive tasks, albeit in a less compromised form. For these reasons and others, schizotypy is considered a part of the extended-phenotype of schizophrenia and as such can be utilised as an analogue sample without some of the confounds associated with illness. 

Objective: The aim of the PhD is to examine the relationship of schizotypal features and brain function and structure in a sample of adolescents and young adults (age 16-25 years). This will attempt to provide further evidence for the placement of schizotypy on the continuum, along with insights into pathophysiological mechanisms involved in schizophrenia and related disorders. 

Methods: The study involved three main phases: recruitment via an online survey, further neuropsychological testing and brain imaging on selected high schizotypes and controls. The thesis comprises 5 papers/experiments. Paper 1 utilises confirmatory factor analysis (CFA) to examine the factorial structure of the schizotypal personality questionnaire (SPQ) in a community sample aged 16-25 years. It also examined the effects of demographics on schizotypal levels. Paper 2 examined the association between schizotypy and measures of sustained attention and spatial working memory both in a total sample, and in samples split by age and by sex. Paper 3 further examined the association between schizotypy and cognition laboratory tests of attention, executive function and verbal learning/memory. Paper 4 tested the same participants on measures of functional brain asymmetry. Paper 5 used diffusion tensor imaging (DTI) to examine white matter structures in a sample of high schizotypes and controls. 

Results: Paper 1 confirmed that the SPQ is most appropriately modelled by a four-factor structure in an adolescent and young adult sample. Demographic effects on SPQ subscales scores mirrored those seen in clinical samples. Paper 2 found that where small associations between schizotypy and sustained attention/spatial working memory function occurred, these were in relation to either age of sex. Paper 3 demonstrated an association between increased schizotypal features and a slight reduction in performance on verbal learning/memory, but no association with tasks of executive function or attention. In Paper 4, schizotypy was associated with a left-hemifield bias on a computerised line bisection task. Paper 5 found that a group of high schizotypes had an increase in tract coherence in the uncinate fasciculus compared to controls. Furthermore, increasing subclinical hallucinatory experiences were associated with increased tract coherence in the right hemisphere arcuate fasciculus. 

Conclusions: Schizotypy was associated with changes in brain function and structure similar to that demonstrated in more serious mental illness, although to a lesser degree. The current studies suggested that schizotypy is associated with relatively intact prefrontal function, but slight performance bias on measures of medial temporal lobe function. There was also evidence for structural brain changes in schizotypes, with these being indicative of either a protective factor, or a marker of a pathological process. Correlations between hallucinatory experiences and white matter tracts between language regions support theories implicating hyperconnectivity and presentation of symptoms in clinical groups. The functional and structural data collected from this study suggests that the ‘schizotypal’ brain may represent an ‘early’ stage of pathology, but which is likely to be compensated enough such that transition to serious mental illness is unlikely. Further studies could examine similarities and differences between the schizotypal profile and clinical conditions, which would provide further insights into aetiological mechanisms in schizophrenia/psychosis.
Declaration

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Format of Presentation

This thesis is presented in alternative format according to the University of Manchester, Faculty of Medicine and Human Sciences guidelines ‘Presentation of Theses in Alternative Format’ and approved by the Faculty of Medical and Human Sciences.

The rationale was due to the content and the phases in which the series of studies were conducted. As will be discussed, the PhD comprises three main phase of data collection: recruitment of a large sample of participants; neuropsychological testing; and brain imaging. Each phase is comprised of separate papers which form the data section of the thesis. These are numbered Papers 1-5. Although the underlying theme was assessing the association between schizotypy and brain function/structure, each phase and subsequent paper could stand alone as an individual experiment. For this reason the alternative format was considered appropriate. By completing this thesis in the alternative format, it also enables the papers to be submitted for publication in peer review journals. Each paper is written in the format for submission, although without individual reference sections. All references are placed at the end of the thesis.

Preceding the data sections is the general introduction, including rationale for the study. The next section is the methodology section. Each paper has its own methodology section. This additional methodology provides a) rationale for choice of measurements, b) further detailed methods beyond what would be expected in a published article (i.e. procedures and individual task details, c) justification for choice of methods.

Following on from the data section (Papers 1-5) is the general discussion. This draws together various aspects of the study and discusses the implications of the findings, the limitations of the studies, and directions for future work.

All data acquisition, analysis, and writing of manuscripts for the thesis were carried out by the author.
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Chapter 1  General Introduction

1.1 Introduction overview

Schizotypy is considered a personality trait which shares behavioural characteristics and cognitive deficits with those found in schizophrenia. Schizotypy can be considered a part of the extended phenotype of schizophrenia. The behavioural features such as attenuated forms of positive symptoms (e.g. abnormal perceptual experiences, thought disorder etc) and negative signs characterise a schizotype, thus allowing the identification of further psychosocial, cognitive and biological substrates. This not only helps in cementing the place of schizotypal personality on the schizophrenia continuum, but also represents a valid model in which pathophysiological processes can be investigated.

Schizophrenia is a diagnostic entity which covers a heterogeneous syndrome, whereas psychosis is characterised by the presence of hallucinations, delusions and thought disorder, which could be a consequence of a number of psychiatric (e.g. schizophrenia, bipolar disorder), medical or drug induced states. In this review where the term psychosis is used, it refers to the presence of psychotic symptoms as phenomena of the schizophrenia syndrome and the attenuated versions associated with the extended phenotype.

In this introductory chapter, relevant background information will be provided on risk factors and aetiological theories of schizophrenia. Following on is an overview of analogue samples given their intermediary position on the continuum. This leads onto schizotypal samples which are the focus of the PhD. A brief history will be given followed by sections examining:

1) demographic effects on schizotypal levels;
2) the relationship between cognitive performance and schizotypy;
3) lateralised brain function and schizotypy.

The next section reviews some of the literature on white matter connectivity in schizophrenia and related samples. As this study is one of the first to examine white matter structures in a community based schizotypal sample, it is appropriate to frame it in the available literature. The final section outlines the rationale for the PhD, an overview of studies that will be implemented and the hypotheses that are being investigated.
1.2 Schizophrenia

1.2.1 Background

Schizophrenia is one of the most pervasive and disabling mental health issues in modern medicine. It is characterised by delusions, hallucinations, disorganised speech and behaviour and negative symptoms (affective flattening, alogia, avolition) that must be persistent for 6 months or longer according to the Diagnostic and Statistical Manual of Mental Health Disorders [DSM-IV: (APA, 1994)]. It is also associated with social/occupational dysfunction and cognitive deficits (see below). The global lifetime prevalence rate is 4.0/1000 (Bhugra, 2005) with an annual incidence rate in any population of 0.7-1.4 per 100,000 (Jablensky et al., 1992). The illness has a profound impact upon an individual’s well being and their ability to function both day-to-day and socially. Beyond the manifest features of the illness are the influence it has upon both the individual and the society as a whole, with an estimated societal cost in the UK of £6.7billion in 2004/2005 (Mangalore and Knapp 2007).

Although evidence for symptoms of psychosis are documented as far back as Ancient Egyptian times (Kyziridis, 2005), it was not until the late nineteenth century that Emil Kraepelin first described the disorder dementia praecox. The term schizophrenia was coined by Eugen Bleuler in 1911 who brought in the notion of a continuum ranging from the pathological to normal states. Throughout the twentieth century the symptoms of the disorder were further conceptualised: Bleuler (1950) described ‘fundamental’ and ‘accessory’ symptoms that are similar to positive and negative symptoms, whilst Kurt Schneider’s classification of first-rank symptoms included hallucinatory/delusional symptoms and thought disorder (Schneider, 1959).

Recently there have been pushes to reclassify schizophrenia for DSM-5 (van Os, 2009). This proposition, which in addition to distancing the disorder from the socially stigmatising term, can also provide the opportunity to make the public aware of psychotic experiences drawn from scientific studies and how they are a part of psychological experience that people can relate to (van Os, 2009). One reason for this reclassification stems from research suggesting that psychosis/schizophrenia is at an extreme end of a continuum. On this continuum are subclinical psychotic experiences which are similar to clinical populations although differentiated on factors such as frequency, severity, intrusiveness and the ability of the person
to cope, as well as presence of co-morbidities and associated developmental impairment (Johns and van Os, 2001).

1.2.2 Course and treatment
The course of illness is highly variable, due in part to its heterogeneous nature and methodological difficulties in assessing the course over an individual's lifetime (Harvey and Davidson, 2002). It is generally considered that prior to illness onset there is a promorbid (prodromal) phase where certain features such as negative signs are present. Towards the end of this period, positive symptoms increase with eventual florid psychotic experience in first-episode. This onset is most likely to occur between 15-30 years of age, with males associated with an earlier onset (DeLisi, 1992). Initial onset is commonly the first time an individual comes into contact with a mental health professional. There is a wide spectrum of functional outcomes: for example, in a follow-up study of 67 patients over 13 years, 52% were without positive symptoms, 52% without negative symptom, 55% with good/fair social functioning; but only 17% were without symptoms and receiving no treatment (Mason et al., 1995b).

Antipsychotic medication is used primarily to treat the psychotic symptoms. The chance discovery of the effects of chlorpromazine prompted a period of antipsychotic medication development during the 1950s-70s with the introduction of typical antipsychotics such as haloperidol (Shen, 1999). From the 1990s atypical antipsychotics were introduced such as clozapine, olanzapine, and risperidone, aimed at reducing the side-effects associated with first generation medication, as well as having increased efficacy. This increase in efficacy has, however, not been realised (Lewis and Lieberman, 2008). Other interventions such as cognitive behavioural therapy have also been shown to be effective in the treatment of both positive and negative symptoms (Rathod and Turkington, 2005). Similarly, cognitive remediation therapy has also been shown to result in some improvements in psychosocial functioning, symptoms and cognitive deficits (McGurk et al., 2007)

1.2.3 Risk factors for schizophrenia
There is high heritability in schizophrenia indicating significant genetic factors. This heritability is demonstrated in the increased risk of developing schizophrenia in various relative groups: 50% in monozygotic twins and approximately 15-20% in dizygotic twins, siblings and children (Bray and Owen, 2001). There are likely to be multiple genes and alleles
that confer risk for schizophrenia and this genetic susceptibility acts in combination with environmental factors occurring throughout the developmental period (Jablensky and Kalaydjieva, 2003). This genetic predisposition with ‘insults’ at various stages of development are considered to alter the normal course of brain development and form the basis of the neurodevelopmental theory of schizophrenia (Lewis and Murray 1987; Weinberger 1987) (see below).

Risk factors include obstetric complications which are thought to combine with genetic factors (Cannon et al., 2000). Another early risk factor is urbanisation at place of birth and in upbringing (Pedersen and Mortensen 2001a; Pedersen and Mortensen 2001b; Suvisaari et al., 2000). The mechanisms driving this are not fully understood but could be related to obstetric complications, as well as toxic exposures and infections, household crowding, stress and diet (Mortensen, 2000). The effects of childhood trauma are also implicated although methodological issues in studies limits the interpretability (Bendall et al., 2008). In later life, social risk factors include low socioeconomic status, single status and ethnicity (Weyerer, 1994), whilst environmental risks include migrant status (Sharpley et al., 2001) and cannabis exposure (Moore et al., 2007).

1.2.4 Aetiological theories
A considerable amount of research has been undertaken to identify and understand the relationship between such risk factors and the aetiology of schizophrenia or psychotic experiences. A recent review by Linscott and van Os (2010) cites 24 contemporary theories summarising plausible mechanisms of genetic, biological and/or psychological processes. Some of the relevant theories to the current study are briefly discussed below.

1.2.4.1 Neurodevelopmental hypothesis
A neurodevelopmental aetiological process has been proposed (Murray and Lewis, 1987; Weinberger 1987) with a wealth of supporting evidence (see Fatemi and Folsom, 2009; Marenco and Weinberger, 2000). It is hypothesised that schizophrenia is a consequence of developmental processes that have gone awry during critical early pre- and perinatal periods of brain maturation, with later aberrant development during adolescence.
It is suggested there could be a genetic predisposition which interacts with obstetric complications such as complications of pregnancy, abnormal foetal growth and complications of delivery (Cannon et al., 2002). What the consequences of these early ‘insults’ are in terms of neurodevelopment are the focus of intense neurobiological investigation. Processes thought to be involved include complex intracellular and cell-environment interactions which alter the course of normal development (see Lewis and Levitt, 2002). During childhood and adolescence, those who later go through transition demonstrate subtle deficits in motor and cognitive functioning. During a second later period of development in adolescence, where major restructuring of the brain occurs, additional ‘hits’ prior to onset (risk factors mentioned previously) can cause deviation from normal neurodevelopment (Pantelis et al., 2005). Normal neurodevelopment include refinements in synaptic connections and functional integration in regions such as the prefrontal cortex (McGrath et al., 2003), an area associated with both the symptoms and cognitive deficits in patient samples. Where there is deviancy from this normal developmental trajectory, there can be deterioration in brain function and emergence of psychotic symptoms.

### 1.2.4.2 Dysconnectivity hypothesis

Related to the neurodevelopment theories is the hypothesis that schizophrenia could be a disorder of disconnection (Friston, 1998). This hypothesis proposes that the underlying connectivity in the brain (synaptic level and/or white matter connections) could be a final pathway in aberrant development. The departure from normal development results in the failure to achieve proper functional integration within the brain (Friston, 1999), and the disruption in white matter development in schizophrenia could cause the presentation of the symptoms and cognitive deficits (Bartzokis, 2002).

Early theories originally postulated that functional correlates of connectivity at the levels of the synapse were of primary importance, whereas the structural white matter connections were less significant. However with developments in imaging techniques that can examine white matter structures in greater detail, the importance of the structural connections in theories of dysconnectivity have grown. Deficient connectivity both at the level of the neuronal synapse and in white matter structures have been implicated in schizophrenia (Bullmore et al., 1997; Stephan et al., 2009). With regard to white matter connectivity recent advances in magnetic resonance (MR) methods have enabled the identification and quantification of white matter
tracts in vivo. These techniques have demonstrated alterations in white matter connections in schizophrenia patients (Kanaan, Kim et al. 2005; Walterfang et al., 2006; Kubicki et al., 2007; Ellison-Wright and Bullmore 2009). Section 1.6 describes white matter abnormalities in schizophrenia and related samples.

The notion of dysconnectivity is not solely associated with reduced connectivity, rather it is a concept that reflects abnormalities in brain connections (Stephan et al., 2009). Indeed, increases in tract coherence have also been observed in clinical samples, particularly in relation to hallucinatory symptoms (Rotarska-Jagiela et al., 2009). Currently it is not fully understood whether these structural changes are a consequence of functional changes at the level of the synapse.

1.2.4.3 Failure of hemispheric specialisation

Within the confines of the neurodevelopmental hypothesis is the theory suggesting that schizophrenia could be a result of abnormal development of cerebral dominance (Crow, 1990; Crow et al., 1989). The theory proposes that schizophrenia is associated with a failure in establishing cortical asymmetry, particularly the normal left hemisphere dominance for language, possibly due to a gestational event (Marenco and Weinberger, 2000). Crow argues that the dysfunctional development of language dominance could result in a predisposition to psychotic symptoms and problems in communication. Related to this is the proposal that schizophrenia could also result from abnormal connectivity between hemispheres (Crow, 1998), again as a result of abnormal asymmetry. The predominant structure for interhemispheric transfer, the corpus callosum, has been examined extensively in schizophrenia/psychosis samples with functional and structural abnormalities noted (see Coger and Serafetinides, 1990; Woodruff et al., 1995).

1.2.4.4 Dopamine hypothesis

The role of dopamine in schizophrenia/psychosis is well documented, although beyond the scope of this review (see Howes and Kapur, 2009). Briefly, early theories postulated that there was an excess of dopamine function (hyperdopaminergia) in subcortical brain regions (i.e. Davis et al., 1991). The dopamine hypothesis was expanded upon by Howes and Kapur (2009) who reviewed multiple lines of evidence from molecular, genetic, imaging and epidemiological studies. They hypothesise that via genetic predisposition and environmental
factors, multiple ‘hits’ result in an eventual dopamine dysregulation. A consequence is an increased activation in predominantly striatal dopaminergic neurones, which could cause psychosis, possibly via altering the appraisal of stimuli due to aberrant salience (Howes and Kapur, 2009; Kapur, 2003).

In terms of other aetiological processes, the dopamine hypothesis is complimentary to both neurodevelopmental and dysconnectivity theories. For instance, the development of dopaminergic innervation in prefrontal brain regions occurs during adolescence (see Spear, 2000), whereas changes in connectivity in clinical samples has been found in regions innervated by the mesolimbic and mesocortical dopamine pathways (see section 1.6).

### 1.2.5 Cognitive deficits in schizophrenia

Cognitive deficits are a core feature of schizophrenia, often remaining after the amelioration of the positive symptoms and being a limiting factor in the individual’s ability to regain normal functioning. Cognitive deficits are widely reported with evidence suggesting a deficit in almost all cognitive domains (Heinrichs and Zakzanis 1998; Fioravanti et al., 2005). They are present early in the illness as demonstrated in first-episode patients (Mesholam-Gately et al., 2009; Riley et al., 2000), although the extent to which these change over the lifetime is unclear with evidence demonstrating relative stability in some cognitive domains, whilst deterioration in others (Stirling et al., 2003). Not all individuals with a diagnosis of schizophrenia experience such deficits and abilities range from normal functioning through to severe impairment (Heinrichs et al., 1997). Even so, a reported 90% of individuals possess at least one clinically relevant deficit (Palmer et al., 1997; see section 1.4 for further details). Where present, such deficits are shown to impact on functional outcome (Green et al., 2000), possibly through higher order functioning such as social cognition (Vauth et al., 2004).

Treatment of cognitive deficits with traditional medication have shown modest effect sizes in improvement with typical (Mishara and Goldberg, 2004) and atypical antipsychotics (Keefe et al., 1999). Other novel cognitive enhancing drugs have been proposed such as glutamate and nicotinic agonists, as well as compounds such as Modafinil (Galletly, 2009). Non medication treatments such as cognitive remediation therapy have also shown moderate effect sizes in improving cognitive function (McGurk et al., 2007).
1.2.6 Sex differences in schizophrenia

Sex differences are reported in schizophrenia with males associated with higher incidence, earlier onset, increased severity and poorer functional outcome (Aleman et al., 2003; Leung and Chue, 2000; Lewis, 1992). There are also apparent differences in symptoms prior to onset (prodromal symptoms) with males presenting more negative type features (Choi et al., 2009). Understanding sex differences in schizophrenia could enable a better understanding of the pathophysiology of the disorder as well as developing optimum treatment based on sex (Hoff and Kremen, 2002).

A contentious issue is the extent of sex related differences in cognition due to this area of research being fraught with methodological issues including sampling bias and different ages of onset (Hoff and Kremen, 2002). There is, however, a tendency for males to have slightly more impaired cognition particularly in verbal processing, although this could be an exaggeration of normal sex differences (Leung and Chue, 2000). Beyond the methodological issues, other factors that could play a role in sex related performance differences could be biologically based, for example, higher levels of oestrogen in females being associated with better performance on measures of verbal/spatial declarative memory and perceptual-motor speed (Hoff et al., 2001).

1.2.7 Analogue samples

In understanding schizophrenia and psychosis, interest has grown in the use of analogue samples. Such samples include individuals at genetic risk (relatives of patients), clinical risk (help-seeking individuals with subclinical psychotic experiences), and people in the general population with heightened expression of ‘schizotypal’ features. These schizotypal features include attenuated positive symptoms such as mild perceptual abnormalities and unusual beliefs; along with negative features such as constricted affect, lack of friends and social withdrawal (see below). Analogue samples may have shared aetiological factors, as well as possessing similar biological and psychological traits (e.g. Cadenhead and Braff, 2002; van Os et al., 2009). A beneficial aspect of analogue samples is the reduction in confounds associated with illness, including the effects of medication, illness duration, distracting symptomatology and comorbid diagnoses (Cadenhead and Braff, 2002; Hori et al., 2006). The next section reviews some of the more common analogue samples, followed by the introduction of the sample used in current set of studies – psychometrically defined schizotypes.
1.2.7.1 Relatives of patients – genetic high risk

The presence of attenuated symptoms in relatives of schizophrenia patients did not go unnoticed in the conceptualising of schizophrenia. Kraepelin and Bleuler took note of the peculiarities in relatives, although others had commented on such features earlier in the twentieth century (see Kendler, 1985). These characteristics were realised to be mild forms of the clinical condition which afflicted their ill relatives. They were also expressed in relatives with as much heterogeneity as those in patient groups. Certain characteristics were observed more commonly than others, for instance odd or eccentric behaviour was deemed nearly universal, with irritability, social isolation and aloofness also well documented (Kendler, 1985).

Relatives are known to present with higher levels of attenuated positive symptoms and negative signs compared to control groups (Yaralian et al., 2000; Appels et al., 2004) (see section 1.3.7 for further details). Furthermore, relatives are more likely to present with a diagnosis of schizotypal personality disorder compared to matched controls (Baron et al., 1985; Kendler et al., 1993b). Approximately 40% of children of patients with schizophrenia are considered in an at-risk taxon compared to 4% of controls (Erlenmeyer-Kimling, 1989), whereas another study has demonstrated that 10-15% of first-degree relatives will present with some degree of non-affective psychosis (Cadenhead and Braff, 2002). In addition to increased levels of psychopathology, relative samples are also found to have cognitive impairments although usually at an intermediary performance level compared to patient samples (e.g. Sitskoorn et al., 2004).

Relatives of patients are a well established analogue sample but there are limitations. There is still a considerable degree of heterogeneity in presentation (Kendler, 1985). Coupled with this are increases in other psychiatric morbidities including non-schizophrenia related personality disorders, bipolar disorder and depression (Varma and Sharma 1993; Varma, et al. 1997). When using relatives as an experimental group, it would be possible to screen out such co-morbidities, but this would require considerable sample sizes that are not always feasible.
1.2.7.2 High risk groups

Another well documented analogue sample are those considered at high risk due to presence of intermittent or mild subthreshold psychotic experiences: ultra high risk (UHR)’/at risk mental states’ (ARMS), or retrospectively psychosis prodrome. High risk clinics have been established to identify individuals at risk for developing psychosis in the view that early intervention can attenuate, delay and/or prevent psychosis (Yung et al., 1995; 2003; Amminger et al., 2006). Criteria for identifying at-risk candidates have been established, for example the inclusion criteria of the Melbourne clinic PACE (Personal Assessment and Crisis Evaluation Clinic) are: 1) attenuated (subclinical) psychotic symptoms, or psychotic symptoms of subthreshold frequency; 2) history of brief limited intermittent psychotic symptoms (BLIPS) that spontaneously resolve in the previous 12 months; or 3) presumed genetic vulnerability to psychosis plus persistent low functioning for at least 1 month in the previous 12 months (Yung et al., 2006). Similar criteria are used in other high risk studies such as the New York RAP (Recognition and Prevention Program: Cornblatt et al., 2002), Edinburgh High Risk Study (EHRS: Johnstone et al., 2000) and London OASIS (Outreach and Support in South London: Broome et al., 2005) to name a few.

Transition rates to psychosis at 1 year are between 13-54% (Cornblatt et al., 2003, Haroun et al., 2006, Miller et al., 2002, Yung et al., 2003, Yung et al., 2006). In recent years there has been a reduction in transition rates, in part due to clinics identifying and treating UHR cases prior to onset, as well as the inclusion of more false positives due to growing awareness of these facilities and the increase in referrals they receive (Yung et al., 2007).

There are some limitations in using high risk candidates as samples. As a group they can be clinically undifferentiated. For instance individuals in the UHR paradigms can present with other morbidities including mania, depression, anxiety disorder, attention deficit hyperactivity disorder, and personality disorders (Lencz et al., 2004; Meyer et al., 2005). This could have implications on purported relationships between attenuated psychotic symptoms and correlates of interest. Again it is possible to exclude potential confounding variables, but it would require considerable effort to acquire suitable sample sizes. Related to this is actual access to this sample type. It is not always possible to recruit such individuals due to limited number of clinics established for high-risk candidates. As such it can be difficult, or at least require considerable joint collaborations to utilise such high risk samples in research settings. Later
stages of the review will discuss some of the cognitive and imaging literature in UHR samples given the relevance of UHR to the current set of studies.

Another analogue sample that is well documented is the schizotypal sample. These are the focus of the PhD.

1.3 Schizotypy
1.3.1 Background and historical account
The definition of schizotypy is difficult to conceptualise and could even be considered contentious due to the opposing views of schizotypy relative to schizophrenia and whether it is best described in terms of a taxon or dimension (see Beauchaine et al. 2008; Rawlings et al., 2008a; 2008b). The term ‘schizotype’ was first used by Sandor Rado (1953) to shorten ‘schizophrenic phenotype’, which characterised individuals who had an inability to experience pleasure and impaired body awareness. Other symptoms were hypothesised to stem from these main deficiencies (Kendler, 1985). This usage is most closely matched to what is considered in modern times as schizotypal personality disorder (SPD). Extension on this concept was carried out by Paul Meehl who developed a model which integrates both genetic and environmental influences which define schizotypy (Lenzenweger, 2006). Meehl first postulated the quasi-dimensional model (Meehl, 1962, 1990). This theory proposed the existence of a specific gene that causes abnormal development in the central nervous system (CNS) resulting in ‘schizotaxia’. The characteristics of schizotaxia were cognitive slippage (thought disorder), interpersonal problems, anhedonia and ambivalence. Other factors including environmental and other genes (polygenic potentiators including other personality dimensions such as introversion) could interact with these genotypes and push the schizotype towards diagnosable psychosis (Lenzenweger et al., 2003). The model assumes schizotypy is not naturally occurring, is hereditable and has genetic proximity to schizophrenia-spectrum disorder (SSD). There is acknowledgment that attenuated symptoms can be measured continuously in the general population, but the latent construct of schizotypy is not continuous within the general population, but is continuous with a diagnosis of schizophrenia (Lenzenweger and Korfine, 1995).
An alternative account is the ‘fully dimensional’ model where a continuum ranges from normal healthy functioning individuals to those with a clinical diagnosis (Claridge and Beech 1995; Johns and van Os 2001). See Fig. 1 for a comparison of the two models. The fully-dimensional model has roots in the work of Eysenck who emphasised individual differences in personality and theorised that psychoticism represents an extreme end point of a continuous variable (Eysenck and Eysenck, 1976). Psychoticism includes antisocial and aggression as central criteria, but reformulations by Claridge departed from these constructs and focused on the psychosis domain (Rawlings et al., 2008b). Both the fully- and quasi-dimensional models acknowledge variation in the underlying disease process, but it is the ‘fully-dimensional’ model which permits psychotic symptoms to be part of ‘normal’ experience (Claridge, 1997; van Os et al., 2001), whereas the quasi-dimensional theorists are mainly concerned with those beyond a certain threshold.

Fig 1: Taken from Claridge and Beech (1995), pg. 194. Diagram indicating the differences in the quasi- and fully-dimensional models. The fully dimensional model takes into consideration both the clinical states and normal personality differences; whereas the quasi- model acknowledges the continuum but only beyond a ‘threshold’ of clinical significance.
1.3.2 Psychotic experiences in the general population
In support of this continuum theory are the reported levels of psychotic experience in the general population. Subclinical psychotic experiences have been estimated at 8% with a median incidence rate of 3% (van Os et al., 2009). They are frequently expressed at higher rates in adolescents and young adults, although the persistence rates at 3 years are often quite low ranging from 26-31% (Cougnard et al., 2007). These experiences are mainly transitory and can resolve themselves (van Os et al., 2009). Psychotic experiences are associated with known risk factors for schizophrenia, for instance, genetic background, exposure to cannabis, increased stress/traumatic events and urbanicity (or rural living), being male, single status; as well as ethnicity, employment status and educational attainment (Avramopoulos et al., 2002; Goulding et al., 2009; Lahti et al., 2009; Stefanis et al., 2004b; van Os et al., 2001; van Os et al., 2009; Wiles et al., 2006). Presence of attenuated psychotic features are associated with increased help-seeking behaviour, for instance GP attendance and seeking counselling/therapy are increasingly more common in those expressing one, two of three psychotic-like symptoms in otherwise healthy individuals (Murphy et al., 2010). These shared risk factors and changes in behaviour are taken as evidence of the continuum of normal and clinical psychotic experience.

1.3.3 As a model of schizophrenia
Using schizotypy as a model of schizophrenia/psychosis has benefits in research. As described previously, there are confounds associated with clinical groups and other analogous samples. Individuals who score highly on schizotypy measures may permit a more targeted investigation of underlying risk factors for psychotic symptoms (Cadenhead and Braff, 2002). As the individual has not gone through transition, it could also allow identification of protective factors. Similar to clinical samples, heterogeneity can be problematic in schizotypy samples (Lenzenweger et al., 2003). But rather than the confounds of illness, heterogeneity can come in the form of other personality types being associated with those with heightened schizotypal features (e.g. Barrantes-Vidal et al., 2009; 2010).

1.3.4 Measurement of schizotypy
A wide variety of self-report and interview based measures have been developed to assess schizotypal features. The rationale behind the design of these include: 1) the potential to identify individuals at risk for transition; 2) identifying events that precede illness including
possible protective factors; 3) and enable the investigation of substrates without the confounds of illness (Chapman et al., 1995). Table 1 lists some of the more widely used self-report questionnaires. These falls into two broad categories: those that measure specific dimension of symptoms such as positive symptoms, and multidimensional measures that capture all schizotypal features.

Table 1: Questionnaires assessing traits and symptoms of schizotypy/psychosis proneness

<table>
<thead>
<tr>
<th>Measure</th>
<th>Reference</th>
<th>Type</th>
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<tbody>
<tr>
<td>Eysenck Personality Questionnaire (Eysenck and Eysenck, 1975)</td>
<td></td>
<td>Trait</td>
</tr>
<tr>
<td>Physical Anhedonia Scale (PhyAn) (Chapman et al., 1976)</td>
<td></td>
<td>Symptoms</td>
</tr>
<tr>
<td>Perceptual Aberration Scale (PAS) (Chapman et al., 1978)</td>
<td></td>
<td>Symptoms</td>
</tr>
<tr>
<td>Launay-Slade Hallucinations Scale (LSHS (-R)) (Launay and Slade 1981; Bentall and Slade 1985)</td>
<td></td>
<td>Symptoms</td>
</tr>
<tr>
<td>Social Anhedonia Scale (SocAn) (Chapman et al., 1976)</td>
<td></td>
<td>Symptoms</td>
</tr>
<tr>
<td>Magical Ideation Scale (MIS) (Eckblad and Chapman, 1983)</td>
<td></td>
<td>Symptoms</td>
</tr>
<tr>
<td>Impulsive Nonconformity</td>
<td>(Chapman et al., 1984)</td>
<td>Symptoms</td>
</tr>
<tr>
<td>Schizotypal Personality Scale (STA) (Claridge and Broks, 1984)</td>
<td></td>
<td>Syndrome</td>
</tr>
<tr>
<td>Rust Inventory of Schizotypal Cognitions (RISC) (Rust, 1988)</td>
<td></td>
<td>Symptoms</td>
</tr>
<tr>
<td>Schizotypy Scale (Venables et al., 1990)</td>
<td></td>
<td>Symptoms/traits</td>
</tr>
<tr>
<td>Schizotypal Personality Questionnaire (SPQ) (SPQ-B) (Raine, 1991)</td>
<td></td>
<td>Syndrome</td>
</tr>
<tr>
<td>Oxford Liverpool Inventory of Feeling and Unusual Experiences (O-LIFE) (Mason et al., 1995a)</td>
<td></td>
<td>Symptoms/traits</td>
</tr>
<tr>
<td>Peters et al Delusional Inventory (PDI-40, PDI-21) (Peters et al., 1999; 2004)</td>
<td></td>
<td>Symptoms</td>
</tr>
<tr>
<td>Community Assessment of Psychic Experiences (CAPE) (Stefanis et al., 2002)</td>
<td></td>
<td>Symptoms/traits</td>
</tr>
<tr>
<td>Schizotypic Syndrome Questionnaire (SSQ) (van Kampen, 2006)</td>
<td></td>
<td>Symptoms</td>
</tr>
</tbody>
</table>

Based on (Chapman et al., 1995; Claridge and Beech 1995; Vollema and van den Bosch 1995)

The next section discusses the three measures that will be used in the PhD. These are the Schizotypal Personality Questionnaire (SPQ: Raine, 1991), Peter’s et al Delusional Inventory
(PDI-21: Peters et al., 2004) and Launay-Slade Hallucinatory Scale (LSHS-R: Launay and Slade 1981; Bentall et al., 1989).

1.3.4.1 Schizotypal Personality Questionnaire

The SPQ was designed based on DSM-III-R clinical definition of schizotypal personality disorder (SPD: American Psychiatric Association, 1984). It is a 74-item yes/no self administered questionnaire (see Appendix 1) which contains elements from the nine features of SPD. As such it correlates highly with clinically assessed schizotypy (Raine, 2006). The nine features of SPD are represented in the 9 subscales which form the SPQ: Unusual Perceptual Experiences, Odd Beliefs/Magical Thinking, Ideas of Reference, Suspiciousness, Excessive Social Anxiety, No Close Friends, Constricted Affect, Odd Behaviour, and Odd Speech. The scale has high internal (total 0.9, subscales 0.71-0.78) and test-retest (0.82) reliabilities, and also adequate convergent, discriminant and criterion validity (Raine, 1991). A shortened 22-item screening version has also been developed, the SPQ-Brief (Raine and Benishay, 1995).

The SPQ is the main measure of schizotypal features in the PhD. The rationale for this selection is presented in the Methodology Chapter Section 2.1 (Pg. 83).

1.3.4.1.1 Factor structure of the SPQ

Schizotypy is a multidimensional construct that has similarities to the multidimensionality of schizophrenia symptoms (Vollema and van den Bosch, 1995). Schizophrenia has gone from early conceptualisations based on positive and negative symptoms, to a 3-factor model with an additional ‘disorganised’ factor (Arndt et al., 1991; Liddle, 1987). In accordance, factor models of schizotypal features have also examined whether they are modelled by 3- or even 4-factor constructs. The importance of determining the factor structure of schizotypal measures is borne out of efforts to compare schizotypal features with those of schizophrenia. Even with the multitude of measures assessing schizotypal features, there is relative consistency in identifying positive and negative-type factors. Third and fourth factors are more varied across measures with additional factors such as ‘disorganised’, ‘impulsive nonconformity’ or ‘paranoid’ being suggested (e.g. Vollema and van den Bosch, 1995, Stefanis et al., 2004a).
With respect to the SPQ, a variety of 2-, 3- and 4-factor models have been proposed, with the majority of earlier work reflecting the 3-factor Disorganised model of Raine et al (1994). This Disorganised model comprises Cognitive Perceptual, Interpersonal and Disorganised factors. Table 2 lists the subscale loadings onto the three factors. The Cognitive-Perceptual dimension is analogous to the Positive dimension of schizophrenia, Interpersonal the Negative, and Disorganised features common to both schizotypy and schizophrenia. Although the positive dimensions of both schizophrenia and schizotypy are comparable, the similarities between the negative and disorganised factors are more ambiguous (Venables, 1995). Similar measures have had their ability to match schizophrenia symptomatology questioned. For example via the O-LIFE positive features are considered analogous, but again there is greater uncertainty with the negative and disorganised features (Introvertive Anhedonia, Cognitive Disorganisation) and their equivalents in schizophrenia symptoms (Cochrane et al., 2010).

Table 2 – Factor loadings of the SPQ (Raine et al., 1994).

<table>
<thead>
<tr>
<th>Factor</th>
<th>Loadings of SPD subscales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive-Perceptual</td>
<td>Unusual Perceptual Experiences, Odd Beliefs/Magical Thinking, Ideas of Reference, Suspiciousness (dual loading)</td>
</tr>
<tr>
<td>Interpersonal</td>
<td>Excessive Social Anxiety, No Close Friends, Constricted Affect, Suspiciousness (dual loading)</td>
</tr>
<tr>
<td>Disorganisation</td>
<td>Odd Behaviour, Odd Speech</td>
</tr>
</tbody>
</table>

The 3-factor structure of the SPQ has been replicated in various samples including: undergraduates (Raine et al., 1994; Gruzelier 1996), a Taiwanese community sample (Chen et al., 1997), older participants (average age 40) (Badcock and Dragovic, 2006), psychiatric inpatients and outpatients (Vollema and Hoijtink 2000; Rossi and Daneluzzo 2002), adolescents (aged 16) (Fossati et al., 2003), first-degree relatives of schizophrenia patients (Calkins et al., 2004); along with personality disordered patients, inpatient adolescents and military conscripts (studies cited in Raine, 2006). Alternative factor models of the SPQ have also been proposed (Stefanis et al., 2004a; Wuthrich and Bates, 2006). Confirmatory factor analysis (CFA) is a technique where different models are compared with goodness of fit indices. Early studies confirmed the 3-factor model was the best fitting (Fossati et al., 2005;
Vollema and Hoijtink, 2000). However, modified 3-factor models (Wuthrich and Bates, 2006) or a four-factor paranoid model (Stefanis et al., 2004a) have also been proposed. The modified 3-factor model has more cross loadings of subscales onto both the positive and negative latent factors; whereas the 4-factor solution includes an additional paranoid factor. This paranoid factor has loadings from the subscales Ideas of Reference, Suspiciousness and Excessive Social Anxiety; although Suspiciousness and Excessive Social Anxiety also load onto the negative factor. In recent CFA studies support has grown for modified Disorganised models (Bora and Arabaci, 2009; Wuthrich and Bates, 2006) and Stefanis’ paranoid model (Compton et al., 2009). A number of variables influence model fit including the sample in which the data was derived. For instance, Reynolds and colleagues (2000) note that cultural differences, gender, inclusion of clinical patients, social status and religiosity could all influence the underlying factor structure. With these taken as potential mediating factors, the Raine et al (1994) model was shown to be invariant across all groups (Reynolds et al., 2000). A recent interest has focussed on testing whether other models are similarly replicable in different age and sex groups (Bora and Arabaci, 2009). One of the main aims of the first paper is to examine competing models in a sample from the general population aged 16-25 years.

1.3.4.2 Peter’s et al Delusions Inventory (PDI-21)
The PDI-21 (Peters et al., 2004) is a self-report measure examining delusional experiences (see Appendix 2). It was based on the longer version, Peters Delusional Inventory (PDI: Peters et al., 1999), which is based on the Present State Examination (PSE: Wing et al., 1974). It measures: 1) delusions of control; 2) misinterpretations, misidentifications, and delusions of reference; 3) delusions of persecution; 4) expansive delusions; 5) delusions concerning various types of influence and primary delusions; 6) simple delusions based on guilt, depersonalization, and hypochondriasis; 7) and disturbed thinking including thought reading, insertion echo and broadcast (Peters et al., 1999).

1.3.4.3 Hallucinations and the Launay-Slade Hallucinatory Scale (LSHS)
The LSHS(-R) (Launay and Slade 1981; Bentall et al., 1989) is a 12-item self report instrument designed to measure predisposition to hallucinatory experiences (see Appendix 3). Items measure different aspects of hallucinatory experience and can be grouped into five areas: vivid thoughts, intrusive thoughts, auditory hallucinations, vivid daydreams, and visual hallucinations.
1.3.5 Presence of subclinical psychotic experiences and schizotypy features

Schizophrenia is estimated as affecting 1% of the population, whereas SPD is estimated at 3% (Cadenhead and Braff, 2002). Figures on the prevalence of schizotypy are harder to predict due to the lack of cut-off scores and the fact it may not always be fully expressed. Despite these limitations, Meehl (1990) predicted a base rate of 10% of the population having schizotaxia, which has been supported empirically using the prevalence of positive schizotypy (Lenzenweger and Korfine 1992; Linscott et al., 2006). Other studies considering the continuous notion of psychotic experience have demonstrated slightly higher rates of subclinical psychotic experience, for example, community samples at 4-17% (van Os et al., 2001) and 10-28% (Verdoux and van Os, 2002). The disparity between high base rate of schizotypy and lower estimates of SPD could partly be explained by the theory of there being two distinct populations: one with a more severe prognosis, where an early-onset schizophrenia-related subtype with comorbid clinical conditions is present; and a second with a later onset and fluctuating symptoms which does not reach DSM criteria for SPD (Raine, 2006). Raine proposed ‘neuroschizotypy’ and ‘pseudoschizotypy’ as these two entities. Although originally aimed at SPD, these constructs are also applicable to psychometric schizotypes. Neuroschizotypy is considered to have an increased genetic and neurobiological basis with greater interpersonal (negative) features, and potential higher risk for schizophrenia; whereas ‘pseudoschizotypy’ has a weaker genetic and neurobiological basis, is associated with more cognitive-perceptual features, is likely an outcome of postnatal environmental and psychosocial influences, is expressed at variable levels and relatively transitory (Raine, 2006).

The persistence of subclinical psychotic experiences has been the focus of investigation. In one study psychotic experiences were monitored over a 20 year period (Zurich Study) (Rossler et al., 2007). Again, two distinct profiles were proposed; ‘schizophrenia nuclear symptoms’ and ‘schizotypal features’. The former associated with attenuated symptoms of the clinical condition, whereas the latter was representative of SPD. Levels of psychotic experience in both profiles diminished over the 20 years and both were associated with negative social consequences (i.e. conflict at work, with household members, separation etc) (Rossler et al., 2007). In other studies over a shorter timeframe, 8% of those reporting psychotic experiences at initial assessment were still experiencing them at two year follow-up (Hanssen et al., 2005). Dominguez and colleagues (2009) examined the rates and persistence in a longitudinal study.
examining adolescent psychotic experiences (from age 15). Rates of expression were approximately 22%, with persistence occurring in 30-40% of cases. The authors suggest the difference in persistence rates with Hanssen et al (2005) could be due to a younger sample and their tendency to report more subclinical psychotic experiences (see below) (Dominguez et al., 2009). In following-up the adolescent sample, they also found that persistence of these experiences in some cases could lead to clinical relevance. Approximately 40% of new cases of clinically relevant psychotic experience could be traced back to subclinical psychosis up to 8 years previously (Dominguez et al., 2009).

Specific symptoms such as hallucinations are also common in the general population with an estimated 10-40% of the general population reporting some form (Johns and van Os, 2001, Verdoux and van Os, 2002). This normal hallucinatory experience is also found in children aged 5 years (Schreier, 1999). The Dunedin study found the prevalence of hallucinations at 8% in 11 year olds of which only a small proportion were sleep related (McGee et al., 2000), whereas a general figure of 6-33% is given for ages 11-21 (Laroi, 2006). It has been suggested that childhood hallucinations have little prognostic value (Schreier, 1999), but adolescents who report auditory hallucinations are at increased risk of having concurrent psychopathology and four times greater risk for diagnosis of Axis 1 disorder (Dhossche et al., 2002).

Heightened expression of schizotypy/psychosis-proneness is also associated with increased risk for affective disorders, so rather than a specific risk for psychosis/schizophrenia, these measures could be highlighting a risk for psychopathology generally (Verdoux and van Os, 2002).

1.3.6 Transition rates to schizophrenia and other psychiatric conditions
Due to time and cost constraints, there is limited longitudinal data on transition rates in psychometrically defined high schizotypes. In one study, individuals with elevated scores on a combination of the Perceptual Aberration Scale (PAS) and Magical Ideation Scale (MIS) were at an increased risk for psychosis at a 10 year follow-up, but did not develop schizophrenia at a significantly higher rate than seen in the normal population (Chapman et al., 1994). At follow-up they were found to report more psychotic-like experiences and had increased presence of psychosis in their relatives, so hence were considered at risk. In a similar study, high scorers on combined MIS and revised Social Anhedonia Scale (R-SAS: Eckblad et al.,
1982) also presented with more psychiatric illnesses than control groups at 10-year follow up, but again specificity to schizophrenia was absent (Kwapil et al., 1997). A third study followed-up individuals originally selected for high scores on PAS/MIS, R-SAS or controls at 5 years (Gooding et al., 2005). Although none were clinically diagnosed, the Structured Clinical Interview for DSM-IV (SCID) demonstrated that 3.4% of original PAS/MIS and 6.3% of original R-SAS participants had diagnosable schizophrenia spectrum disorders, whereas controls had no diagnosable cases. The at-risk groups were also associated with significantly more psychotic-like experiences than the control group. Finally, the Dunedin study found that an increase in reported hallucinations and delusions at age 11 years was associated with a 16 times greater risk for schizophreniform disorder at age 26 (Poulton et al., 2000). As noted earlier, persistence of attenuated symptoms could be a more accurate predictor of transition. For instance Dominguez and colleagues (2009) demonstrated that 40% of new clinical cases of psychosis had presence of persistent subclinical symptoms up to 8 years previously.

Genetic susceptibility in schizotypy has been proposed as altering risk for transition (Kwapil et al., 1997). There are also protective factors and/or a lack of maladaptive factors that are critical in the development of full blown psychosis/schizophrenia or other mental illnesses, such as neuropsychological deficits, brain structural differences, and environmental factors. Having a clear understanding of the profile of schizotypy will shed light on its relationship to clinical diagnoses, as well as informing what constitutes heightened risk for the more severe conditions.

1.3.7 Schizotypal levels in first degree relatives

Individuals with a family history of schizophrenia have elevated schizotypy scores such as heightened expression of cognitive-perceptual features (Yaralian et al., 2000). However other studies have shown first-degree relatives score unexpectedly lower than control groups on positive symptoms (Appels et al., 2004). Similarly, prevalence of negative features varies dependent on the study (Appels et al., 2004; Calkins et al., 2004). Such differences could be related to a number of methodological issues. Firstly, defensive responding has been suggested as a possible source of response bias (Mohr and Leonards, 2005), although this has been challenged (Calkins et al., 2004). Relatives who are familiar with the signs and symptoms of schizophrenia may be sensitised to their own risk, so underreport their own experiences. This is supported by results which indicate the less ‘well known’ features such as negative signs are
elevated in relatives compared to controls (Vollema et al., 2002; Appels et al., 2004). Secondly, related to defensive responding is issues with recruitment methodology. By informing participants it was a biological study investigating personality, the natural tendency to respond defensively was shown to be minimised (Yaralian et al., 2000). This effect of research context has been proven experimentally (Mohr and Leonards, 2005). Thirdly, genetic proximity appears to be crucial as studies that have used parents of patients tend to report lower scores (Appels et al., 2004). Children of patients often report higher levels of positive schizotypy compared to siblings and parents, with siblings scoring significantly higher than parents (Vollema et al., 2002). Despite methodological issues and contradictory findings, heightened levels of schizotypy are a feature of relatives, indicating a genetic susceptibility for these traits, and provides evidence for links between schizotypal features and schizophrenia.

1.3.8 Demographic effects on schizotypy

1.3.8.1 Age and schizotypy levels

Younger samples (college students) tend to report higher mean scores on the SPQ compared to older groups (university students) (Fossati et al., 2003). Lower scores in older groups has also been replicated using the SPQ in a Taiwanese sample (Chen et al., 1997), and in a mature sample approximately 40 years of age (Badcock and Dragovic, 2006). As referred to previously, a longitudinal study examined schizotypal features at five separate time points over a 20 year period (Rossler et al., 2007). There was a general age related decline in subclinical psychotic experiences with only a small proportion showing persistently high levels. Levels were highest in the early 20s, followed by a gradual decline into the fourth decade (Rossler et al., 2007). In a cross-sectional study investigating schizotypy levels in late childhood and early adolescence (via the Junior Schizotypy Scales: Rawlings and MacFarlane, 1994), higher scores were found in adolescents compared to children (Fonseca-Pedrero et al., 2008). This increase in schizotypal features suggests that adolescence is a period of heightened expression, preceded by lower levels in childhood, and a subsequent decline in adult years.

Increasing age is also associated with a decline in self-reported delusions as measured by the PDI (Verdoux et al., 1998; Jung et al., 2008; Varghese et al., 2008). In a large sample of 2441 participants, hallucinations and delusions were measured by the Composite International Diagnostic Interview CIDI (2 hallucination and 17 delusion items) and PDI-21 in 18-23 year
olds (Scott et al., 2008). Younger participants were more prominent in the upper quartile of PDI-21 delusional held beliefs. The authors note that reduction in delusions is apparent in a relatively brief timeframe, which is the critical stage of transition from adolescence to adulthood.

Age-related changes in the expression of hallucinatory experiences in the general population have also been examined. In a longitudinal study using the hallucinatory scales Youth Self Report (Achenbach, 1991) and Young Adult Self Report (Achenbach, 1997), it was demonstrated that approximately 6% of 11-18 years old experienced some form of hallucination but this decreases to 3% by ages 19-26 (Dhossche et al., 2002). The decrease was attributed to a reduction in auditory hallucinations. In contrast, via the Hallucination Questionnaire, levels of auditory hallucinations were similar in both 14-15 year olds and 18-60 year olds (Pearson et al., 2008). There was no association between age and prevalence of auditory and/or visual hallucinations in adolescents aged 13-17 as measured by the Youth Self Report (Scott et al., 2009a), although reported hallucinations at age 14 were associated with an increase in delusion-like experiences at age 21 (Scott et al., 2009b)

1.3.8.1.1 Why the decrease in levels?

The reduction in schizotypal levels appear to be related to the transition from adolescence to adulthood. This coincides with a period of development during adolescence which is associated with biological (including neurodevelopment) and behavioural changes (see Spear, 2000). Extent of schizotypal features is relatively stable in adult populations, which is perhaps indicative that the transitional period is crucial in this reduction. There are various possible explanations for the decrease in schizotypal features. Firstly, it may represent a genuine decrease in levels which reflects maturational processes. For instance, there is ongoing brain maturation in the prefrontal cortex in both grey and white matter during adolescence (Giorgio et al., 2010; Schmithorst and Yuan 2010). These include changes in extent of dopamine innervation in prefrontal regions (Spear 2000). As these particularly late developmental changes occur, a ‘side effect’ could be transitory increases in some attenuated positive symptoms during adolescence. As the majority of people pass safely through this critical risk period for whatever reason (protection from or lack of risk factors), the functionally and structurally mature brain may no longer predispose the individual to altered states and this could mirror the reduced schizotypal levels found in adults.
An alternative but not mutually exclusive explanation could be that the decreases may reflect changes in normal psychological development occurring during adolescence. It has been suggested that schizotypy scales also measure aspects of normal adolescent behaviour (DiDuca and Joseph, 1999) coupled with younger people being associated with strange belief systems (Stefanis et al., 2002), whereas older samples may have more conservative views and are more reluctant to report unusual beliefs (Verdoux et al., 1998; Lincoln and Keller 2008). During adolescence a striving for individuality could lead to over inflation and/or young adults could begin to acknowledge that some beliefs may not be socially acceptable. Research into cluster A personality disorders including SPD have suggested that reductions in levels occurring during adolescence are associated with the individuals maturation of their own identity, along with a greater appreciation of the outside world and the subsequent perceived usefulness of the social conventions and beliefs (Cohen et al., 2005). Adolescents’ world views are also formed in a period of social and biological change. Some of these could be interpreted as an expression of schizotypal tensions within the family, grandiosity, egocentrism, fantasy and imaginary audiences, and unrealistic optimism (Harrop and Trower, 2001). The adolescent period is also associated with heightened risk for psychopathology in general, with longitudinal studies demonstrating a peak in depression rates (Hankin et al., 1998). It is therefore possible that schizotypy is difficult to differentiate from other changes in personality or proneness to other psychopathologies. However, once the individual passes through this tumultuous developmental period there is a generalised reduction in levels. Those who retain high schizotypal levels into early adulthood could be at particular risk for transition.

1.3.8.2 Sex differences in schizotypy, delusions and hallucinations

SPQ (SPQ-Brief [-B])

Table 3 lists a selection of studies that have examined sex differences on the subscales of the SPQ. As demonstrated there are relatively well replicated sex differences on a number of scales. For instance, males are almost universally associated with an increase in the scores on No Close Friends and Constricted Affect which loads onto negative type factors. This is similar to clinical samples where males are associated with increased negative symptoms (Leung and Chue, 2000). Females score higher on the subscales of Odd Beliefs/Magical Ideation and Excessive Social Anxiety. Odd Beliefs loads on to positive type factors and again
could be considered to mirror the increase in positive symptoms in schizophrenia (Leung and Chue, 2000). Furthermore, the increase in Excessive Social Anxiety in females could be seen as analogous to the excess in paranoid type ideation in schizophrenia samples (Andia et al., 1995).

Table 3: Studies that have examined sex differences on SPQ subscales.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sex</th>
<th>Ideas of Reference (IoF)</th>
<th>Unusual Perceptual Experience (UPE)</th>
<th>Odd Beliefs/Magical Ideation (OBMG)</th>
<th>Suspiciousness (Su)</th>
<th>Excessive Social Anxiety (ESA)</th>
<th>No Close Friends (NCF)</th>
<th>Constricted Affect (CA)</th>
<th>Odd/Eccentric Behaviour (OEB)</th>
<th>Odd Speech (OS)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Raine, 1992)</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>n= 787 (m/f 403/384), undergraduates. Effect sizes 0.17-0.32. Did not control for multiple comparisons</td>
</tr>
<tr>
<td>(Miller and Burns, 1995)</td>
<td>♂</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♂</td>
<td>♀</td>
<td>♂</td>
<td>n=1179, (m/f 433/726), ages 17-43 (M 19.04) undergraduates. Effect sizes (0.29-0.34). Bonferroni correction applied. Females higher on OBMG, males higher on ESA and Su</td>
</tr>
<tr>
<td>(Bora and Arabaci, 2009)</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>n=1024, (m/f 402/622), ages 16-90, community sample. Age was added as a covariate in comparisons.</td>
</tr>
<tr>
<td>(Fossati et al., 2003)</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>n=1732, (m/f 542/1190), ages 14-28, college and university. Bonferroni correction applied.</td>
</tr>
<tr>
<td>(Badcock and Dragovic, 2006)</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>n=352, (m/f 168/184), ages 18-79 (M 39.9) community. Did not control for multiple comparisons</td>
</tr>
<tr>
<td>(Roth and Baribeau, 1997)</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>♀</td>
<td>n=257, (m/f 120/137), 18-26 (M 21.4) undergraduate. Effect sizes 0.26 – 0.59. Did not control for multiple comparisons</td>
</tr>
</tbody>
</table>

♂ = males; ♀ = female; Symbol represents this group scored higher

It is possible that male and females have different developmental trajectories that result in schizotypal features peaking at different ages. In a sample of undergraduate students, females had a negative correlation between age and total SPQ-B and factor scores, whereas in males, increasing age was associated with a decline on the interpersonal and disorganised dimensions only (Mata et al., 2005). Further studies have also indicated differences in SPQ scores in older participants. For example, older males approximately 40 years old express higher levels on the subscales of ‘No Close Friends’ and ‘Constricted Affect’, whereas females score higher on ‘Social Anxiety’ and ‘Odd Beliefs’ subscales although these were lower than those reported in the younger female sample (Badcock and Dragovic 2006). It is possible that during specific age ranges males and females could have varying levels of specific schizotypal features which are variable over the lifetime.
Delusions and hallucinations

There appear to be limited sex effects on extent of delusions as measured by the PDI-40 (Peters et al., 1999; Jung et al., 2008) and PDI-21 (Peters et al., 2004; Preti et al., 2007a). This lack of difference is apparent in both younger (18-30 year olds) and older participants (60-75 year olds) (Laroi et al., 2006). However, others have found that in a sample of 18-23 year olds, females were represented more in the highest quartile on total PDI-21 scores (Scott et al., 2008). Studies examining sex differences in hallucinatory behaviour as measured by the LSHS have found limited differences (Aleman et al., 2001; Feelgood and Rantzen 1994; Laroi et al., 2006; Launay and Slade 1981; Waters et al., 2003). Although via the Hallucination Questionnaire, females had higher scores in both adolescent and adult samples (Pearson et al., 2008).

1.3.8.3 Why differences in expression in relation to sex?

It is likely that sex differences during adolescence and early adulthood impact upon the expression of schizotypal/subclinical psychotic experiences. Adolescence in particular is a period of dynamic change which has sex-specific trajectories (see Spear, 2000). Research in externalising (conduct disorders) and internalising problems during adolescence have highlighted these sex differences. For instance differences in environmental risk factors, levels of exposure to similar environmental risks, different biological risk factors including gene expression, and subsequent different thresholds for interactions between them, have all been suggested as differentiating between the sexes (Zahn-Waxler et al., 2008). In studies examining personality types, female adolescents (aged 13-17) are associated with the highest levels on negative emotionality (proneness to worry, irritability), alienation (perceived mistreatment, suspicion of deception) and aggression (distress of others, being vengeful) (Ryan, 2009). It is likely that such psychosocial and biological risk factors could also influence expression of schizotypal features. During adolescence, the presence of schizotypal features could be an exacerbation of psychological development and as such, reflects naturally occurring sex differences. Why differences continue in older subjects is not clear. Identifying factors involved would be important both for schizotypy research, but also for clinical research as it may help in developing more effective sex specific treatment (Hoff and Kremen, 2002).
1.4 Schizotypy and cognition

Cognitive deficits are one of the most pervasive and debilitating aspects of schizophrenia. They are independent of symptoms and are related to long-term outcome (Green et al., 2004). It can, however, be difficult to assess cognitive performance in clinical samples due to the influence of confounding factors such as distracting symptomatology and medication effects (Hori et al., 2006). Similarly, studies which investigate deficits in relatives of patients can be hindered by a number of methodological issues such as young offspring going through transition, proximity to the proband, and lack of control for relatives psychopathology (Heydebrand, 2006). As schizotypy is proposed as part of the extended phenotype of schizophrenia, it would be expected that cognitive deficits are also present in those with increased schizotypal features.

This next section examines cognitive deficits in schizotypal samples. As there is an extensive literature, a focus for this review is on sustained attention, spatial working memory, executive function and verbal learning/memory. It must be noted that other domains are also affected in schizotypal samples such as social cognition and theory of mind (Jahshan and Sergi, 2007) as well as reasoning biases (Sellen et al., 2005), but are not included in this review. Table 4 is a selection of studies that have investigated the effects of schizotypy on cognition in relation to the domains that are a focus of this review. Following on are sections on each cognitive domain.
Table 4: Selection of studies examining the effects of schizotypy on cognition. A particular focus is on measures of attention, spatial working memory, executive function and verbal learning/memory.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Authors</th>
<th>Task(s)</th>
<th>Sample</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Attention</strong></td>
<td>(Steel et al., 2002)</td>
<td>Distractor cueing task</td>
<td>Community n=36 (m/f 24/12), age 27.4</td>
<td>Healthy controls completed O-LIFE and cueing task. High positive schizotypy scores showed smaller distracter cueing effects than lower scores.</td>
</tr>
<tr>
<td></td>
<td>(Cimino and Haywood, 2008)</td>
<td>Stroop</td>
<td>Convenience sample n=36, age 26.1. Top and bottom 30% on O-LIFE total</td>
<td>High group slower and less accurate – deficits attributed to switching during task performance</td>
</tr>
<tr>
<td></td>
<td>(Stelton and Ferraro, 2008)</td>
<td>Stroop task, Simon task</td>
<td>University sample n=75 (m/f 37/38), age range 19-45.</td>
<td>No differences found between high and low groups split on STA.</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td>(Spaulding et al., 1989)</td>
<td>CPT derivate, Backward masking, Finger lift, WCST derivative</td>
<td>Sz n=99, Sty MMPI High n=20, Sty MMPI elevated n=19, HC n=140.</td>
<td>Sz deficits on all. No difference between Sty MMPI elevated and HC. Sty MMPI High impaired on backward mask, vigilance (CPT) compared to HC.</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td>(Lenzenweger et al., 1991)</td>
<td>CPT-IP</td>
<td>University sample, n=75 (m/f 34/41), age 18.3</td>
<td>Selected from 726 who completed PAS into high (+2sd) and controls. High PAS group associated with decreased sensitivity compared to controls</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td>(Obiols et al., 1993)</td>
<td>CPT-IP</td>
<td>Military conscript sample n=68 (all male), age 20.8</td>
<td>From initial 343 participants completing STA and PAS. High group selected on 1.5sd above mean (n=35) and controls from below mean. High group had significantly poorer sensitivity (d’) than controls</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td>(Chen et al., 1997) see also (Chen et al., 1998a)</td>
<td>CPT-AX (degraded and non-degraded)</td>
<td>Community sample from systematic sampling. Adolescents n=115 (m 55%), age 14. Adult n=345 (m 48%), age 41.3</td>
<td>The interpersonal and disorganised factors of SPQ associated with poorer performance in adults in degraded and undegraded CPT version respectively. In adolescents there was no association with SPQ factors.</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td>(Chen et al., 1998a) see also (Chen et al., 1997)</td>
<td>CPT-AX (degraded and non-degraded)</td>
<td>Community sample from systematic sampling. Adolescents n=115 (m 55%), age 14. Adult n=345 (m 48%), age 41.3</td>
<td>All participants completed SPQ and PAS. CPT performance associated with sty measures. Age was associated with decrease in performance, whereas males had marginal better performance on degraded versions. Authors highlight the importance of demographic matches in studies.</td>
</tr>
<tr>
<td>Domain</td>
<td>Authors</td>
<td>Task(s)</td>
<td>Sample</td>
<td>Finding</td>
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<tr>
<td>Attention (sustained)</td>
<td>(Rawlings and Goldberg, 2001)</td>
<td>CPT-X, -AX &amp; -IP</td>
<td>University sample, n=100 (m/f 57/43), age 22.3</td>
<td>Participants completed the O-LIFE. On CPT-X cognitive disorganisation negatively correlated with sensitivity and positively correlated with response bias. CPT-IP sensitivity negatively correlated with unusual experiences and cognitive disorganisation dimensions. Reaction times in CPT versions associated with O-LIFE dimensions.</td>
</tr>
<tr>
<td>Attention (sustained)</td>
<td>(Lenzenweger, 2001) same sample as other Lenzenweger studies</td>
<td>CPT-IP</td>
<td>University sample, n=57 (m/f 27/30), age 19.0</td>
<td>From sample pool n=1684, high (+2sd) PAS and controls selected. No difference in performance indices, but Sty associated with slower response times.</td>
</tr>
<tr>
<td>Attention (sustained)</td>
<td>(Gooding et al., 2006)</td>
<td>CPT-IP (with and without distractions)</td>
<td>University sample n=393, (m/f 164/229)</td>
<td>Sample derived from n=6384. Selected for high scores (+2.d.) on PAS and/or MIS (positive Sty), or (+2sd) on SocAn (negative sty) or controls. Both high groups had reduced sensitivity.</td>
</tr>
<tr>
<td>Attention (sustained)</td>
<td>(Bergida and Lenzenweger, 2006) See also (Lenzenweger et al., 2007)</td>
<td>CPT-IP</td>
<td>Community sample n=305, (female 61.3%), age 30.1. Completed SPQ</td>
<td>Correlations between SPQ and performance controlling for age, sex and educational level. Reality distortion factor (positive schizotypal features) associated with decreased sensitivity and increased random errors.</td>
</tr>
<tr>
<td>Attention (sustained)</td>
<td>(Lenzenweger, McLachlan et al., 2007); see also (Bergida and Lenzenweger, 2006)</td>
<td>CPT-IP, eye-tracking dysfunction measurements</td>
<td>Community sample n=294, (female 60.9%), age 30.1. Completed SPQ</td>
<td>Using finite mixture modelling for identifying latent structure with tasks as markers of psychosis liability. Two groups formed with performance deficit group with higher factor and total SPQ scores. Cognitive Perceptual dimension associated with decreased sensitivity.</td>
</tr>
<tr>
<td>Attention (sustained)</td>
<td>(Alvarez-Moya, Barrantes-Vidal et al., 2007)</td>
<td>CPT-IP</td>
<td>1498 12-13 year olds completed CPT-IP.</td>
<td>Selected on poor performance (d’) and matched controls and followed after 10 year period. Completed various behavioural measures including O-LIFE. Poor performers on CPT associated with higher negative Sty and other cluster C personality traits at 10-year follow-up.</td>
</tr>
<tr>
<td>Domain</td>
<td>Authors</td>
<td>Task(s)</td>
<td>Sample</td>
<td>Finding</td>
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</tr>
<tr>
<td>Attention (sustained)</td>
<td>(Bedwell et al., 2009)</td>
<td>CPT-AX (degraded)</td>
<td>University sample, n=52 (m 38%), age 19.2</td>
<td>1328 participants screened on SPQ-B and selected on high (top 10%) or controls. Participants completed SCID-I and schizotypal personality disorder section of SCID-II. Correlations only found between interview based sty measures and CPT performance.</td>
</tr>
<tr>
<td></td>
<td>(Chan et al., 2009)</td>
<td>SART</td>
<td>Community and university sample, n=125 (m/f 62/63. Completed SPQ)</td>
<td>Upper and lower 10% selected. High schizotypes (m/f 43/26), low schizotypes (m/f 19/37). Low schizotypes had better efficiency score (combines accuracy and speed of responding)</td>
</tr>
<tr>
<td>Attention (sustained), executive</td>
<td>(Bedwell et al., 2006)</td>
<td>CPT-AX (degraded), WCST, Span of apprehension</td>
<td>University sample (n=40), age 20.4</td>
<td>From 1145 participants completing SPQ-B, top 6% selected for high group and a control group selected. High group were impaired on CPT only compared to controls. Cognitive Perceptual factor was associated with omission errors.</td>
</tr>
<tr>
<td>Attention (sustained), memory</td>
<td>(Cohen et al., 2006)</td>
<td>Visual reproduction, block design, spatial span, logical memory, LNS, digit span, CPT degraded</td>
<td>University sample, n=172 (m/f 77/97), age 18-19</td>
<td>Selected from 3498 participant completing SocAn, PAS and MIS. High SocAn scores (n=85) impaired on visual reproduction and block design.</td>
</tr>
<tr>
<td>Attention (switching)</td>
<td>(Wilkins and Venables, 1992)</td>
<td>Attention switching task (auditory and visual stimuli)</td>
<td>University sample, n=42 (m/f 23/19), age 25.3</td>
<td>Sample derived from 470 who completed PhyAn and Schizophrenia scale, and split into two sty and on control groups. Both sty groups has impaired reaction times in switching compared to controls.</td>
</tr>
<tr>
<td>Attention, executive</td>
<td>(Lenzenweger et al., 2003)</td>
<td>Measures for classification: WCST, eye-tracking dysfunction measurements. Measures for validation: CPT-IP, DRT</td>
<td>University n=57 (m/f 27/30), age 19.0</td>
<td>From sample pool n=1646, high (+2sd) PAS and controls selected. Performance on WCST and eye-tracking with PAS scores used in expectation-maximisation algorithm to produce less heterogeneous groups: controls, false positive Sty, genuine sty. Genuine Sty impaired on CPT-IP and DRT compared to controls; false positives were not.</td>
</tr>
<tr>
<td>Attention, executive, intelligence</td>
<td>(Barrantes-Vidal et al., 2002)</td>
<td>Digit span, DSST, CPT-IP, Verbal fluency, TMT, WCST, WISC-R, Raven Matrices</td>
<td>School sample, n=270 (m/f 141/129), age 13.4</td>
<td>Participants complete PAS, SocAn and PhyAn. Grouped into negative, positive, combined sty and controls. Combined sty impaired on DSST compared to Positive sty and controls. Combined sty impaired on intelligence compared to all groups. Combined and negative sty impaired on verbal fluency. Negative sty impaired on a measure from WCST.</td>
</tr>
<tr>
<td>Domain</td>
<td>Authors</td>
<td>Task(s)</td>
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</tr>
<tr>
<td>Attention, executive, memory</td>
<td>(Ruíz et al., 2008)</td>
<td>Logical Memory, Visual memory span, CPT-IP, COWA, Verbal and semantic</td>
<td>Community sample n=76 completed SPQ-B and test battery</td>
<td>Performance measures factor analysed. Correlations between positive/negative Sty and semantic evocation (fluency tasks)</td>
</tr>
<tr>
<td>Executive</td>
<td>(Lin et al., 2000)</td>
<td>WCST</td>
<td>School sample n=817,(m 48%, age 13-15)</td>
<td>Participants completed SPQ and PAS. Age effects were demonstrated. A sample of high sty compared to controls with no difference in performance.</td>
</tr>
<tr>
<td>Executive</td>
<td>(Spitznagel and Suhr, 2002)</td>
<td>WCST, COWA, Object Alternation Test, Delayed Alternation/Response Test, WASI</td>
<td>University, n=70, (m/f 20/50), age 18-21</td>
<td>Sample from 2000 students selected on SPQ and OCD measures and split into HC, Sty, OCD, and Sty/OCD. No association found between Sty groups and executive function. OCD group impaired in impulse domain.</td>
</tr>
<tr>
<td>Executive</td>
<td>(Dinn et al., 2002)</td>
<td>Verbal fluency, Divergent thinking, Porteus maze, TMT, Stroop, Rey-Osterrieth Test</td>
<td>University sample n=103 (m/f 28/75), age 18.6</td>
<td>Participants completed SPQ-B and other questionnaires. Split into low, control and high groups for positive and negative symptoms. Low negative Sty better performance on TMT and divergent thinking. Positive sty not associated with executive, although links with impulsivity.</td>
</tr>
<tr>
<td>Executive</td>
<td>(Tsakanikos and Claridge, 2005)</td>
<td>Verbal fluency (letters)</td>
<td>University sample n=190 (m/f 91/99), age 23.5</td>
<td>Number of words produced did not correlate with O-LIFE scores. Non-linear relationship present – high scores on positive (+1sd) associated with increase in words; high scores on negative (+1sd) associated with decrease.</td>
</tr>
<tr>
<td>Executive</td>
<td>(Krabbendam, Myin-Germeys et al., 2005)</td>
<td>Verbal fluency (animal names)</td>
<td>Random population sample including relatives n=425 (male 41.4%), age 47.3</td>
<td>Completed the CAPE and SIS-R. Male’s worse performance associated with positive, negative and depressive symptoms. No association in females. In male family pairs, high positive sty predictive or poor performance in relative; not found in female family pairs.</td>
</tr>
<tr>
<td>Executive</td>
<td>(Laws et al., 2008)</td>
<td>Category and letter fluency, Zoo map subtest, Hayling sentence completion, Dysexecutive questionnaire</td>
<td>University sample n=65 (m/f 10/55), age 22.0</td>
<td>Sample split into two groups based on mean SPQ-B scores. No significant difference in executive tasks. High SPQ-B group did report more executive problems on behavioural measure.</td>
</tr>
<tr>
<td>Executive</td>
<td>(Asarnow et al., 1983)</td>
<td>Span of Apprehension, Trails A and B, DSST</td>
<td>Community Sample n=50 (all male)</td>
<td>Poor Span of apprehension associated with high scores on PAS and MIS                                                                uby.</td>
</tr>
<tr>
<td>Domain</td>
<td>Authors</td>
<td>Task(s)</td>
<td>Sample</td>
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<tr>
<td>Executive</td>
<td>(Avons et al., 2003)</td>
<td>Random generation task, memory updating task</td>
<td>University sample n=59 (m/f 13/46), age 21.4</td>
<td>Selected from 265 participants completing O-LIFE, split into low (-1.25SD of mean) and high groups (+1.25SD). High group had lower performance on one measure from updating task.</td>
</tr>
<tr>
<td>Executive function</td>
<td>(Suhr and Spitznagel, 2001)</td>
<td>WCST, TMT, Stroop</td>
<td>University sample, n=108 (m/f 34/74)</td>
<td>Initial sample of c. 3500 completed either SPQ or PAS &amp; MIS. Factor analysis of questionnaires into positive, negative and disorganised. High negative scores associated with lower WCST performance.</td>
</tr>
<tr>
<td>Executive function, spatial working memory</td>
<td>(Park et al., 1995)</td>
<td>DRT, WCST, DSST</td>
<td>University sample n=51 (m/f 26/25), age 19.0</td>
<td>From a sample of 1684 students completing PAS, 23 controls and 28 high scorers selected. High group performed worse on DRT, and less able to maintain set on WCST.</td>
</tr>
<tr>
<td>Executive, memory intelligence</td>
<td>(Noguchi et al., 2008)</td>
<td>WCST, WMS-R, WAIS-R</td>
<td>Community sample n=124 (m/f 24/100), age 46.3.</td>
<td>Verbal IQ negatively correlated with SPQ subscales Odd beliefs and odd speech. No SPQ subscales correlated with memory, attention/concentration, performance IQ or executive function.</td>
</tr>
<tr>
<td>Executive, attention, working memory</td>
<td>(Giraldez et al., 2000)</td>
<td>Stroop, CPT-AX, Word recognition, visual test of working memory, TMT, verbal fluency</td>
<td>School random sample, n=82 (m/f 46/36), age 12.71</td>
<td>Participants completed MSTQ – upper and lower 30% and 20% compared for positive, negative and impulsive non-conformity factors. High negative symptoms associated with poor performance on Stroop, CPT, verbal fluency, TMT, working memory, and word recognition.</td>
</tr>
<tr>
<td>Executive, verbal memory</td>
<td>(Spitznagel and Suhr, 2004)</td>
<td>COWA, AVLT, Digit Span, WCST, TMT</td>
<td>University n=84 (m/f 28/56), age 19</td>
<td>Sample selected on high scores on SPQ (top 5.5%) with and without high depressive scores (BDI) and controls. High sty and depressed increased performance on WCST compared to high sty, as well as increased immediate recall (AVLT) compared to sty and controls.</td>
</tr>
<tr>
<td>Executive, working memory</td>
<td>(Tallent and Gooding, 1999)</td>
<td>WCST, DRT</td>
<td>University sample, n=178 (m/f 77/101), age 19.0</td>
<td>2496 participant completed PAS, MIS, PhyAn and SocAn. Selected +2SD on positive symptoms (Per-Mag group), +2 SD negative (SocAn) and control &lt;0.5SD. Controls made fewer errors on DRT. SocAnh reduced performance on WCST categories achieved, and SocAnh and PerMag reduced on WCST failure to maintain set.</td>
</tr>
<tr>
<td>Domain, Task(s)</td>
<td>Authors</td>
<td>Sample</td>
<td>Finding</td>
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</tr>
<tr>
<td>Executive, working memory</td>
<td>Diwadkar et al., 2006</td>
<td>Genetic high risk n=33 (15 females), controls n=34 (16 females)</td>
<td>High risk split into those with sty traits (PAS, MagId) and those without. High risk with sty impaired on WCST compared to non sty high risk and controls. Both high risk deficits in visual working memory in older participants.</td>
<td></td>
</tr>
<tr>
<td>Executive, working memory</td>
<td>Matheson and Langdon, 2008</td>
<td>University sample n=97 (females approx 60%) Male age 21.7, female 24.9</td>
<td>SPQ cognitive perceptual and interpersonal deficits negatively correlated with LNS performance. Cognitive perceptual associated with matrix reasoning</td>
<td></td>
</tr>
<tr>
<td>Memory (semantic)</td>
<td>Kiang and Kutas, 2006</td>
<td>University sample n=60, (m/f 26/34), age 20.9</td>
<td>Participants completed SPQ. No correlation between number of responses and SPQ scores. High SPQ scores associated with more atypical words for one category.</td>
<td></td>
</tr>
<tr>
<td>Memory (verbal)</td>
<td>LaPorte et al., 1994</td>
<td>University sample n=409, (females 72%), age 20</td>
<td>Participants completed Chapman scales: PAS, MIS and SocAn. No correlations found between performance and scales – but increased PAS associated with better recall when controlling for BDI and drug/alcohol use. No difference between high (+2sd) and low combined PAS and MIS.</td>
<td></td>
</tr>
<tr>
<td>Memory, executive, social functioning</td>
<td>Jahshan and Sergi, 2007</td>
<td>University sample n=92, (m/f 38/54), age 20.1</td>
<td>Sample derived from 2108 participants on SPQ-B, with 52 high (top 4.8% sample) and 40 low (bottom 7.2%). High group impaired on social functioning but not on social- or neurocognitive function.</td>
<td></td>
</tr>
<tr>
<td>Memory, executive, emotional intelligence, social functioning</td>
<td>Aguirre et al., 2008</td>
<td>University sample n=95, (m/f 20/76), age 20.8.</td>
<td>Sample derived from 2102 participants on SPQ-B, with 40 high (top 3.8% sample) and 56 low (bottom 8.1%). High group impaired on emotional intelligence (MSCEIT) and social functioning.</td>
<td></td>
</tr>
<tr>
<td>Memory, information processing</td>
<td>Simons, Jacobs et al. 2007</td>
<td>298 mono- and dizygotic females twin pairs. Age range 18-46. Completed CAPE</td>
<td>Significant correlations between information processing and positive and negative dimensions. Genetic factors involved in correlation with negative dimension</td>
<td></td>
</tr>
<tr>
<td>Working memory</td>
<td>Park and McTigue, 1997</td>
<td>University sample, n=89 (m/f 39/50), age 19.1</td>
<td>Negative factor of SPQ correlated (trend level) with working memory score. Subscale ‘no close friends’ significantly correlated with performance.</td>
<td></td>
</tr>
<tr>
<td>Domain</td>
<td>Authors</td>
<td>Task(s)</td>
<td>Sample</td>
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</tr>
<tr>
<td>Working memory</td>
<td>(Warnick and Allen, 2005)</td>
<td>WAIS: information, vocabulary, digit span, digit symbol substitution, spatial span</td>
<td>Community: High sty with family history n=10, high sty without n=13, Age 19.9</td>
<td>From pool of 1165, above 2sd on Chapman scales. Split into positive family history of schizophrenia or not. Digit and spatial span forwards and backwards more impaired in positive family history.</td>
</tr>
<tr>
<td>Working memory</td>
<td>(Kerns and Becker, 2008)</td>
<td>N-back</td>
<td>University sample n=66 (m/f 37/29), age 18.7</td>
<td>Disorganised schizotypy as measured by Cognitive Slippage Scale was used to group participant into high (+2sd) and controls (&lt;0.5). High group were less accurate on n-back 3 condition</td>
</tr>
<tr>
<td>Working memory</td>
<td>(Schmidt-Hansen and Honey, 2009)</td>
<td>N-back</td>
<td>University sample, n=289 (m/f 45/244), age 19.8</td>
<td>Participants completed the O-LIFE and split on the mean score. Reduced performance in high positive group compared to low, and in low negative group compared to high.</td>
</tr>
<tr>
<td>Working memory</td>
<td>(Lenzenweger and Gold, 2000)</td>
<td>Verbal Memory (recall) measures, Letter-number sequencing</td>
<td>University sample, n=57 (m/f 27/30), age 19.0</td>
<td>From sample pool n=1684, high (+2sd) PAS and controls selected. No difference in performance between the two groups</td>
</tr>
</tbody>
</table>

AVLT – Auditory Verbal Learning Test; BDI – Beck Depression Inventory; CFT – Category Fluency Task; COWA – Controlled Word Association Test; CPT (-IP) – Continuous Performance Task (Identical Pairs); CVLT - California Verbal Learning Test; DRT – delayed response task; DSST - digit symbol substitution test; LNS – Letter-Number Sequencing Task; MIS – Magical Ideation Scale; MSCEIT - Mayer–Salovey–Caruso Emotional Intelligence Test; MSTQ – Multidimensional Schizotypal Traits Questionnaire; PAS – Perceptual Aberration Scale; PhyAn – Physical Anhedonia Scale; SART – Sustained Attention to Response Task; SDMT - Symbol Digit Modalities Test; SIS-R – Structured Interview for Schizotypy-Revised; SocAn – Social Anhedonia Scale; SPQ (-B) – Schizotypal Personality Questionnaire (-Brief); STA – Schizotypal Personality Scale; TMT – Trail Making Test; WAIS-R – Wechsler Adult Intelligence Scale-Revised; WCST – Wisconsin Card Sorting Task; WISC-R – Wechsler Intelligence Scales for Children-Revised; WMS-R – Wechsler Memory Scale-Revised
1.4.1 Sustained attention

1.4.1.1 Background
Sustained attention is one of the four components of the attentional system proposed by Mirsky et al., (1991). Referred to as the ‘sustain’ component or ‘vigilance’, it is capable of maintaining focus and alertness over time. Brain regions associated with attention tasks are often difficult to localise, although functional magnetic resonance imaging (fMRI) has identified predominantly right hemispheric activation in the anterior cingulum, mesial frontal lobe and nucleus caudate; and bilateral activation in superior frontal gyrus, posterior insula and thalamus (Hager et al., 1998). Ability on these tasks develops during childhood and adolescence with age 10 years considered the point in which performance plateaus with only late minor improvements (Betts et al., 2006). Via the continuous performance task (CPT), a longitudinal study has demonstrated a reduction in omission errors (missed targets) and quicker reaction times in ages 8-13 years, with an initial rapid development followed by gradual improvement (Rebok et al., 1997). Similarly, increased sensitivity (d’) (the ability to discriminate signal and noise) and reduced false alarm rate improve considerably in the age range 6-14 years (Lin et al., 1999), with a possible decline in ability after early adolescence (Chen et al., 1998). Sex has been found to be a mediating variable in developmental changes, with boys having greater sensitivity than girls (Lin et al., 1999; Rebok et al., 1997).

1.4.1.2 Measures of sustained attention
An important caveat into the neuropsychology of attention research is the choice of tasks. Not only are there numerous tests of attention, but within specific tasks there are various levels of difficulty. For instance, the continuous performance task (CPT) has multiple versions. In the most basic form (CPT-X) the participant responds solely to specific letters/digits from a displayed sequence. An alternative is the identical pair’s version (CPT-IP) where the participant responds when two identical symbols are presented in succession. This higher demand version relies on greater cognitive capacity and brings other processes online such as working memory (Borgaro et al., 2003). Distractions can also be used where the visual stimulus are accompanied by auditory distraction, or degraded versions where the visual stimuli are harder to detect. These differences in task have a bearing on the interpretation on results regardless of the field of study (Borgaro et al., 2003).
**1.4.1.3 Sustained attentions deficits in schizophrenia samples, SPD, relatives, and ARMs**

Deficits in sustained attention are often present in schizophrenia patients (Cornblatt and Keilp, 1994; Orzack and Kornetsky, 1966). Performance on distraction versions of the CPT can discriminate between schizophrenia patients and their siblings/controls, whereas in non-degraded versions siblings have intermediate performance between patients and controls (Chen et al., 1998b; Franke et al., 1994). A meta-analysis of 11 studies investigating CPT performance in relatives indicate a significant moderate mean weighted effect size (Sitskoorn et al., 2004). Performance in relatives has also been shown to correlate with scores on the Interpersonal and Disorganised schizotypal factors (Chen et al., 1997; Chen et al., 1998b), although some have found association with performance in relation to genetic proximity (Laurent et al., 2000, Laurent et al., 1999). This led to a suggestion that performance and schizotypy could represent two independent risk factors. Performance on CPT-IP is also impaired in SPD patients compared to controls and other personality disordered patients, but less severe than demonstrated in schizophrenia patients (Roitman et al., 1997).

In high risk studies there are mixed findings in the extent of sustained attention deficits. The Edinburgh high risk study found no difference between their genetic high-risk group and controls on the CPT-IP (Cosway et al., 2002), in contrast to previous studies (Chen et al., 1998b; Franke et al., 1994; Laurent et al., 1999). There was also no difference in performance between high risk groups with attenuated psychotic symptoms and those without, suggesting symptoms also had limited influence on sustained attention in this sample (Cosway et al., 2002). Similarly in another high risk group paradigm those with clinical risk due to symptom severity did not have impaired performance, although those with genetic proximity were impaired on the CPT-IP (Myles-Worsley et al., 2007).

**1.4.1.4 Sustained attention in schizotypy**

From Table 4 there is evidence of a sustained attention deficit in schizotypal groups. Early studies found deficits on the CPT-IP in individuals with high scores on the PAS (Lenzenweger et al., 1991). These effects were independent of concomitant psychological state factors (i.e. depression and anxiety) (Lenzenweger et al., 1991) and education level (Obiols et al., 1993). In a series of studies Chen and colleagues (1997; 1998a) investigated CPT function in a Taiwanese sample. Adolescents and adults with high total SPQ had performance deficits on
degraded and non-degraded versions of the CPT. Higher scores on the Interpersonal Dimension were also associated with reduced performance on the degraded CPT in adults only (Chen et al., 1997). Within the adolescent sample, no factor of the SPQ was associated with performance. However, both adolescent and adult samples with higher scores on the PAS had decreased sensitivity (Chen et al., 1997; Chen et al., 1998a). It is unclear why the positive symptoms as measured by the PAS were associated with CPT performance deficits, but this deficit was not replicated when using the Cognitive-Perceptual factor of the SPQ. An association with attenuated positive features as measured by the SPQ-B has, however, been found in another study (Bedwell et al., 2006). Participants with high scores on negative schizotypy have a similar decrease in sensitivity (Gooding et al., 2006), but not always replicated (Cohen et al., 2006). Gooding et al., (2006) suggest this could represent dissociable pathways that manifest in performance deficits on the CPT-IP. Those with heightened positive schizotypy could possess greater attentional deficits, whereas negative schizotypy is associated with impairments in working memory (see below).

Further studies have sought to examine the effects of schizotypy on sustained attention in adolescent samples. Those who scored in the bottom decile on the CPT-IP did not have any significant difference in levels of schizotypy as measured by the PAS and social anhedonia scale (Obiols et al., 1999). This has been supported in other adolescent samples where no performance differences were found on the CPT-IP when categorised into high positive, high negative, or high on both features compared to controls (Barrantes-Vidal et al., 2002). The negative findings in adolescent groups suggest that schizotypal effects may not be evident until adult levels of performance are reached. The CPT could, however, have predictive value in later presentation of schizotypal features. In a retrospective study, performance on the CPT-IP was associated with schizotypal levels 10 years later (Alvarez-Moya et al., 2007). At ages 12-13 years the bottom 10% of sensitivity scores and the control group were selected and followed-up. After approximately 8-10 years those in the bottom 10% of CPT were associated with significantly higher scores on the Introvertive Anhedonia subscale of the O-LIFE (Alvarez-Moya et al., 2007). This suggests that early attentional deficits could be a risk factor or early marker for later schizotypy.

Reaction times are also measured via the CPT. Longer reaction times have been found in groups with high scores on the PAS (Lenzenweger, 2001) and disorganised factor of the O-
LIFE (Rawlings and Goldberg, 2001). Other studies, however, have failed to find this association (Neumann & Walker, 1999; Park et al., 1995). Where increased reaction times are found, this has been interpreted as a general information processing deficit rather than specificity to a particular cognitive domain (Schreiber et al., 1992).

1.4.2 Spatial Working Memory

1.4.2.1 Background

Working memory is the ability to hold information, allowing comprehension, thinking and planning (Baddeley, 1996; Goldman-Rakic, 1996). It is proposed to have three subsystems including the phonological loop, visuo-spatial sketchpad and central executive (Baddeley, 1996). Functional MRI studies have identified the bilateral prefrontal cortex (PFC) to be active during working memory (van Asselen et al., 2006). Development of working memory occurs throughout childhood and adolescence. This improvement in ability matches the neurodevelopment of the PFC (Conklin et al., 2007), with functional localisation to the right hemisphere occurring around ages 5-7 (Tsujii et al., 2009), and subsequent increases in activation in the left middle and superior frontal gyri including dorsolateral prefrontal cortex (DLPFC) and posterior parietal regions in ages 12-17 (Schweinsburg et al., 2005). Behavioural data suggests different development trajectories for separate working memory components For instance, performance ability on backward span tasks and self ordered searching develops during ages 9-17 years (Conklin et al., 2007), and improvements in delayed response tasks in ages 14-20 years (Zald and Iacono, 1998).

1.4.2.2 Measures of spatial working memory

Spatial working memory can be assessed with a variety of neuropsychological tasks including delayed-response (DRT), backward span, and self-ordered search tasks. These tasks are likely to be measuring a construct of executive function as the tasks require both ‘maintenance’, in holding information and ‘manipulation’ where the information is processed and updated (Manoach, 2003).

1.4.2.3 SWM deficits in schizophrenia samples, SPD, relatives, and ARMs

Schizophrenia samples are associated with significant impairments in working memory including spatial working memory as demonstrated in a meta-analysis (Forbes et al., 2009).
This meta-analysis failed to find any particular type of symptoms associated with impairment, although some studies have implicated negative symptoms (e.g. Carter et al., 1996; Pantelis et al., 2001). Deficits in working memory performance have also been demonstrated in SPD (Mitropoulou et al., 2005; Roitman et al., 2000) and those with a positive family history of psychosis (Warnick and Allen, 2005). In a comprehensive study investigating a variety of verbal/auditory and visual working memory tasks, relatives’ performance was intermediary to that of schizophrenia patients and controls (Barrantes-Vidal et al., 2007). Via the DRT, deficits have also been demonstrated in clinical high risk adolescent groups (Smith et al., 2006); and via backward span tasks, in symptomatic high risk groups (Myles-Worsley et al., 2007). However, these deficits are not thought to differentiate those who do or do not develop psychosis, so represents a vulnerability marker rather than a trait marker for transition (Wood et al., 2003).

1.4.2.4 SWM deficits in schizotypy

To date fewer studies have investigated spatial working memory function in psychometrically defined schizotypes compared to attention. Table 4 lists the findings from studies that have examined spatial working memory performance. On the DRT, individuals scoring high on the PAS had impaired performance compared to controls (Park et al., 1995), whilst another study found a trend correlation between impaired performance and the negative factor of the SPQ (Park and McTigue, 1997). A further study sought to compare performance between groups selected on negative (Social Anhedonia scale) or positive (Perceptual-Magical Ideation) schizotypal features (Tallent and Gooding, 1999). Both groups produced more errors compared to controls, but similar levels of performance to each other.

In summary, there are subtle performance differences in schizotypes which have been linked to both positive and negative symptoms. It is possible that similar to the clinical literature, there is limited interaction between state and trait features, but instead independent processes caused by similar subtle abnormalities in underlying brain structures. Spatial working memory function is associated with prefrontal regions (van Asselen et al., 2006). These regions are also implicated in the formation of negative symptoms in schizophrenia (Wible et al., 2001). There appears to be less evidence for the structural/functional correlates of positive symptoms and working memory. Further studies in schizotypes are required to examine the extent to which attenuated symptoms are related to spatial working memory.
1.4.3 Executive Function

1.4.3.1 Background

Executive function is proposed as a complex construct that controls underlying basic cognitive processes to ensure a flexible contextually correct response (Miller and Cohen, 2001). There are multiple domains considered to be part of the executive system including set shifting, planning, inhibition, fluency, contextual memory and working memory (discussed previously). Development of executive function begins in early life and develops throughout childhood and adolescence, with dissociable developmental trajectories observed in different domains (Huizinga et al., 2006). Multiple brain regions are involved in executive processes, with lesion studies originally identifying the role of prefrontal brain regions (see Shallice, 1988). Imaging studies have added a degree of localisation with identification of areas of functional importance including the DLPFC and anterior cingulate cortices, as well as sub-cortical and parietal regions (Carpenter et al., 2000; Eisenberg and Berman 2010).

There are a variety of tasks that measure prefrontal function. Some more common examples include the Wisconsin Card Sorting Task (WCST) which measures cognitive flexibility and set shifting; Trail Making Tests (TMT) that measure task switching; and FAS which measure verbal fluency.

1.4.3.2 Deficits in schizophrenia samples, SPD, relatives, and ARMs

There is widespread executive dysfunction in schizophrenia patients, demonstrated on tasks including the WCST (Laws, 1999), verbal fluency (Henry and Crawford, 2005) and problem solving (Rushe et al., 1999a). There is, however, no conclusive pattern of deficits, probably attributable to the widespread processes involved in executive function. The negative symptoms tend to be most correlated with performance (O'Leary et al., 2000), whereas positive symptoms appear to have little association (Berenbaum et al., 2008). Functional imaging studies have identified regional differences in activation (see Eisenberg and Berman, 2010). A recent meta-analysis demonstrated qualitatively similar regions of activation compared to controls, but often with reduced levels of activation in DLPFC, anterior cingulate cortex (ACC) and parts of the thalamus (Minzenberg et al., 2009). There were also areas in the
PFC that had increased areas of activation in patients which could suggest compensatory brain function (Minzenberg et al., 2009).

SPD patients have been shown to have deficits compared to non-schizophrenia related PDs and controls on the WCST and TMT (Diforio et al., 2000; Trestman et al., 1995). Family studies have identified deficits in a variety of executive tasks including those measuring verbal fluency, cognitive flexibility and inhibition (Sitskoorn et al., 2004; Heydebrand 2006). The degree of genetic loading appears important, with those from multiply affected families showing greater degree of impairment (Birkett et al., 2008). Attenuated negative symptoms are also linked to performance where one study demonstrated inferior performance in relatives with high negative symptoms compared to relatives with low negative symptoms (Laurent et al., 2001). High risk groups also appear to have prefrontal functioning deficits, for example impairments have been found on the WCST (Gschwandtner et al., 2006; Pflueger et al., 2007) and fluency tasks (Hambrecht et al., 2002; Lencz et al., 2006; Simon et al., 2007). However, deficits in executive function are not always found (see Brewer et al., 2006). Factors that could influence whether deficits are observed could be related to the precise ‘type’ of high-risk candidate. This is evident in comparison between converters and non-converters; with the former demonstrating greater reduction in ability on the TMT (Wood et al., 2007).

**1.4.3.3 Deficits in schizotypy**

Table 4 gives a selection of studies that have examined executive functioning in community based schizotypes. Performance deficits on executive tasks are less robust than those in attention and spatial working memory.

In tests of set shifting and cognitive flexibility such as the WCST, individuals with high general schizotypal levels tend not to show performance deficits (Aguirre et al., 2008, Bedwell et al., 2006). However, when categorised on negative schizotypal features, there are deficits in both high scoring adolescent (Barrantes-Vidal et al., 2002) and adult groups (Suhr and Spitznagel, 2001; Tallent and Gooding, 1999). This specificity to negative features is supported by studies that have found no effect in high positive schizotypes (Barrantes-Vidal et al., 2002; Lin et al., 2000; Suhr and Spitznagel, 2001), although some have suggested there
could be subtle performance differences in high positive groups such as failure to maintain set (Park et al., 1995; Tallent and Gooding, 1999).

As a measure of task switching, the trail making test (TMT) is also relatively well studied. In some studies, high schizotypy groups tend not to be impaired (Asarnow et al., 1983; Barrantes-Vidal et al., 2002; Matheson and Langdon, 2008; Spitznagel and Suhr, 2004; Suhr and Spitznagel, 2001), although low negative scorers have been shown to complete the task more quickly than average and high negative scorers (Dinn et al., 2002). In adolescent groups, high negative scorers have also been found to have reduced performance (Giraldez et al., 2000).

On verbal fluency tasks, there is reduced ability in individuals with increased negative features in adolescents (Barrantes-Vidal et al., 2002) and adults (Tsakanikos and Claridge, 2005), although again not always demonstrated (Dinn et al., 2002; Laws et al., 2008). Sex differences could also interact with schizotypy, since males with schizotypal features have impaired performance whereas females do not (Krabbendam et al., 2005). Interestingly, increased positive schizotypal features have been linked to an increase in word production in fluency tasks (Tsakanikos and Claridge, 2005), which could support the hypothesised links between creativity and some schizotypal features (e.g. Nettle 2006), and represent a beneficial aspect to possessing heightened features.

In summary there does not appear to be a definitive deficit in executive functioning compared to sustained attention and spatial working memory, likely in part, to the nebulous construct of ‘executive function’. Where deficits are present, these are mostly related to negative schizotypal features which support the clinical findings. Arguably it is genetic proximity that is most associated with executive function as demonstrated in relatives of patients. Executive functions which are widely reported in schizophrenia represent higher order processing. For deficits to be present in these executive functions, it is perhaps necessary for multiple processes to fail, and/or that schizotypal samples are relatively ‘protected’ from prefrontal pathology, or at least there is a degree of normal functioning, particularly in crucial regions such as the DLPFC.
1.4.4 Verbal learning/memory

1.4.4.1 Background

Verbal memory involves an encoding phase where initial processing create a memory trace, followed by retrieval phases (Paller and Wagner, 2002). There is linear improvement in verbal learning/memory ability during ages 6-12 years, with only minor improvements during adolescence (Waber et al., 2007). Imaging studies have demonstrated multiple brain regions involved during episodic encoding (‘learning’) and retrieval, including the medial temporal lobes (including hippocampal formation), DLPFC, and fusiform gyrus (Baker et al., 2001, Fletcher et al., 1995, Karlsgodt et al., 2005; Wagner et al., 1998). The medial temporal lobe is the region which binds together outputs from cortical regions to create the memory trace (Paller and Wagner, 2002).

1.4.4.2 Deficits in schizophrenia samples, SPD, relatives, and ARMs

Deficits in verbal learning and memory are a reliable finding in schizophrenia samples (Heinrichs and Zakzanis, 1998, Rushe et al., 1999b, Saykin et al., 1991). Imaging studies have identified functional abnormalities in the hippocampus (Heckers et al., 1998; Jessen et al., 2003), although studies examining structural changes in the hippocampus and performance impairments are mixed (Torres et al., 1997; Gur et al., 2000). Impaired performance is also observed in SPD patients (Bergman et al., 1998; Mitropoulou et al., 2002) and relatives of patients with a meta-analysis demonstrating verbal recall to have the largest performance differences between relatives and controls of any cognitive measure (Sitskoorn et al., 2004). Measures of verbal learning/memory have also been tested in high-risk groups. On the auditory verbal learning task (AVLT) a high risk group showed impairments on both immediate and delayed recall compared to normative scores (Simon et al., 2007). This is supported in other high-risk samples where performance was significantly impaired on measures including the CVLT and logical memory of the Weschler Memory Scale – Revised (WMS-R: Weschler, 1987) compared to controls (Lencz et al., 2006) and normative data (Niendam et al., 2006). However, in a comparison between high risk individuals who did or did not go through transition and controls, only those who developed psychosis had impaired verbal memory index on the WMS-R (Brewer et al., 2005).
1.4.4.3 Verbal learning/memory deficits in schizotypy

The extent to which performance is altered in schizotypal samples appears to be limited as Table 4 indicates. No performance differences have been found when samples have been categorised based on overall schizotypal levels, for instance two studies categorised their sample into high and low groups based on SPQ-B and found no differences in CVLT performance (Aguirre et al., 2008; Jahshan and Sergi, 2007). Another study examined the effects of different score clusters of the SPQ-B on a neurocognitive factor measuring verbal memory and found no association (Ruíz et al., 2008). Via the AVLT there was no correlation between performance and the negative or positive factors of the CAPE (Simons et al., 2007). Similarly in a large university sample no correlation was found between the Chapman scales and WMS-R, although when controlling for depression and drug/alcohol use, there was an increase in immediate recall in those with high PAS scores (LaPorte et al., 1994). Finally, no performance differences were found between high PAS scores and controls on a verbal recall task (Lenzenweger and Gold, 2000)

The available evidence in schizotypal samples does appear in contrast to data obtained from clinical samples. Verbal memory and learning deficits are some of the most robust in clinical samples, relatives of patients and majority of at-risk groups, whereas there is limited impairment in schizotypes. There is a degree of heterogeneity in terms of tasks used and the samples chosen that could account for this in schizotypy. A particular avenue of research is the assessment of negative features on performance. Some previous studies have focused on schizotypal as a unitary concept and tested whether high scores are associated with performance deficits, whereas others have primarily assessed the impact of attenuated positive symptoms. Only two of the reported studies examined the effects of negative features although both reported no association with performance (Simons et al., 2007; Ruíz et al., 2008). Given the paucity of data examining the effects of negative schizotypal features this is a worthwhile avenue of research, especially given the possibility that intact verbal learning/memory could be relatively spared, and hence represent a risk marker for transition.

1.4.5 Summary of cognitive deficits in schizotypy

It is probable that not all schizotypal individuals have deficits in neuropsychological performance. A spectrum of ability is likely to occur in association with schizotypy, skewed toward normal levels of functioning. This is in contrast to schizophrenia samples where
abilities are skewed toward greater impairment. This could account for the widely reported deficits with moderate to large effects sizes in schizophrenia samples, whereas in schizotypes the presence of intact functioning in a larger proportion of individuals will make it harder to detect subtle performance differences. With these smaller effect sizes, confounding variables could have a greater impact on the results. Although certainly a beneficial aspect to using schizotypal samples is the reduction in confounds of illness; other mediating variables could have a greater impact such as sex and developmental stage.

Furthermore, mixed findings in the literature could be attributable to the approach taken, for instance trait or symptom-based. Within studies that have examined specific type of schizotypal feature, there are differences in extent of impairment on cognition. There is a suggestion that positive features are associated with sustained attention deficits, whereas negative features are associated with (spatial) working memory. It is possible, however, that even overarching constructs such as positive schizotypal features are too broad. It has been proposed that separate models could be required to explain symptoms and cognition in schizophrenia, for instance, separate models for delusions and hallucinations (Berenbaum et al., 2008). This could also be applicable to schizotypy, where the association between specific schizotypal features and cognition could be examined.

Generally, schizotypy is considered an intermediary phenotype on the extended continuum of schizophrenia and as such is likely buffered from more serious mental illness. This could include protective factors and/or they could be missing key risk factors. A possible scenario is that schizotypes do not have sufficiently comprised cognitive performance which could reflect the underlying brain structure/function. A later section examines brain structural differences in relation to schizophrenia, with an emphasis on white matter and structural connectivity.
1.5 Laterality

Some neurodevelopment-based theories have proposed abnormal development of cerebral dominance as a key feature in the aetiology of schizophrenia (Crow, 1990; Crow et al., 1989), a theory that implicates the development of language as critical in its evolution (Crow, 1997a; b). Supporting evidence comes from structural asymmetries in schizophrenia, where patient samples have less ‘normal’ left-greater-than-right volume in the planum temporale and Sylvian fissure, but right-greater-than-left volume in the posterior region of superior temporal gyrus (Sommer et al., 2001a). These differences in structural asymmetry have been suggested to account for the associated language problems in these groups (DeLisi, 2001). Similar structural differences are found in SPD patients although such differences are less pronounced than in schizophrenia (Kawasaki et al., 2004). Other than language function, a variety of measures examining lateralised function have been utilised in both schizophrenia and schizotypal samples. The next section briefly discusses some of these findings, with particular emphasis on tasks to be used in the PhD.

1.5.1 Motor dominance

One of the most obvious markers of cerebral dominance is dominance of motor function. Therefore a straightforward method of assessing its relationship with schizophrenia or schizotypy is examining any overrepresentation of left or non-right handers (ambidextrals). Unusual patterns of motor dominance are commonly reported in the literature, with a higher degree of left- and mixed-handedness in schizophrenia patients compared to controls and other psychiatric groups (Dragovic and Hammond, 2005; Sommer et al., 2001a), although this viewpoint has been challenged in a recent large sample (Deep-Soboslay et al., 2010). Similarly, in schizotypal samples non-right handedness has been found to be associated with heightened expression on a variety of schizotypy measures including the SPQ (Chen and Su, 2006; Kim et al., 1992; Porhe et al., 1997), STA (Gregory et al., 2003), Chapman Scales (Chapman and Chapman, 1987; Chen and Su, 2006), and PDI (Annett and Moran, 2006; Preti et al., 2007). However, other research has found it is in fact mixed-handedness that is associated with heightened expression, suggesting a lack of overall dominance (Annett and Moran, 2006; Chen and Su, 2006; Kim et al., 1992; Stefanis et al., 2006). Somers and colleagues (2009) conducted a meta-analysis of 12 studies (including some of those cited above) to confirm the relationship between motor dominance and schizotypy. Participants from the various studies were categorised into either right or non-right sided participants; and
in a secondary analysis into right, mixed or left-sided participants. In the first analysis higher total schizotypy scores were found in non-right handed participants. In the subsequent analysis with a tripartite comparison, mixed handedness was associated with higher scores relative to right and left-sided participants, although only at a trend level. There was no significant difference in schizotypy scores between strong right and strong left-handed groups. The relationship between positive schizotypy and dominance was also examined. An identical pattern was found with increased positive schizotypy in non-right vs. right participants, as well as in mixed-handed vs. right and left handed participants. No differences were found between right and left-handed participants. Although this study suggests schizotypy is associated with a lack of motor dominance, the authors stressed these effect size were small (Somers et al., 2009).

1.5.2 Language

In addition to a reduction in motor dominance, theories of atypical lateralisation have also been applied to the presence of language asymmetry (Crow, 1997b). Language problems in schizophrenia patients are well documented (see Li et al., 2009). Evidence from fMRI studies have indicated a reduction in language lateralisation in both male and female patients (Sommer et al., 2001b; Sommer et al., 2003), as well as those who are genetically high-risk (Li et al., 2007a; Li et al., 2007b). In patient groups reduced lateralisation is thought to be due to an increase in right hemisphere function, whereas genetic high-risk groups have a reduction in activation in the left frontal regions (Li et al., 2007a). Patterns of reduced laterality may not, however, be specific to schizophrenia; both affective psychoses and psychotic mania patients also exhibit reduced lateralisation when completing language tasks (Sommer et al., 2007), suggesting that reduced laterality could be a marker for particular types of symptoms that are present in a number of serious mental illnesses. Language function has also been investigated in schizotypal/psychosis prone groups. For example, low scores on right hemispheric language tasks (e.g. humour subtest, proverb interpretation and logical grammatical tasks) that are indicative of impaired right-hemisphere language function were found in conjunction with high scores on positive schizotypy scales (Nunn and Peters, 2001). In a review of the literature on language function, Kiang (2010) suggests there is in fact an increase in right hemispheric function which is a deviation from normal strongly left lateralised function, although the author remarked on the heterogeneity of findings in the studies.
1.5.3 Dichotic listening and divided visual tasks

In direct tests of lateralised function, dichotic listening and divided visual field tasks have been implemented. In schizophrenia samples there is sometimes a lack of right ear advantage\(^1\) (Loberg \textit{et al.}, 1999), which has been found to be associated with hallucinatory behaviour (Green \textit{et al.}, 1994). This was not confirmed in a meta-analysis of dichotic listening task performance, where no significant decrease in lateralised function was found in patients compared to controls (Sommer \textit{et al.}, 2001a). The meta-analysis did highlight considerable heterogeneity across studies, compounded by small effect sizes. The authors suggested these may have accounted for the lack of significant difference in extent of lateralised function in their meta-analysis.

Generally in schizotypes there appears to be a reduction in asymmetric performance on dichotic listening tasks, particularly in male samples (Lencz \textit{et al.}, 1995). However, the pattern of asymmetries is not always as expected. In schizotypy samples the picture appears even more complex than the schizophrenia literature. In one study a high schizotypy group had an increased right ear advantage on the dichotic listening task (Raine and Manders, 1988), indicating improvement in left hemisphere function. However, another study found that a high scoring male sample on the Schizotypal Personality Scale (STA) had improved left ear performance, whereas high STA females had a decreased right ear performance (Rawlings and Borge, 1987). Considered together these two studies appear to present contradictory evidence. Raine and Mander (1988) demonstrated that contrary to the clinical literature, there was evidence of a greater left hemisphere function, possibly indicating greater lateralised function. Rawlings and Borge (1987) did find the anticipated effect of reduced functional specialisation of the left hemisphere but in females only, whereas their male high schizotype sample could be representative of an increase in right hemisphere function. There is evidence of sex differences in normal lateralised function, where females have less lateralised function (McGlone, 1980), which could partly explain sex differences in the latter study. In effect, a reduction in cerebral dominance would be most noticeable in those with a baseline of increased asymmetric function. Further demonstration of a sex difference has been found on the chimeric faces task (Mason and Claridge, 1999). For this task individuals are presented

\(^{1}\) The dichotic listening task usually shows a right ear advantage. This is due to the sound presented to the right ear but being processed in the contralateral hemisphere, the left hemisphere which is dominant for language. Sound to the left ear has the additional step of being transmitted first to the right hemisphere, then back to the left causing a slight delay.
with faces showing a happy expression on one side of the face and a sad expression on the other side. The brief presentation of the face usually elicits a bias to the expression on the left sided face due to the right hemispheric dominance in processing left hemispace (see section 5.4). In examining high scoring positive schizotypes there was no bias in the male sample indicating reduced right hemispheric attentional processing (Mason and Claridge, 1999). However, this is not to say that females are not affected by a reduction in dominance; in a series of experiments of equal sex ratio assessing measures of lateralised function, high scorers on measures of positive schizotypy of both sexes did not show the typical normal asymmetry in performance on line-drawing and semantic go/no-go (Asai et al., 2009).

In summarising the early findings, one of three propositions were suggested in relation to left hemispheric involvement in lateralised task performance in relation to schizotypy: underactivation, overactivation, or dysfunctional interhemispheric transfer (Lencz et al., 1995). In instances where high schizotypes have increased lateralised function as demonstrated in the study by Raine and Manders (1988), it is suggested that schizotypal samples could represent an optimal performance in an inverted U shape across the continuum (Raine and Manders, 1988). Due to the extent of mixed findings, such conclusions should be treated cautiously.

1.5.4 Spatial attention
Spatial attentional ability is thought to be predominantly a function of the right hemisphere (Weintraub and Mesulam, 1987). For this reason tasks that measure spatial attention are ideally placed for assessing the degree of cerebral dominance.

1.5.4.1 Line bisection
The line bisection task is a well validated measure of assessing hemispheric allocation of visuospatial attention (see Jewel and McCourt, 2000). The most common versions require the participant to manually bisect a series of horizontal lines. The use of these types of task has been well documented in the assessment of hemispatial neglect patients, where the classic deficit is the neglect of the left hemifield and subsequent bisection to the right of veridical centre due to a right hemisphere lesion. In healthy populations there is also a degree of performance bias in bisecting lines to the left of centre, a phenomenon known as ‘pseudoneglect’ (Bowers and Heilman, 1980). A meta-analysis has demonstrated this to be a
small but significant effect although influenced by many extraneous factors including sex, age, handedness, line length and position, and cueing (Jewell and McCourt, 2000). It is suggested that the presence of pseudoneglect is due to asymmetries in the neural substrates that underpin visuospatial attention (McCourt and Jewell, 1999). Each hemisphere has attentional capabilities, with the right hemisphere mapping left hemispace and vice versa. Due to the functional dominance of the right hemisphere, however, the salience of the left hemispace is increased resulting in the bias towards the left on horizontal lines. This bias has been simulated in mathematical models which account for the phenomena seen in neglect patients (Anderson, 1996). Confirmation is also provided from fMRI data, which demonstrates increased activation in the right hemisphere fronto-parietal attentional network (Cicek et al., 2009). This degree of asymmetry in spatial attention and the relative ease in testing has made line bisection studies a straightforward measure of asymmetry in schizophrenia samples. If, as the theories suggest, schizophrenia is associated with a failure of cerebral dominance then functional asymmetries should be less prominent and otherwise normal phenomena such as pseudoneglect should no longer be present. This has been tested in clinical samples although the findings are mixed. Whilst some studies have indeed found a lack of pseudoneglect on a variety of bisection/trisection tasks in schizophrenia patients (Zivotofsky et al., 2007), contradictory evidence is found in studies where patients have a further leftward bias than controls (hyperpseudoneglect) (Michel et al., 2007), or a general greater variance in performance (Barnett, 2006).

Line bisection tasks have also been used in schizotypal samples and similar to the schizophrenia literature there is no consensus. In schizophrenia samples there is sometimes a lack of pseudoneglect which is interpreted as a failure of right hemisphere dominance (Zivotofsky et al., 2007), whereas in schizotypy (particular positive schizotypy) there is in fact an increased leftward bias (Mohr et al., 2003). This effect is, however, sometimes only demonstrated in male participants (Brugger and Graves, 1997), or not observed at all (Liouta et al., 2008). Conflicting results have also come from other measures of spatial attention such as Rey-Osterrieth Complex Figure Test (CFT) where positive symptoms only have been found to be associated with a leftward bias (Taylor et al., 2002), whilst negative symptoms were unrelated with performance differences (Gooding and Braun, 2004). Positive symptoms again have been associated with a greater leftward bias on a number line bisection task (Brugger et al., 2010) and the chimeric faces task (Luh and Gooding, 1999).
It has been proposed that these changes in spatial attentional function could be due to an increase or decrease in hemispheric dopaminergic function (Brugger and Graves, 1997; Mohr et al., 2003). Bracha (1989) originally described a subset of schizophrenia patients with right-sided neuroleptic induced parkinsonism, left-sided tardive dyskinesia, a tendency to turn to the left, and neglect of right hemispatial field. These features were proposed to be a consequence of hyperdopaminergia in the right hemisphere and hypodopaminergia in the left hemisphere. The increase in right hemisphere activation supports the theories of Gruzelier and colleagues who suggested that schizotypal personality and schizophrenia are associated with an imbalance of hemispheric function (Gruzelier, 1991; Gruzelier et al., 1995).

1.5.4.2 Landmark task

The landmark task also measures visuospatial attention. The task is a forced choice paradigm in which the participant decides whether a horizontal line is bisected either to the left, right or centrally. Computerised or tachistoscopic presentation of the lines are believed to reduce involvement of eye scanning (McCourt and Olafson, 1997), a confound highlighted in the meta-analysis of traditional line bisection tasks (Jewell and McCourt, 2000). Landmark tasks have been shown to activate similar brain regions to traditional line bisection tasks during fMRI experiments; including bilateral parietal regions (predominantly right hemisphere), left cerebellum hemisphere, bilateral visual processing areas, anterior cingulate and prefrontal cortex (Fink et al., 2001). McCourt et al (2008) examined the extent of pseudoneglect via this paradigm in a sample of schizophrenia patients and controls. Healthy controls were found to have a similar performance bias to line bisection tasks, with an erring to the left side in their choice. The schizophrenia patients, however, on average did not deviate from the central position in their choice. Interestingly, as the task was repeated with both right and left hand, the normal pattern of correlation between performance errors with both hands was not present in the patient sample. As such, the authors concluded that not only was the schizophrenia sample associated with inefficient right hemispheric function, but the communication between hemispheres may have been deficient suggesting interhemispheric dysfunction (McCourt et al., 2008). To date, no study has examined forced choice tasks in spatial attention in schizotypal samples. From the schizophrenia literature, the hypothesised reduction in lateralis function is demonstrated where patients do not exhibit the leftward bias. However, given the findings on other attentional tasks in relation to schizotypy, it is unclear whether
schizotypes will have either no leftward bias or an exaggerated bias.

1.5.5 Interhemispheric transfer
As noted in earlier studies, observed changes in hemispheric function could be, in addition to hyper-/hypofunctional changes, a result of changes in connectivity between homologous areas (Lencz et al., 1995). Abnormalities in interhemispheric connections have been proposed in the aetiology of schizophrenia (Crow, 1998), a theory that incorporates an explanation of the paradox of sex differences in age of onset and brain development (Crow et al., 2007). It is proposed that misconnectivity between functional regions of both hemispheres, particularly those late evolving such as prefrontal regions, and those critical in reciprocal connections of asymmetric language regions (i.e. temporal lobes) are particularly affected (Crow, 1997c). The majority of connections pass though the corpus callosum. There are localised changes in the extent of connectivity in the corpus callosum dependent on functional sulcal asymmetries, which are also influenced by sex and handedness (Luders et al., 2003). It is proposed that one route to lateralised dominance is via an inverse relationship where decreasing interhemispheric connectivity parallels increasing asymmetry. Although asymmetric dominance is commonly noted in cognition, many processes are reliant on efficient transfer of information across hemispheres, a route thought to be dysfunctional in schizophrenia samples (David, 1994). In support of this are neuropsychological and imaging studies that have identified subtle abnormalities in the corpus callosum in patient groups (Arnone et al., 2008; Coger and Serafetinides, 1990; Woodruff et al., 1995).

Tasks such as the crossed finger localisation task (CFLT) (Satomi et al., 1991) can directly assess interhemispheric transfer. Successful task completion is reliant on transfer of tactile stimulus and motor control between hemispheres. The importance of the corpus callosum in successful task completion is confirmed on occasions where participants with partial or full cerebral commissurotomy have significantly impaired performance (Geffen et al., 1985). Improving interhemispheric transfer has also been demonstrated to be related to ongoing development, with improvements in performance occurring across childhood (Galin et al., 1977; O'Leary, 1980), and is thought to be a product of ongoing axonal myelination (Quinn and Geffen, 1986). Performance deficits have been demonstrated in schizophrenia patients compared to controls (Rushe et al., 2007). To date no studies have investigated whether this marker of reduced interhemispheric transfer is present in related samples.
1.5.6 Summary

From the clinical literature there is evidence for and against reduced cerebral dominance associated with schizophrenia/psychosis. Structural changes in dominance found in clinical samples are relatively well replicated, but this does not appear to equate to functional differences compared to control groups. Therefore, the evidence in support of theories implicating abnormalities in dominance as a key mediator in development of schizophrenia is contentious. In schizotypal samples, research has almost exclusively examined functional dominance with tasks assessing motor, language and spatial attentional ability. As theories propose a failure of dominance, it would be expected that reduced ability in tasks that rely heavily on either hemisphere such as language or spatial attention would be evident in schizotypal groups. However, the evidence indicates a rather complex pattern of hemispheric function. Some of the studies reviewed suggest that increased function of the right hemisphere is associated with attenuated positive symptoms as demonstrated on patterns of spatial attentional performance. Other studies have indicated reduced right hemisphere function on language tasks thought to rely on right hemisphere function, along with suggestions that left hemisphere performance is increased, as demonstrated on dichotic listening tasks. Perhaps the most parsimonious explanation is that schizotypy is associated with an imbalance of hemispheric function (Gruzelier et al., 1995), which may be specific to language and spatial attention. Finally, for successful completion of lateralised function there is also reliance on communication between hemispheres. Research in clinical groups does suggest impairments in interconnectivity between hemispheres, but this is yet to be examined in schizotypal samples. By examining performance on measures of lateralised function and interhemispheric transfer, it will be possible to test whether proposed aetiological mechanisms thought to be involved in schizophrenia are present in samples from the extended phenotype.
1.6 Diffusion imaging

As described previously (section 1.2.4.2), abnormal connectivity within the brain has been implicated in the aetiology of schizophrenia/psychosis (Friston 1998; Stephan et al., 2009). With the development of diffusion tensor imaging (DTI) techniques, it is now possible to examine white matter structures in greater detail. The next section describes DTI methods, along with their application to schizophrenia and related samples.

1.6.1 Measurement of diffusion and tractography

DTI enables the directionality of white matter to be determined by measuring the random passive movement of water molecules (Brownian motion). In human tissue, water movement is not uniform. Freely diffusing movement of water molecules is restricted by structures such as axonal fibre bundles and their myelin sheaths (definition of diffusion anisotropy is provided below). By encoding this diffusivity of water movement, a tensor can be fitted which represents an estimation of the orientation of the dominant direction of diffusion within a structure enabling directionality of white matter tracts to be quantified (Parker, 2004). The tensor is calculated from 9 diffusion coefficients (Basser et al., 1994), and via diagonalisation of the tensor, eigenvectors can be extracted in which $\varepsilon_1$ is the principal direction of diffusion in the tissue ($\varepsilon_2$ and $\varepsilon_3$ are the other extracted eigenvectors and provide minor directional information). The diffusion coefficients of each eigenvector are also provided which is a measure of diffusivity in each direction ($\lambda_1, \lambda_2, \lambda_3$). The eigenvalues can be used to calculate the diffusion anisotropy of a voxel. The most commonly used scalar measure in DTI analysis is fractional anisotropy (FA – see definition below) (Pierpaoli and Basser, 1996).

FA values range from 0 – 1, from complete free diffusion (isotropic) to entirely anisotropic; for instance grey matter will have relatively low values, whereas the major white matter tracts such as the corpus callosum will have high values. FA values can be considered a measure of tract coherence (see definition below) although it is likely to be influenced by the integrity of the fibres, axonal diameter and packing density, the extent of myelination, and geometric factors including crossing, splaying and curving fibres (Beaulieu, 2002; Parker, 2004). Where reductions in FA have been observed, it is assumed these are reflecting less coherent connectivity, but could be representing any number of factors including the diameter and/or number of axons, thinner myelin sheaths, more crossing fibres, less signal to noise in the data.
or a combination of these (Kubicki et al., 2005b; Jones et al., 2006). The downstream effects of these connectivity changes are not fully understood and could have many interpretations. A possibility is that a decrease in axonal diameter and number of axons could cause reduced neuronal transmission, whereas less myelination could result in the slowing transmission due to current loss, both of which could have effects on local field potentials at the synaptic level (Konrad and Winterer, 2008). Complementary techniques can give insight into the functional correlates of altered connectivity, such as those correlating changes in regional activation as measured by fMRI, with structural changes connecting these regions via DTI (Camchong et al., 2009; Kim and Kim 2005; Olesen et al., 2003; Vernooij et al., 2007).

Diffusion data can be analysed in a number of ways (see Methodology Chapter). Briefly there are three main techniques: regions of interest (ROI) analyses, whole brain voxel based analysis (VBA), and tractography. All have been applied to the study of white matter structures in schizophrenia samples.

To help in understanding, definitions are given for some terms used in the previous section and throughout the thesis.

**Diffusion anisotropy:** Anisotropy is a term to define a property of any substance which movement is directionally dependent. This is the opposite to something that has the characteristics of isotropy where no constraints on direction exist. In relation to imaging, diffusion anisotropy is the movement of water molecules due to Brownian motion constrained by physical structures such as the axons of nerve cells, myelin sheaths etc. Since these structures restrict the direction of water diffusion, there is anisotropic movement of the molecules.

**Fractional anisotropy:** This is a quantitative measurement of diffusion anisotropy derived from the directionality of diffusion of water molecules. Diffusion tensor imaging uses mathematical tensors that model both the direction and extent of diffusivity of water molecules in each voxel of the brain. The output is the FA value of a voxel which ranges from 0 (isotropic, unconstrained diffusion) to 1 (anisotropic, water molecules constrained to straight line diffusion). Lower FA values can be found in voxels in areas that have reduced linear structures constraining the direction of water diffusion (i.e. grey matter); whereas higher FA
values are found in voxels in regions where linear structures exist (i.e. axons, myelin sheaths). FA values can be used as an indicator of tract coherence.

**Tract coherence:** In white matter tracts where voxels have high FA values, these are deemed as having greater tract coherence since the FA values indicate increased directionality of water diffusion. Greater coherence may be due to larger and/or more numerous axons, healthy myelin sheaths etc. Higher coherence is generally considered a ‘healthier’ representation of white matter tracts since disease processes can alter axonal density, extent of myelination etc, which in turn reduces neuronal transmission and the subsequent knock-on effects on brain function. However, actual FA values can be influenced by other factors such as extent of branching/crossing axons. In such examples, there is no uniform direction of water diffusion in the voxel due to axons in different planes. This lowers the FA value of the voxel even though it may have a higher degree of connectedness.

1.6.2 **Applications of DTI**

A variety of research areas have utilised DTI, including brain development and pathological changes found in neurological and psychiatric disorders. Part of the current study examines white matter structures in a schizotypal sample. This sample is from the age range 16-25 years and as such, the importance of ongoing developmental changes are acknowledged.

1.6.2.1 **Normal development**

White matter development continues from the early prenatal brain through to the 3rd decade, followed by a decline in later life (Paus *et al*., 2001). FA values are significantly higher in adult groups compared to children suggesting that ongoing development occurs during adolescence (Klingberg *et al*., 1999; Schmithorst and Yuan, 2010). This is in contrast to the reductions in grey matter volumes occurring during the same developmental period (Giorgio *et al*., 2010). Development of white matter in childhood/early adolescence is more closely related to pubertal age rather than chronological age (Asato *et al*., 2010). There is also evidence of sex differences in white matter development in the adolescent brain (see Lenroot and Giedd, 2010). Behavioural changes are related to these structural changes, for example, in a sample of children and adolescents (8-18 years), fMRI activation during working a memory task was shown to correlate with increased fronto-parietal FA values (Olesen *et al*., 2003).
The importance of these developmental changes particularly during adolescence could have a bearing on studies investigating younger samples. As such, the current study will ensure that comparison groups are matched for age. Although of interest in its own right, developmental changes in white matter structures could be a confounding variable if comparison groups are not matched closely. Other potential confounding variables such as sex (Choi et al., 2010; Lenroot and Giedd, 2010) and IQ differences (Yu et al., 2008) will also be matched.

1.6.3 DTI in schizophrenia and related samples
DTI is a useful tool in examining the proposed altered connectivity in schizophrenia and as such a large number of studies have utilised these methods. With the rapid increase in DTI studies in schizophrenia samples, it is outside the scope of this PhD to review all the findings, although a number of recent review articles and meta-analyses cover this area extensively (see Ellison-Wright and Bullmore, 2009; Kanaan et al., 2005; Konrad and Winterer, 2008; Kubicki et al., 2007; Kyriakopoulos and Frangou, 2009). Below is a summary of the findings in schizophrenia. As the study is investigating white matter structures in schizotypal samples, a greater emphasis is placed on related samples such as high-risk groups. There is also a section with specific emphasis on the arcuate and uncinate fasciculi as these tracts are being investigated in the current study.

1.6.3.1 Schizophrenia
There is evidence for reduced tract coherence in a variety of white matter regions. Whole brain analyses have demonstrated FA reductions in predominantly frontal and temporal regions (Kubicki et al., 2007), including all fibre types (projection, short and long association, and commissural fibres). Specifically in projection fibres, reduced FA values have been found in the internal capsule in chronic schizophrenia (Kubicki et al., 2005a) and first episode patients (Szeszko et al., 2005). There are lower FA values in the uncinate fasciculus, cingulum bundle and arcuate fasciculus which include some of the major white matter tracts connecting prefrontal and temporal regions (Kubicki et al., 2007). There are also well documented differences in the corpus callosum (Arnone et al., 2008). Asymmetries that are often reported in the brains of normal populations are not always present in schizophrenia samples such as the uncinate fasciculus (Kubicki et al., 2002; Park et al., 2004).
The extent to which age impacts FA levels in schizophrenia patients is ambiguous. Exacerbated decreases in arcuate fasciculus have been found in younger patients compared to age matched controls, although this difference was not found in an older group in one study (Jones et al., 2006). As illness duration was not controlled for, it is possible that the younger aged pathology is related to extent of illness duration rather than age per se. Others have in fact suggested the age by illness interaction is reversed and it is older patients that have the most pronounced FA reductions reflecting a neurodegenerative process (Mori et al., 2007). Both possibilities are plausible where schizophrenia is characterised by a delay in white matter maturation and further progressive changes during later stages of illness. Further studies including longitudinal data are required to determine how white matter develops in schizophrenia and what, if any, are the functional outcomes of these differences.

Studies are also examining the clinical and cognitive correlates of white matter structures. For example, performance on a Stroop task correlates with FA values in the cingulum bundle which connects prefrontal, cingulate, parietal and temporal regions (Kubicki et al., 2009). It is, therefore, suggested that the executive deficits in schizophrenia could, in part, be attributed to altered coherence in this region. But attempts to couple white matter pathology with cognition in schizophrenia is problematic due to confounds including heterogeneity of samples and methodological factors such as differences in acquisition and analyses (Kubicki, 2010). Clinical correlates of FA share a similar set of issues, but despite this, interesting associations have been demonstrated. For instance, positive symptoms have been associated with the degree of tract coherence in certain regions including reduced FA values in the anterior cingulum in early-onset patients (Tang et al., 2010), as well as increased FA in bilateral arcuate fasciculi in chronic patients (Rotarska-Jagiela et al., 2009).

### 1.6.3.2 First-episode patients

There is considerable interest in the progression of white matter changes in schizophrenia and whether they are a cause or epiphenomenon of the disorder. First-episode (FE) patients present a set of conditions in which brain structures can be examined with fewer confounds described previously. FA reductions have been found in FE patients compared to controls (Cheung et al., 2008; Federspiel et al., 2006; Hao et al., 2006; Luck et al. 2010a; Perez-Iglesias et al., 2010a; Peters et al., 2008; 2010; Price et al., 2008 Szyszko et al., 2005).
The relationship between clinical and cognitive correlates has also been examined in FE samples. For instance, in minimally medicated FE patients, correlations were found between impaired performance on measures of executive and motor function and reduced FA values in white matter tracts connecting frontal and temporal cortices, and between cortical and subcortical regions (Perez-Iglesias et al., 2010b). Similarly, symptoms are associated with alterations in tract coherence, such as severity of negative symptoms and decreased FA in bilateral uncinate fasciculus (Szeszko et al., 2008).

1.6.3.3 High risk groups

As discussed earlier, high risk groups can be defined in terms of genetic high risk and/or those help seeking individuals presenting subclinical attenuated psychotic experiences (prodromal stage). In terms of genetic high risk, differences in left FA volumes in frontal and temporal regions have been observed (DeLisi et al., 2006). A VBA study have also identified reduced FA values bilaterally in the cingulate and angular gyri (Hoptman et al., 2008). Interestingly, they also identified increases in FA values in deep left frontal and brainstem regions (bilateral pontine tegmentum). Hoptman and colleagues (2008) speculate this could be reflecting loss of crossing fibres which are known to reduce FA values as there is no principal diffusion direction in which FA is calculated, and/or a result of excessive dopaminergic tone causing hypertrophy of connections. In a comparison of schizophrenia, high risk and control participants, schizophrenia patients were shown to have reduced FA values in the bilateral uncinate fasciculus, left arcuate fasciculus and anterior limb of the internal capsule (ALIC) compared to controls (Munoz Maniega et al., 2008). Siblings of patients had reduced values in the ALIC only compared to controls. The authors proposed the ALIC could be a marker of genetic vulnerability.

In high risk groups identified by attenuated symptoms, FA differences have been found in the superior longitudinal fasciculus as indicated by VBA (Karlsgodt et al., 2009). This FA decrease was also predictive of a reduction in social and role functioning at 15 month follow-up. Peters et al (2008) used tractography techniques to compare FA values in the arcuate, uncinate and corpus callosum between high-risk, FE patients and schizoaffective patients. They found no significant differences between any groups. In a follow-up study comparing participants from the high-risk group who had gone through transition with those who had not and controls, there was again no differences in FA values in similar tracts (Peters et al., 2010).
Caution is required, however, due to relatively small sample size (n=7 transition), but it was suggested that changes to white matter structures may occur post initial psychotic breakdown (Peters et al., 2010).

To date only one study has examined white matter structures in a healthy volunteer group with psychotic-like experiences (Volpe et al., 2008). Higher degree of psychotic experiences were associated with increased FA values in the left arcuate fasciculus, whereas low psychotic experiences group has increased FA in right arcuate fasciculus, corpus callosum and fronto-parietal tracts. This study did suffer with a number of limitations including small sample size (total n=13) and considerable sex bias in comparison groups which limits the interpretability. Research with complimentary samples could lend support to the theories of altered structural connectivity in schizophrenia, as well as having the potential for diagnostic applications in the armoury of early intervention clinics.

### 1.6.3.4 Arcuate and uncinate fasciculi (AF and UF)

The current study will investigate two particular tracts: the arcuate and uncinate fasciculi (AF and UF). Table 5 lists the studies that have examined either or both of these tracts in schizophrenia and related samples. These tracts were chosen as evidence suggests changes in coherence are found in clinical samples (see Table 5). There is also theoretical importance in these tracts. The AF connects temporoparietal regions with inferior frontal regions and is a key tract between the language areas: Broca and Wernicke areas. Its proposed role in the language network is thought to account for the observed asymmetry in greater fibre density and increased FA values in the left hemisphere (Nucifora et al., 2005; Powell et al., 2006). Due to its proposed involvement in language, it would be a key candidate region for dysfunction given the prominence of communication disturbances in schizophrenia (Docherty et al., 1996).

The UF is a fronto-temporal tract connecting prefrontal and orbitofrontal cortices with rostral superior, inferior and medial temporal regions, including the entorhinal, perirhinal, and parahippocampal gyri (Spoletini et al., 2009). It is thought to be involved in reward-processing, decision making and episodic memory (Asato et al., 2010; Kubicki et al., 2005). Asymmetry has also been reported in this tract in the general population with right greater-than left FA values (Rodrigo et al., 2007), although this has been challenged (Hasan et al.,
As both medial temporal and prefrontal function and structure are implicated in schizophrenia, the major connection between these regions is of critical importance.

In summarising the findings from Table 5, there is generally a decrease in FA values in the left AF in chronic schizophrenia (Burns et al., 2003; Kubicki et al., 2005; Munoz Maniegar et al., 2008; Phillips et al., 2009), although some studies have indicated that patients with hallucinations have increased FA values in the left AF (Hubl et al., 2004) or bilateral AF (Rotarska-Jagiela et al., 2009). A number of studies using whole brain VBA have however failed to find any difference in the AF in chronic (Shergill et al., 2007; Skelly et al., 2008) or first episode patients (Perez-Iglesias et al., 2010a). Similarly via tractography methods, some studies have failed to find a difference in younger or older patients (Voineskos et al., 2010), FE patients, or individuals at high-risk (Peters et al., 2008; Peters et al., 2010). Finally, reduced FA values were observed in the right AF in healthy volunteers with psychotic experiences, but they also had increased FA in the left AF (Volpe et al., 2008).

There are FA reductions in bilateral UF in chronic (Burns et al., 2003; Hubl et al., 2004; Kawashima et al., 2009; McIntosh et al., 2008; Mori et al., 2007; Munoz Maniega et al., 2008; Sussmann et al., 2009) and FE patients (Szeszko et al., 2008), as well as SPD patients (Nakamura et al., 2005). Others have found reductions specifically in the left hemisphere in younger patients only (Voineskos et al., 2010), with a suggestion that there is accelerated decline in FA values in patient groups (Rosenberger et al., 2008). The normal pattern of asymmetry is also less evident in schizophrenia samples although there are conflicting results possibly related to specific region of the UF (Kubicki et al., 2002; Park et al., 2004). Some studies have failed to find differences in the UF via VBA/ROI (Perez-Iglesias et al., 2010; Rotarska-Jagiela et al., 2009; Shergill et al., 2007; Skelly et al., 2008), or tractography methods in chronic (Jones et al., 2006; Mandl et al., 2010; Phillips et al., 2009), FE (Price et al., 2008) or high risk groups (Peters et al., 2008; Peters et al., 2010). Even though a reduction in FA values was not found in FE patients per se, lower values were found in the core regions of the tract, which the authors interpreted as altered connectivity (Price et al., 2008). Interestingly some studies including bipolar/affective psychoses groups have identified a similar FA reduction (McIntosh et al., 2008; Sussmann et al., 2009), or intermediary levels between schizophrenia patients and controls (Kawashima et al., 2009). This suggests that
white matter structural changes may be a more appropriate marker of psychosis generally rather than schizophrenia.

In summary, there is evidence for altered connectivity in the AF and UF in a variety of samples. There is perhaps a greater degree of reduction in FA values in the UF. There could, however, also be increases in connectivity in the AF which could play a role in symptom formation. There is considerable heterogeneity in findings in both the AF and UF which is symptomatic of DTI in general. It is suggested that DTI studies do not provide a clear consensus on white matter changes due to inconsistent results (Kubicki et al., 2005b). These are related to methodology differences in acquiring and processing the data, as well as samples chosen. Differences in image sequence used to acquire the data leads to variable data quality which could influence results. Similarly there are various analytocal methods, all with some limitations, although there is growing consensus for the application of tractography given its ability to overcome some of these issues (see Methodology Chapter). Other sources of heterogeneity are the confounding variables associated with illness such as duration of illness, age, medication effects, sex and individual differences; all of which could influence results in unknown ways (Konrad and Winterer, 2008). It is possible however, to try and minimise at least the confounds of illness by utilising analogue samples.
Table 5: DTI studies that have directly examined the arcuate and uncinate fasciculi in different sample types. The table lists sample, magnetic field strength of scanner and number of diffusion direction, analysis method, findings and additional comments.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample (mean age)</th>
<th>Scan</th>
<th>Analysis method</th>
<th>Findings</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>(Burns et al., 2003)</td>
<td>30 Sz (36.4); 30 HC (35.7)</td>
<td>1.5T, 6 directions</td>
<td>VBA</td>
<td>Trend reduction in FA in UF, sig reduction in left AF. No volumetric differences between groups.</td>
<td></td>
</tr>
<tr>
<td>(Park et al., 2004)</td>
<td>23 Sz (43); 32 HC (44)</td>
<td>1.5T, 6 directions</td>
<td>VBA, Investigated asymmetry in tracts</td>
<td>In HC left-greater-than right FA in CC, CB, optic radiation, right greater-than-left in ALIC, UF, SLF. In Sz similar asymmetry patterns in CB and CC.</td>
<td>Normal asymmetry was less pronounced or not present in Sz group including the UF.</td>
</tr>
<tr>
<td>(Kubicki, Park et al., 2005a)</td>
<td>21 Sz; 26 HC (ages unknown although between 18-55)</td>
<td>1.5T, 6 directions</td>
<td>VBA, Investigated changes with DTI and Magnetisation Transfer (MTR)</td>
<td>FA reduced in Sz in fornix and CC; bilateral CB, SOFF and internal capsule; right IOFF, and left AF.</td>
<td>MTR showed similar regional decreases in Sz indicating FA reductions could be caused by myelin/axonal disruption</td>
</tr>
<tr>
<td>(Shergill et al., 2007)</td>
<td>33 Sz (32); 40 HC (34)</td>
<td>1.5T; 65 directions</td>
<td>VBA</td>
<td>Sz had decreased FA in bilateral SLF and genu of CC.</td>
<td>In Sz hallucinations associated with increase in FA in superior SLF and anterior cingulum.</td>
</tr>
<tr>
<td>(Mori et al., 2007)</td>
<td>42 Sz (40.0); 42 HC (39.2)</td>
<td>1.5T, 6 directions</td>
<td>VBA and ROI</td>
<td>Sz had reduced FA in bilateral frontal and temporal lobes, UF, CB and genu and splenium of CC.</td>
<td>In Sz negative correlation between widespread FA and age, and between FA and duration of illness.</td>
</tr>
<tr>
<td>(Skelley et al., 2008)</td>
<td>25 Sz (34.2); 25 HC (34.7)</td>
<td>3T, 12 directions</td>
<td>VBA</td>
<td>Lower FA values in Sz in midbrain white matter, internal capsule, CB, left ILF, thalamic radiation, forceps minor, and right IOFF</td>
<td>Negative correlations between PANSS positive and left UF and SLF. Positive correlation between PANSS negative and right insula.</td>
</tr>
<tr>
<td>(Rotarska-Jagiela et al., 2009)</td>
<td>24 Sz with paranoid type with hal (aged 39.0); 24 HC (39.2)</td>
<td>3T, 6 directions</td>
<td>VBA</td>
<td>Sz decrease FA in prefrontal, external capsule, pyramidal tract, IOFF, ILF, SLF and CC. Sz increase FA in AF. Values correlated with severity of auditory hal and length of illness.</td>
<td>Discuss the possibility of hyperconnectivity in certain regions in Sz.</td>
</tr>
<tr>
<td>(Szeszko, Robinson et al., 2008)</td>
<td>33 FE Sz (25.1); 30 HC (25.9)</td>
<td>1.5T, 25 directions</td>
<td>VBA</td>
<td>Sz had reduced FA in temporal lobes corresponding to bilateral UF, left IOFF, and left SLF.</td>
<td>In Sz lower FA in UF correlated with severity of negative symptoms and worse verbal learning/memory.</td>
</tr>
<tr>
<td>Authors</td>
<td>Sample (mean age)</td>
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<td>Analysis method</td>
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<tr>
<td>(Perez-Iglesias et al., 2010a)</td>
<td>62 FE Sz (30.8); 54 HC (29.9)</td>
<td>1.5T, 25 directions</td>
<td>VBA</td>
<td>FA lower in bilateral SLF, ILF, forceps major, anterior and superior thalamic radiation and CC.</td>
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<tr>
<td>(Hubl et al., 2004)</td>
<td>13 HC 13 Sz with hal, 13 Sz without hal. Age and sex matched</td>
<td>1.5T, 6 directions</td>
<td>VBA and ROI of AF</td>
<td>Sz with hal higher FA values in left AF compared to Sz without hal and HC. Sz in total had lower FA than HC in many regions (SLF, UF, ILF).</td>
<td>Study demonstrated that Sz with hallucinations associated with greater FA values in left AF</td>
</tr>
<tr>
<td>(Munoz Maniega et al., 2008)</td>
<td>31 Sz (37); 22 genetic HR (30); 51 HC (35)</td>
<td>1.5T, 51 directions</td>
<td>VBA and ROI of AF, UF, cingulum and ALIC</td>
<td>VBA demonstrated reduced FA in Sz in bilateral UF and ALIC, and left AF compared to HC. ROI analysis demonstrated genetic HR also reduced FA in ALIC compared to HC.</td>
<td></td>
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<tr>
<td>(Sussmann et al., 2009)</td>
<td>42 BD (39.6); 28 Sz (38.0); 38 HC (37.2)</td>
<td>1.5T, 51 directions</td>
<td>VBA and ROI of ALIC and UF</td>
<td>Both BP and Sz had reduced FA values in ALIC, anterior thalamic radiation and UF compared to HC. In Sz there was positive association between FA in UF and Hamilton depression scale, but not PANSS.</td>
<td>Similar sample to McIntosh et al (2008) but with different methodology. Study suggesting similar structural changes in Sz and BP</td>
</tr>
<tr>
<td>(Volpe et al., 2008)</td>
<td>13 HC (29.7). Split into low and high psychotic subjects based on MMPI-2</td>
<td>1.5T,6 directions</td>
<td>VBA</td>
<td>High psychotic group had higher FA values in left AF. Low psychotic group had higher FA values in CC, right AF and fronto-parietal fibres</td>
<td>Sample was not sex matched – only 1 male in low group and 2 females in high group. Could be confounding variable</td>
</tr>
<tr>
<td>(Kubicki et al., 2002)</td>
<td>15 Sz (43); 18 HC (43)</td>
<td>1.5T, 6 directions</td>
<td>Single slice ROI</td>
<td>No difference between groups, although group by hemisphere interaction: controls had left-greater-than right FA values in UF but not in Sz.</td>
<td>In Sz only, lower right UF FA correlated with executive function; lower left UF with lower immediate recall.</td>
</tr>
<tr>
<td>(Nestor et al., 2004)</td>
<td>14 Sz (40.7); 14 HC (41.9)</td>
<td>1.5T, 6 directions</td>
<td>ROI single slice of UF and CB. Correlated FA values with neuropsych performance</td>
<td>Sz decreased performance on measures of episodic-declarative memory associated with reduced FA in left UF, whereas executive performance associated with left CB.</td>
<td>ROI single slice does not cover entire tracts. Study demonstrates that reduced FA values could explain reduced cognitive performance.</td>
</tr>
<tr>
<td>(Nakamura et al., 2005)</td>
<td>15 male SPD (37.7); 15 HC (32.7)</td>
<td>1.5T, 6 directions</td>
<td>ROI of UF and CB</td>
<td>SPD had reduced FA in UF only. Right UF values correlated with positive symptoms (ideas of references, suspiciousness, restricted effect and social anxiety)</td>
<td>SPD left UF FA values correlated with cognitive performance (intelligence, verbal and visual memory and executive performance)</td>
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<td>Authors</td>
<td>Sample (mean age)</td>
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<tr>
<td>(Kawashima et al., 2009)</td>
<td>15 Sz (24.5); 15 affective psychosis (24.9); 15 HC (23.1)</td>
<td>1.5T, 6 directions</td>
<td>ROI of UF and CB regions. FA and Dm values investigated</td>
<td>Reduced FA in bilateral UF in Sz patients. Affective psychosis group intermediate but not sig different from Sz or HC.</td>
<td>ROI analysis so regions may contain fibres from neighbouring tracts. Exploratory correlations showed no association between UF and PANSS in either patient group.</td>
</tr>
<tr>
<td>(Jones et al., 2006)</td>
<td>14 Sz (median 34); 14 controls (median 44)</td>
<td>1.5T, 64 directions</td>
<td>Tractography of SLF, CB, UF and IOFF.</td>
<td>No significant difference between groups found, but age associated decrease in IOFF in HC not seen in Sz group.</td>
<td>Younger Sz had reduced SLF FA compared to age matched HC, which was no longer present in older group.</td>
</tr>
<tr>
<td>(Rosenberger et al., 2008)</td>
<td>27 Sz (39.1); 32 HC (42.4)</td>
<td>1.5T, 6 directions</td>
<td>ROI/Tractography of IOFF, UF and CB</td>
<td>Age related decline in FA of CD and UF in Sz. Cross-sectional design so caution in predicting age associated decline in FA. Study suggests greater decline in white matter in patients.</td>
<td></td>
</tr>
<tr>
<td>(Phillips et al., 2009)</td>
<td>23 Sz (34.7); 22 HC (30.90)</td>
<td>1.5T, 30 directions</td>
<td>Tractography: bilateral AF, ILF, UF</td>
<td>Sz had lower FA values in left AF and bilateral ILF. Volume reduction in left AF as well. Negative association between positive symptoms and right ILF FA</td>
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<tr>
<td>(McIntosh et al., 2008)</td>
<td>25 Sz (37.2); 40 BP (39.9); 49 HC (35.3)</td>
<td>1.5T, 51 directions</td>
<td>Tractography of UF and anterior thalamic radiation</td>
<td>Both patient groups reduced FA in UF and anterior thalamic radiation. FA values not related to age, illness duration, medication or psychopathology</td>
<td>Similar sample to Sussman et al. (2009) but with different methodology. Study suggesting similar structural changes in Sz and BP</td>
</tr>
<tr>
<td>(Mandl et al., 2010)</td>
<td>40 Sz (26.8); 40 HC (28.0)</td>
<td>1.5T, 32 directions</td>
<td>Tractography of genu of CC and bilateral UF</td>
<td>No difference in FA values between Sz and HC. FA values did not correlate with clinical measures</td>
<td>Higher mean MTR found in right UF of Sz. Mean MTR correlated with negative symptoms in left UF.</td>
</tr>
<tr>
<td>(Vosneskos et al., 2010)</td>
<td>25 young (&lt; 55yo) Sz; 25 younger HC; 25 older (&gt;55yo) Sz; 25 older HC</td>
<td>1.5T, 23 directions</td>
<td>Tractography: bilateral UF, IFOF, AF, ILF, CB and genu and splenium of CC</td>
<td>Younger Sz had sig lower FA than younger HC in left UF and right CB. Older groups did not differ between each other.</td>
<td>No correlation between PANSS scores or MMSE and FA in either Sz group.</td>
</tr>
<tr>
<td>(Price et al., 2008)</td>
<td>19 FE Sz (23.8); 23 controls (29.6)</td>
<td>1.5T, 54 directions</td>
<td>Tractography (PICO) of UF</td>
<td>No significant difference in UF FA values between groups.</td>
<td>In examining squared coefficient of variation, Sz patients did have reduced FA in core regions of the tract indicating altered connectivity.</td>
</tr>
<tr>
<td>Authors</td>
<td>Sample (mean age)</td>
<td>Scan</td>
<td>Analysis method</td>
<td>Findings</td>
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<tr>
<td>Peters et al., 2008</td>
<td>10 male FE Sz (age 21.2); 10 male UHR (age 21.6); 10 male HC (age 21.1)</td>
<td>3T, 16 directions</td>
<td>Tractography: bilateral CB, UF, AF and genu and splenium of CC</td>
<td>No differences in tract FA values between any groups.</td>
<td>Small sample size. Sample also used in Peters et al (2010).</td>
</tr>
<tr>
<td>Peters et al., 2010</td>
<td>10 male UHR (21.2); 7 UHR who had gone through transition (22.6); 10 male HC (21.1)</td>
<td>3T, 16 directions</td>
<td>Tractography: bilateral CB, UF, AF and CC</td>
<td>In sample of UHR, 7 had gone through transition at 24 months. Compared on pre-psychosis data. No differences in FA values between any groups.</td>
<td>Authors suggest that white matter changes could occur at onset of psychosis or sometime after. Small sample size.</td>
</tr>
</tbody>
</table>

1.5T/3T – Tesla – strength of magnetic field; AF – arcuate fasciculus; ALIC – anterior limb of internal capsule; BP – bipolar disorder patients; CB – cingulum bundle; CC – corpus callosum; Dm – mean diffusivity; FA – fractional anisotropy; FE – first episode; hal – hallucinations; HC – healthy controls; OFF – inferior occipitofrontal fasciculus; ILF – inferior longitudinal fasciculus; MPI – Minnesota Multiphasic Personality Inventory; MMSE - Mini Mental Status Exam; MTR – magnetisation transfer; PANSS - Positive and Negative Syndrome Scale; PICo - probabilistic index of connectivity; ROI – region of interest analysis; SLF – superior longitudinal fasciculus; SPD – schizotypal personality disorder; SOFF – superior occipitofrontal fasciculus; Sz – schizophrenia patients; UF – uncinate fasciculus; UHR – ultra high risk; VBA – voxel based analysis;
1.7 **Rationale**

As demonstrated in the literature review, schizotypal features and psychotic-like experiences are relatively common in the general population. The prevalence and incidence rates of attenuated symptoms are many times higher than the full clinical syndromes. Individuals who score highly on measures such as schizotypal questionnaires represent a group who can be placed on an extended continuum and therefore represent a suitable analogue sample. Non-clinical participants with schizotypal features are relatively easy to access and are free from the confounds associated with serious mental illness. If schizotypy is genuinely on the same trait continuum as schizophrenia, it can be therefore hypothesised that a schizotypal sample will have similar characteristics to patients with schizophrenia, namely associations between extent of symptoms/features and demographics, and the presence of cognitive impairments and white matter dysconnectivity. However, these are expected to be more attenuated than those found in clinical samples. In these studies, I am particularly interested in examining the effects of schizotypy in the age range 16-25 years, a transitional period associated with an increase risk of developing serious mental illness. By identifying deviance from normal development, it could help in understanding factors associated with transition.

1.7.1 **Overview of the PhD, hypotheses and aims**

Fig. 2 is a flow chart outlining the PhD. The PhD comprises three phases which correspond to data collection. On the flow diagram, each phase of the PhD is comprised of separate studies that are referred to as *Papers*. This next section outlines each phase and the subsequent papers, along with the aims and hypotheses. Further details can be found in the separate papers (*Papers 1-5*), and the main Methodology Chapter.

**Phase 1**

This is the main recruitment phase of the studies. An internet based method of data collection enables the collection of a large sample of questionnaire and cognitive measures in a relatively short period of time. The purpose of this is threefold: firstly, large sample sizes allow the investigation into the effect of demographics on schizotypal levels, and examination of the SPQ factor structure. Secondly, the collection of a large data sample will allow associations between sustained attention and spatial working memory to be examined. This can be carried out in the total sample, but also in samples categorised by
age and by sex. Finally, from the large sample, it is possible to select individuals to be invited back for further cognitive testing and brain imaging (Phases 2 and 3).

**Paper 1**

The aim of the *first paper* is to confirm the multidimensional nature of the schizotypy construct by examining the latent factor structure of the SPQ in a large sample of adolescent and young adults. Various models have been proposed and the study aims to investigate which is best fitting for the current sample. Secondly, if schizotypy is representative of a continuum, it is expected that attenuated features will abide to the same demographic influences as clinical disorders. Therefore, it is hypothesised that males will report more negative type features, whereas females more attenuated positive features. It is further hypothesised that adolescence is a period heightened expression of schizotypal features. Therefore, it is predicted that adolescents will score higher on the SPQ subscales.

**Paper 2**

If schizotypy is an extended-phenotype of schizophrenia, there will be further similarities with the clinical syndrome. For instance, schizophrenia is associated with considerable cognitive deficit. The literature reviewed also demonstrates that schizotypal samples have some degree of cognitive deficits. These are often more subtle than found in clinical samples which could lead to difficulties in detecting them and could partly explain the degree of heterogeneity in the literature. Factors such as developmental stage and sex effects could interact with schizotypal levels in their association with cognition. It is the aim of the *second paper* to examine the associations between schizotypy on cognitive performance in a large sample, and whether age or sex interacts in this relationship. It is hypothesised that impaired cognition will be associated with heightened schizotypal features. Furthermore, due to sex differences during the transitional period from adolescence to adulthood, there could be differential associations between schizotypy and cognition in relation to sex and age.

**Phase 2**

This will involve selecting a sample of participants from the Phase 1 to complete a neuropsychological test battery. This will enable a closer investigation of the effects of schizotypy on specific cognitive processes. Two main areas will be examined; traditional cognitive tasks investigating domains such as attention, executive function and verbal
learning/memory; and tasks examining lateralised brain function and interhemispheric transfer.

**Paper 3**
The third paper examines performance on the cognitive test battery assessing predominantly prefrontal and medial temporal lobe function. The hypothesis states that high schizotypy scores will be associated with impairments on measures of attention, executive function and verbal learning/memory. Correlations will be calculated between each subscale of the SPQ to determine whether a particular type of schizotypal feature is associated with performance.

**Paper 4**
The aim of the fourth paper is to explore the association of schizotypy with hemispatial attentional asymmetry as a means of testing the hypothesis that in schizotypy, as in schizophrenia, the brain is characterised by disturbed functional lateralisation. A further aim of this paper is to test the prediction that presence of schizotypal features will be associated with decreased performance on a measures of interhemispheric transfer of information.

**Phase 3**
This will involve acquiring structural brain images from a subgroup of participants. White matter structures will be examined via diffusion tensor imaging (DTI).

**Paper 5**
The fifth paper compares fractional anisotropy (FA) values in the arcuate and uncinate fasciculi between schizotypes and controls. Schizophrenia is hypothesised to be a disorder of dysconnectivity. In line with studies examining white matter in clinical groups, it is predicted that differences in FA values will be observed between schizotypes and controls. Correlations between attenuated symptoms and degree of tract coherence will also be examined to determine whether schizotypal and attenuated hallucinatory/delusional features are associated with degree of tract coherence as an indirect measure of white matter connectivity.

In summary, these linked studies are aiming to provide confirmatory evidence for the placement of schizotypy on the continuum of schizophrenia. With the identification of
behavioural, psychological and biological features, it is possible to build a profile of a schizotype. This can open up avenues of research including the exploration of mechanisms in the aetiology of disorders and processes involved in symptom formation, along with the identification of potential diagnostic markers for use in high risk clinics.
Fig 2: Flow diagram detailing the three main phases of the PhD. Each phase is associated with papers that are found in the remaining thesis.

**Phase 1**
**Recruitment Phase**
Web based survey, hosting:
1. Schizotypal Personality Questionnaire
2. Spatial working memory task
3. Continuous performance task

*Paper 1:*
- Examination of SPQ factor structure.
- Demographic effects on schizotypy levels.

*Paper 2:*
Investigate associations between schizotypy and SWM/CPT performance.

**Phase 2**
**Follow-up testing**
Participants invited back to complete test battery.

*Paper 3:*
Associations between schizotypy and performance on attention, executive function and verbal learning/memory tasks.

*Paper 4:*
Associations between schizotypy lateralised function and inter-hemispheric transfer.

**Phase 3**
**Diffusion tensor imaging**
12 participants selected as a high schizotypy group
12 participants selected as a control group

*Paper 5:*
- Comparing groups on FA values in arcuate and uncinate fasciculi.
- Correlating FA values with schizotypal features.
Chapter 2  Methodology Chapter

There are methodology sections in each of the papers. This chapter focuses on potential issues associated with choices of methodology and provides further details where space constraints do not allow in the individual papers. Areas of discussion are:

1. The SPQ as the main measurement of schizotypy,
2. Internet data collection,
3. The recruited sample,
4. Schizotypal levels of the sample,
5. Phase 1 online cognitive tasks: including rationale, design, performance indices, and outliers.
6. Phase 2 Face-to-face testing: including procedure, task selection, and normality of data.
7. Further details about DTI and tractography techniques, and why these techniques were chosen over alternative methods.

2.1 The SPQ as the main measurement of schizotypy

This section covers the rationale for the choice of SPQ as the main instrument to measure schizotypy. The intention was to select an instrument that could measure schizotypal features as considered as attenuated versions of schizophrenia symptoms. There are a number of questionnaires that measure schizotypal features/symptoms, so it had to be decided which was appropriate for the current set of studies. This section is an extension of the introductory information about the SPQ in the General Introduction (see section 1.3.4.1 Pg. 27).

2.1.1 SPD and schizophrenia

Since the SPQ was based on schizotypal personality disorder (SPD), the links between SPD and schizophrenia need to be highlighted. SPD base rates are higher than schizophrenia, with an estimated prevalence of 2-3% (Cadenhead and Braff, 2002). It is thought to share similar aetiological and pathophysiological mechanisms as schizophrenia, as well as having similar response to treatments (Keshavan et al., 2004; Koenigsberg et al., 2003; Kumar et al., 2008; Siever and Gunderson, 1983) and sharing some cognitive deficits (e.g. Trestman et al., 1995, see Section 1.4, Pg. 38). SPD is considered a trait marker for schizophrenia, and as such is used in criteria to identify individuals who may be in the prodromal phase of schizophrenia (i.e. high risk clinics, Yung et al., 1996). Furthermore, SPD dimensional scores have been used to predict those that would later convert to psychosis (Mason et al., 2004)
There is evidence for a genetic link between schizophrenia and SPD, for instance relatives of schizophrenia patients are more likely than matched to controls to have SPD (Baron et al., 1985; Kendler et al., 1993b), and relatives of SPD patients have an increased chance of developing schizophrenia (Kendler et al., 1993a). The elevated rates of SPD in relatives compared to the general population are evidence that there is a predisposition to schizophrenia which can be manifested as schizotypal features. Partly for these reasons schizotypal personality has at least some of the genes associated with schizophrenia and is considered an endophenotype for schizophrenia (Lenzenweger, 2006). An endophenotype is a measurable trait or state on the pathway to the disease which shares at least some of the biological mechanisms associated with the clinical state (Gottesman and Gould, 2003). Endophenotypes are discrete, genetically determined phenotypes which are part of the complex illness (Braff and Freeman, 2002). If SPD is considered an endophenotype, the use of the SPQ as a measure of stable schizophrenia-like related symptoms can be justified, since it taps into this predisposition to schizophrenia.

2.1.2 Design of the SPQ

Raine (1991) commented that few instruments assessed the multidimensionality of schizotypy (including the PAS, PhyAn, and SocAn which focus on specific symptoms), so the aim was to develop a measure covering all schizotypal trait features as defined by DSM-III-R (American Psychiatric Association, 1984). Unitary instruments were considered useful for identifying single symptom clusters, but the design of the SPQ comprehensively models all 9 components of SPD.

For the design of the questionnaire, items were taken from various sources including existing interview schedules for schizophrenia and SPD including: Present State Examination (PSE: Wing et al., 1974); the Scale for the Assessment of Negative Symptoms (SANS: Andreasen 1989); the Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II; Spitzer et al., 1987); and, the Schedule for Affective Disorders and Schizophrenia (SADS; Endicott and Spitzer 1978). Items were also taken from published questionnaires measuring schizotypal features i.e. STA scale (Claridge and Broks 1984); the Schizotypy scale (Venables et al., 1990); the Perceptual Aberration scale (Chapman et al. 1978); and, the Magical Ideation scale (Eckblad and Chapman 1983). The resulting SPQ had high convergent validity (0.81) with previous schizotypal measures such as the STA (Raine, 1991).
2.1.3 The factor structure of SPQ in relation to schizophrenia

In terms of its relationship to schizophrenia, some evidence in support has come from factor analysis studies in control and patients samples. Section 1.3.4.1.1 (Pg. 27) discusses the factor structure of the SPQ. Briefly, there is support for 3- and 4-factor models in the literature (Raine et al., 1994; Stefanis et al., 2004a; Wuthrich and Bates, 2006). In both the 3- and 4-factor models, there are representative factors of positive, negative and disorganised symptoms. These are comparable to models of schizophrenia symptoms (Arndt et al., 1991; Lenzenweger and Dworkin, 1996; Liddle, 1987) and are taken as evidence of the link between the two (Reynolds et al., 2000). Section 1.3.4.1.1 lists the replicability of these models in various samples. The SPQ has been shown to have the same factor structure in schizophrenia patients (Rossia and Deneluzzo, 2002) and nonpsychotic first-degree relatives of patients (Reynolds et al, 2000). Raine et al (1994) hypothesised that schizophrenia symptoms may be an exacerbation of these schizotypal features seen in the general population, a theory which lends support to the continuum hypothesis of schizophrenia/psychosis.

2.1.4 SPQ in relation to other questionnaires

There are numerous questionnaires assessing schizotypal features, so why chose the SPQ? Measurement choice can be driven by theoretical stand-point, for example different perspectives on whether schizotypal features are qualified as symptom-, syndrome-, or personality-orientated (see section 1.3.4, Table 1, Pg. 27). However, it is suggested that all rationalise schizotypal features as existing on a continuum with schizophrenia-type psychosis (Johns & van Os, 2001; Vollema & van den Bosch, 1995). Most scales have good psychometric properties, particularly the SPQ (Vollema & van den Bosch, 1995). The SPQ also has relatively high convergent validity with psychosis-proneness measures, for instance Wuthrich and Bates (2005) found high correlations between the Chapman scales and SPQ subscales (i.e. positive and negative-like symptoms correlated highly (0.6-0.8) across respective scales). Other studies have examined overlap between schizotypal features as measured by the SPQ and prodromal symptoms, where 67% of schizotypal diagnosed patients met criteria for prodromal symptoms, and 26% prodromal patients met criteria for SPD (Woods et al., 2009).

Another measure that is widely used in schizotypy research is the multidimensional O-LIFE scale (Mason et al., 1995a). The O-LIFE avoids ‘stronger’ clinical wording as it was
believed this would make it more suitable for a non-clinical population (Mason and Claridge, 2006). A recent study compared SPQ and O-LIFE scores in 270 undergraduate students (Asai et al., 2011). The two measures were strongly correlated overall and between respective factors (correlations 0.5-0.8). This again suggests that theoretically different instruments measure a similar construct of schizotypy.

2.1.5 Methodological and empirical reasons for SPQ selection

From a pragmatic standpoint, a choice of measure had to be considered in terms of length of administration. Completing online surveys is known to cause fatigue/drop outs, with research suggesting increased participant retention with fewer items (Cohen et al., 2010). It is probable that longer measures such as the O-LIFE or multiple Chapman scales may suffer even more with incomplete entries and drop outs.

Finally, the breadth of studies that have used the SPQ in research is encouraging and testament to its usefulness. The SPQ has been used in a multitude of studies in fields such as genotypic association studies (e.g. Avramopoulos et al., 2002), family based vulnerability studies (e.g. Calkins et al., 2004; Vollema et al., 2002; Yaralian et al., 2000), examination of effects of schizophrenia related risk factors (e.g. Stefanis et al., 2004b), on the examination of the multifactorial nature of the schizotypal features (Section 1.3.4.1.1), cognitive studies (Section 1.4), assessment of differences in vulnerability to schizophrenia (e.g. Badcock and Dragovic, 2006), language performance (i.e. Kiang 2010), as well as being adopted in ultra-high risk studies (Ziermans et al., 2009).

2.1.6 Summary of rationale for selection of SPQ

In summary, this thesis takes the stance that SPD is linked to schizophrenia, and can be considered an attenuated form on the extended phenotype of the broadly defined schizophrenia syndrome. Scales such as the SPQ assess schizotypal features as described by DSM, and will be helpful in allowing the association between schizotypal and other correlates to be examined in otherwise healthy populations. SPQ covers a wide range of schizotypal features, whilst having good psychometric properties including reliability and convergent validity, making it an ideal candidate.
2.2 Internet data collection

The use of the internet for data collection can have both benefits and costs (see Table 1). For the first stage of the PhD (Phase 1) a large sample was required for two reasons: 1) to produce enough data points to enable data modelling techniques such as CFA which are reliant on large sample sizes; 2) and enable the identification of enough individuals with varying schizotypal levels who would be prepared to undergo further testing. The quickest and most cost effective method is online data collection. It is reported that in 2009 70% (18.3 million households) had access to the internet in the UK (Office for National Statistics, 2009), so the sampling pool participants were drawn from are representative of the general population. As the focus of this PhD is not an epidemiological study, how representative the sample is of the general population is also less important. Even so, research has indicated that data collected from respondents online has a similar socio-demographic profile to that collected offline (Schillewaert and Meulemeester, 2005).

Two cognitive tasks were placed online to enable the collection of a large dataset on performance in relation to schizotypy levels. It took approximately 30-45 minutes to complete the online system. If this was attempted in a laboratory setting with just a single researcher, to sample the proposed 1,000 participants would take upwards of 500-700 hours in testing time alone, a somewhat daunting task! However, with an online system it is of course not possible for the experimenter to be present during testing. This does have associated problems (see below), but one benefit in potentially reducing the confounding effect of lack of motivation. As the participants could easily stop taking part, there is no sense of being forced to stay during the tasks which can sometimes confound laboratory experiments (Reips, 2000).

There are problems associated with the non-presence of experimenter during the completion of online tasks. Firstly, task selection had to be considered in terms of what is possible on an internet website. This was especially important for the spatial working memory task where certain tasks such as the delayed response task could be susceptible to “cheating” (see below, section 2.5.1). Secondly, it is unclear whether the participant would fully understand what a task entails (methods were used to overcome this – see below). Thirdly, the environment in which the tasks are completed is not controlled. It is unclear how the tasks were undertaken or whether there were any distractions. Laboratory studies have very controlled environments to minimise potential confounding effects. A partial
solution was to examine the data and remove extreme statistical outliers similar to laboratory based studies (see below, sections 2.5.1.3 and 2.5.2.3).

**Table 1**: Table listing some of the pros and cons of using web-based data collection.

| Pros                                                                 | Cons                                                              |
|----------------------------------------------------------------------|                                                                  |
| Large sampling pool – increasing statistical power                   | Inability to control environment                                  |
| Automation of data collection – time and cost savings                | Multiple submissions                                              |
| Not constrained to laboratory                                        | Increased drop outs                                               |
| Reduced coercion                                                     | Requirement for technical expertise in creating website          |
| Increased accessibility beyond university samples                    | Sampling pool and % of respondents difficult to assess            |
| Reduction in experimental effects – including reduced motivational confounds |                                                                  |
| Greater anonymity and potential for truthfulness                    |                                                                  |
| Responses can be less socially desirable                            |                                                                  |


There are problems associated with the non-presence of experimenter during the completion of online tasks. Firstly, task selection had to be considered in terms of what is possible on an internet website. This was especially important for the spatial working memory task where certain tasks such as the delayed response task could be susceptible to “cheating” (see below, section 2.5.1). Secondly, it is unclear whether the participant would fully understand what a task entails (methods were used to overcome this – see below). Thirdly, the environment in which the tasks are completed is not controlled. It is unclear how the tasks were undertaken or whether there were any distractions. Laboratory studies have very controlled environments to minimise potential confounding effects. A partial solution was to examine the data and remove statistical outliers similar to laboratory based studies (see below, sections 2.5.1.3 and 2.5.2.3).

Finally high drop-out rates are usually found in online studies, with figures reported as high as 80% (Dandurand et al., 2008). Clearly this can have implications on the study. To assess the extent of drop-outs and whether there was anything intrinsically different between those that completed everything or not, comparisons were made between various groups. The website was designed to store data after each stage, so it was possible to determine the sample size at each point and compare drop-outs with those that completed everything. The only unquantifiable groups were those that received some form of advertisement (email, letter or electronic notice) and did not act upon them, or those that
read the information sheet but decided not to take part. All other stages of completion were quantifiable. Table 2 lists demographics and SPQ scores for the total sample and those that dropped out at various stages. Approximately 151 people dropped out after consenting to take part but prior to submitting SPQ responses (data not shown), with another 286 dropping out during the experiment. In total, 70.3% of respondents completed the online survey.

### Table 2: Demographics and SPQ scores for various drop-out stages and the final sample.

<table>
<thead>
<tr>
<th>Groups (see legend at bottom of table)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>1036</td>
<td>151</td>
<td>59</td>
<td>227</td>
</tr>
<tr>
<td>%</td>
<td>70.3</td>
<td>10.3</td>
<td>4.0</td>
<td>15.4</td>
</tr>
<tr>
<td>Female %</td>
<td>70.9%</td>
<td>No data</td>
<td>65.1%</td>
<td>70%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>19.24 (2.53)</td>
<td>No data</td>
<td>19.07 (2.44)</td>
<td>18.65 (2.35)</td>
</tr>
<tr>
<td>Years in education (years)</td>
<td>14.15 (2.17)</td>
<td>No data</td>
<td>14.20 (2.58)</td>
<td>13.33 (2.50)</td>
</tr>
<tr>
<td>SPQ total</td>
<td>27.83 (12.90)</td>
<td>No data</td>
<td>25.82 (13.49)</td>
<td>27.66 (14.03)</td>
</tr>
</tbody>
</table>

**Group Legend**: 1 = Completed everything, 2 = dropped out after consenting, 3 = Dropped out after SPQ, 4 = dropped out during rest of online experiment

Statistical analysis on the various drop-out groups demonstrates no significant sex differences between any of the groups ($\chi^2(2), N = 1321 = 0.82, p = 0.67$). There was a significant difference in age of participant between groups ($F(2, 1321) = 5.26, p < 0.01$, eta squared ($\eta^2 = 0.000$)) with post-hoc tests (Bonferroni) indicating that those who dropped out during the experiment were younger than those that completed everything (groups 1 vs 4). Similarly, years in education was significantly different ($F(2, 1291) = 12.47, p < 0.01$, $\eta^2 = 0.002$) with post-hoc tests (Bonferroni) showing that those who dropped out during the experiment had less years in education than those that completed everything (groups 1 vs 4). However, there was no significant difference in total SPQ scores between groups ($F(2, 1317) = 0.63, p = 0.53$, $\eta^2_p = 0.001$). In summary, drop outs were expected in the current study, and where differences do occur, such as age and years in education, they are negligible. Importantly, there was no difference in SPQ scores.

In conclusion, online data collection was a viable and practical method for data collection and the benefits outweighed the negatives. It must also be noted that online data collection was primarily used as means of recruiting a large sample in which participants were selected for further controlled testing.
2.3 The recruited sample

Since the study inclusion criteria was age 16-25 years, participants were recruited from educational institutes. Younger participants were recruited from local colleges and schools. The study was promoted to a number of educational institutes in the North-West of England by emails/letters to schools/colleges and arranging appointments to discuss the study with senior staff. Schools/colleges that agreed to participate included Holden Lane High School (comprehensive school, Stoke-on-Trent), Manchester Grammar School, Pendleton College (Salford), Xaverian College (Manchester), St John Rigby College (Wigan), Cheadle and Marple College, and Eccles College.

Due to anonymity/confidentiality guidelines issued by the University Ethics Senate Committee, it was not possible to identify which institute a participant was recruited from. It is known, however, that few students were recruited from schools (Holden Lane High School and Manchester Grammar School) since the schools required parental consent for all participants recruited through them. From approximately 2,000 parental letters/consent forms issued, only 20 were received. From the 20 received parental consent forms, there was also no guarantee that the child would complete the online study. Future studies which intend to sample participants under the age of 16 would benefit from other consent procedures such as parental opt-out, rather than opt-in. For the current study this was not permissible by Ethics guidelines.

Due to these issues surrounding recruitment of school students, it is appropriate to state that almost all 16-18 year olds samples were recruited from colleges (approximately 600 participants for the initial sample – Paper 1). It is also known definitively, that no student from either school took part in later stages of the study (face-to-face testing or brain imaging).

Since this was not an epidemiological study, complete sociodemographic data was not collected. For an indication of the sociodemographics of the areas in which in the schools/colleges are located, Appendix 4 presents data taken from the 2001 Census data is provided for the Ward areas, Local areas, Region, and England as a whole. The data indicates that on measures of employment, health, housing and general education these schools/colleges are in Ward/Local areas that are representative or more deprived than England generally. It can be stated with relative confidence that the 16-18 year old sample were unlikely to be significantly different from the general population. In terms of the
sociodemographic of the older sample, it is less clear how representative this sample is. Since the majority of the 19-25 year olds were a student population, these were likely to be a mobile population in the region. Future epidemiological studies of schizotypy would benefit from a detailed collection of sociodemographic data.

Another pertinent question is the level of educational achievement in the sample and how this could have a bearing on such aspects of the study as cognitive performance. This was demonstrated during the second phase of the study where the sample had an above average IQ. This has implications for all the studies. In defence of this study and its recruitment method, it is difficult to target a young population that are not in formal education.

A large proportion of research in the schizotypy relies on university samples. These convenience samples do have benefits in terms of ease of access and availability, but could have implications on the generalisability of the results to the general population. One drawback is the underreporting of schizotypal features by individuals in later life. The current study investigated the correlates of schizotypy during adolescence and early adulthood, so use of student samples was more representative. Some of the issues with student sampling include the sex ratio, age of participant, education levels and social desirability in answering questionnaires. The extent to which a university sample is representative has recently been examined (Lincoln and Keller, 2008). In a comparison of psychotic experiences in student and community samples, the community sample were found to endorse fewer items on two measures of psychotic like experiences, the LSHS and PDI-40. However, when the samples were matched on age, these differences were no longer present. The authors did note there were a greater number of people not endorsing any items from the general population, whereas students, although showing similar levels in general, were more likely to endorse at least one item. Students were thought to have less concern over social desirability of such experiences/beliefs (Lincoln and Keller, 2008). So, even though university samples are not entirely representative of the whole population, this is predominantly driven by the age of the participants rather than intrinsic factors related to student status.

2.4 Schizotypal levels in the samples

Over the course of the PhD studies, there are various samples derived from the original internet sample. This section compares SPQ levels for each sample in relation to published norms.
Table 3 reports SPQ scores from the current study along with other example studies, and Table 4 compares reported scores between studies. With regard to the main internet sample, this is not significantly different to the two samples originally reported by Raine (1991). There are some significant differences with other samples, but not so large to cause concern. The erring towards the higher end of normal range of this PhD’s sample could be due to the inclusion of an adolescent group, which is partially confirmed in the comparison of the adolescent only sample with that of Fossati et al (2003) school students.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Age (SD)</th>
<th>Sex ratio (f/m)</th>
<th>Total SPQ score (SD)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Papers 1 and 2 (Phase 1)</strong></td>
<td>994</td>
<td>19.25 (2.54)</td>
<td>708/286</td>
<td>27.75 (12.77)</td>
<td>Complete online dataset</td>
</tr>
<tr>
<td><strong>Papers 1 and 2 adolescent sample (16-19 years) (Phase 1)</strong></td>
<td>588</td>
<td>17.45 (1.05)</td>
<td>415/173</td>
<td>28.90 (12.69)</td>
<td></td>
</tr>
<tr>
<td><strong>Papers 1 and 2 adult sample (20-25 years) (Phase 1)</strong></td>
<td>406</td>
<td>21.87 (1.59)</td>
<td>293/113</td>
<td>26.09 (12.72)</td>
<td></td>
</tr>
<tr>
<td><strong>Papers 3 and 4 (Phase 2)</strong></td>
<td>109</td>
<td>19.91 (2.67)</td>
<td>77/32</td>
<td>32.52 (14.58)</td>
<td></td>
</tr>
<tr>
<td><strong>Paper 5 – Total sample (Phase 3)</strong></td>
<td>24</td>
<td>21.21 (2.73)</td>
<td>13/11</td>
<td>31.62 (16.59)</td>
<td></td>
</tr>
<tr>
<td><strong>Paper 5 – control group (Phase 3)</strong></td>
<td>12</td>
<td>21.37 (3.33)</td>
<td>6/6</td>
<td>17.00 (8.46)</td>
<td></td>
</tr>
<tr>
<td><strong>Paper 5 – high group (Phase 3)</strong></td>
<td>12</td>
<td>21.05 (2.11)</td>
<td>7/5</td>
<td>46.25 (6.12)</td>
<td></td>
</tr>
<tr>
<td><strong>Raine SPQ manual sample 1</strong></td>
<td>302</td>
<td>Not reported</td>
<td>166/136</td>
<td>26.90 (11.00)</td>
<td>Instrument development sample - undergraduates</td>
</tr>
<tr>
<td><strong>Raine SPQ manual sample 2</strong></td>
<td>195</td>
<td>Not reported</td>
<td>95/100</td>
<td>26.30 (11.40)</td>
<td>Instrument development sample - undergraduates</td>
</tr>
<tr>
<td><strong>Halls and Habbit (1996)</strong></td>
<td>100</td>
<td>22 years</td>
<td>56/44</td>
<td>23.49 (10.94)</td>
<td>UK undergraduates</td>
</tr>
<tr>
<td><strong>Fossati et al (2003) school sample (14-19 years)</strong></td>
<td>929</td>
<td>16.43 (1.45)</td>
<td>641/288</td>
<td>27.70 (10.48)</td>
<td>Italian high school students</td>
</tr>
<tr>
<td><strong>Stefanis et al (2004a)</strong></td>
<td>1355</td>
<td>20.90 (1.90)</td>
<td>All male</td>
<td>27.60 (12.30)</td>
<td>Israeli military conscripts</td>
</tr>
</tbody>
</table>
Table 4: Comparison of total SPQ score between PhD and published studies.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>a Vs f</td>
<td>1.04</td>
<td>0.30</td>
</tr>
<tr>
<td>a Vs g</td>
<td>1.45</td>
<td>0.14</td>
</tr>
<tr>
<td>a Vs h</td>
<td>2.88</td>
<td>0.00</td>
</tr>
<tr>
<td>a Vs k</td>
<td>6.39</td>
<td>0.00</td>
</tr>
<tr>
<td>a Vs l</td>
<td>0.29</td>
<td>0.77</td>
</tr>
<tr>
<td>b Vs i</td>
<td>2.00</td>
<td>0.05</td>
</tr>
<tr>
<td>c Vs j</td>
<td>2.27</td>
<td>0.02</td>
</tr>
<tr>
<td>d Vs f</td>
<td>4.17</td>
<td>0.00</td>
</tr>
<tr>
<td>d Vs g</td>
<td>4.12</td>
<td>0.00</td>
</tr>
<tr>
<td>d Vs h</td>
<td>5.03</td>
<td>0.00</td>
</tr>
<tr>
<td>e Vs f</td>
<td>1.94</td>
<td>0.05</td>
</tr>
<tr>
<td>e Vs g</td>
<td>2.04</td>
<td>0.04</td>
</tr>
<tr>
<td>e Vs h</td>
<td>2.93</td>
<td>0.00</td>
</tr>
</tbody>
</table>

In the subsequent PhD samples (Phases 2 and 3), there are significant differences with majority of published studies. For Papers 3 and 4 (face-to-face testing) there was a planned effort to test individuals that scored around average and high on the SPQ. Similarly the recruitment of participants for Paper 5 (brain imaging) resulted in a higher than usual total SPQ score. This was due to the selection of specific high scorers so that comparison in brain structure could be examined between high schizotypes and a control group. Table 3 demonstrates that high schizotypes from Paper 5 have a high mean Total SPQ (46.25) and can be deemed representative of a group with heightened schizotypal features.

2.5 Phase 1 online cognitive tasks

Paper 2 examines the associations between schizotypal features and performance on sustained attention and spatial working memory tasks in a large internet sample. These sections are to be read in conjunction with Paper 2 methodology section to minimise repetition. However for understanding, brief descriptions will be given where necessary.

2.5.1 Spatial working memory task

Please read Paper 2 section 2.2.2 (Pg. 142) which gives a full description of how the task is completed. The section below will provide the rationale for task selection, creation of the performance indices and identification of outliers. An understanding of the task will be required to understand the terminology below.
2.5.1.1 Rationale

As described in Paper 2, the task is a self-ordered search task that assesses spatial working memory function. The rationale for task selection was based on various factors. Firstly as detailed in section 1.4.2 (Pg. 49) of the General Introduction, SWM deficits are present along the schizophrenia continuum, including schizotypes. However, compared to other cognitive domains such as attention, there have been fewer studies examining the associations with schizotypy. The current study therefore looked to add to the current literature of schizotypy, particularly in those going through transition from adolescence to adulthood.

The rationale for specific SWM task choice was influenced predominantly by methodological factors. In the schizotypal literature Delayed Response Tasks (DRT) are most often used, but these were considered incapable of preventing cheating. Since the task was administered on the internet, an examiner could not observe the participant during task completion. DRTs, which require remembering the location of a dot onscreen, could easily be manipulated by a participant placing a finger on the computer screen. Self-ordered search tasks are not as susceptible to manipulation. An issue with these types of task is there relative complexity. Since this was an online task, the instructions had to be conveyed in a clear way to ensure understanding. This was achieved by written instructions, a video demonstrating how to complete the task, along with the creation of performance indices and careful examination of outliers (see below) to ensure those that potentially misunderstood the task were excluded from analyses.

2.5.1.2 Performance indices

As detailed in Paper 2 Section 2.2.2 (Pg 142), the participant could make two types of errors in this task: between search error and within search error. From initial examination of the errors, it became apparent that some participants may have been pressing the boxes during the task in a random order since some had extremely large number of errors (100+). This could reflect two scenarios: 1) either a participant forgot the location of the coins and selected boxes randomly to complete the task; or 2) a participant did not understand the task and selected boxes randomly. Either situation could confound the sample: a single trial could skew an individual’s result; or the participant could be excluded as they fall outside conventional limits for outliers. Due to this it was necessary to create performance indices that could accommodate instances where large numbers of errors were made.
It was considered that total correct number of trials would be most appropriate performance measure. However this gives no indication into the type of errors being created. Between search errors represent a working memory score since this represents the participants ability to remember coin location during the trial; whereas the within search error score is representative of a strategy score since a strategy of searching sequentially would ensure a limited number of errors. Therefore, separate composite performance indices were required to capture between and within search errors.

This led to the creation of between and within search error scores (BSES and WSES respectively). These summary scores were created by examining whether an error (either between or within search error) was made on any of the 12 trials. Where an error was made in a trial, this was scored as 0, whilst no errors scored 1 (conducted separately for between and within search errors). This meant that any excessive errors were simply rounded to 0. A maximum score of 12 for both WSES and BSES was possible. Although this method does lose some of the fine detail in extent of errors produced, it does reduce the undue effect of a trial in which the participant may have selected boxes randomly.

Table 5 lists means ($SD$) and normality data for the final data set (n.b. this data includes the final sample after exclusions – see below). Table 6 lists the Spearman correlations between the three measures. Although not included in further analyses, total number of correct trials is included to demonstrate the association between BSES/WSES and total correct trials. There were strong correlations between BSES/WSES and total correct trials. There is a moderate correlation between WSES and BSES, suggesting they are measuring similar but not identical constructs.

Table 5: Mean ($SD$) scores, values of skewness/kurtosis, and number of participants at ceiling level for each SWM performance measures of the overall dataset.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sample size</th>
<th>Mean ($SD$)</th>
<th>Skewness</th>
<th>Kurtosis</th>
<th>No. at ceiling level</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWM Within Search error score (WSES)</td>
<td>949</td>
<td>10.53 (1.49)</td>
<td>-1.222</td>
<td>1.489</td>
<td>31% (n=293)</td>
</tr>
<tr>
<td>SWM Between Search error score (BSES)</td>
<td>949</td>
<td>8.94 (2.33)</td>
<td>-0.783</td>
<td>0.079</td>
<td>12% (n=115)</td>
</tr>
</tbody>
</table>
Table 6: Correlation between performance measures on the SWM

<table>
<thead>
<tr>
<th></th>
<th>Total correct score</th>
<th>WSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>WSES</td>
<td>0.67 *</td>
<td></td>
</tr>
<tr>
<td>BSES</td>
<td>0.94 *</td>
<td>0.50 *</td>
</tr>
</tbody>
</table>

* - p < 0.001

2.5.1.3 Outliers and exclusions

So as to overcome the possible risk of contamination from random responders, criteria were established to identify and excluded such cases. Since there was a large dataset, there was the opportunity to exclude cases without unduly altering the power of the study. The rationale for exclusion criteria is detailed below. Even though total number of between and within search errors were not used as performance measures (see above), they were used as indicators in identifying participants that may not have understood the task. As such these errors along with correct number of trials were used as part of the exclusion criteria. This is the step-by-step process for exclusion:

1) Examination of performance on the practice trial (3-box configuration) and total number of correct trials. The practice configuration consisted of 3 boxes which is presumed to be easy to complete if the participant understood the task. If any participant failed the 3-box configuration, their performance across all 12 remaining trials was examined. If they subsequently failed all 12 trials it is probable they failed to understand the task. Excluded 15 participants.

2) Similar to point 1, where participants failed the practise trial (3-box) and then only had one correct trial. Excluded 10 participants.

3) Those who completed practice (3-box) trial but subsequently failed all 12 trials. 8 cases identified all of which had extremely high levels of between search errors (all greater than 60 errors). Excluded 8 participants.

4) Examined those with only 1 correct trial (4-box configuration). 20 cases in total of which 8 had already been excluded. The remaining cases had very high between search errors (>60), so excluded. Additional 12 participants excluded.
5) Examined total number of between and within search errors. This was a procedure to check whether those with large number of errors were due to misunderstanding the task or simply an erroneous trial that had skewed the results.

i. Within search errors. Examined those with greater than 20 errors (approximately 4 $SD$ above total mean number of errors). Eleven cases identified of which 4 had previously been excluded. The remaining 7 were examined case by case - they performed correctly other than on 1 or 2 trials. Therefore presumed to have understood the task and included.

ii. Between search errors. Examined greater than 60 errors ($4 SD$ above mean). This identified 59 cases of which 39 had previously been excluded. Again the remaining 20 were examined and appeared to have failed on 1 or 2 trials, but otherwise completed the task successfully, so were included.

In total 45 participants were excluded from SWM analysis. To check there was no selection bias in this method of exclusion, comparisons were made between included and excluded participants, with no significant differences found in age ($t(992) = -0.77, p = 0.44$) or SPQ ($t(992) = 1.47, p = 0.14$). The remaining 949 participants were included in the analyses – see Paper 2.

2.5.2 CPT

*Paper 2 section 2.2.3 (Pg. 144)* gives a full description of how the task is completed. This section provides the rationale, performance measures, and outliers.

2.5.2.1 Rationale

There is a wealth of data pointing to deficits in sustained attention across the schizophrenia continuum (see General Introduction section 1.4.1.3, Pg. 49). The continuous performance task (CPT) is a widely adopted instrument to assess sustained attention. As detailed in section 1.4.1.2 (Pg. 42) there are multiple versions ranging from the simplest CPT-X, through to versions that require working memory function (i.e. CPT-IP). Since higher demand versions are reliant on additional cognitive processes (Bogaro *et al.*, 2003), it is not always straightforward determining the dissociable factors when deficits are found in relation to various conditions (e.g. heightened schizotypal features, schizophrenia etc). For
this reason the CPT-X was chosen since this is predominantly a pure measure of vigilance. The CPT-X specifically is well validated and already used extensively in computer testing paradigms, making it straightforward to develop for online administration.

2.5.2.2 Performance indices

For the CPT, a sequence of letters on a computer screen was displayed on screen at a rate of one letter per 500ms. The participant responded with a keyboard press when the letter “e” was observed. The task was 4 minutes in length. Performance indices for this task were: sensitivity (d’: from signal detection theory – the ability to detect targets and reject false alarms); response time; and MAD (mean absolute deviation from the median). MAD was calculated from the median score for average response time for each target, and taking a mean score of the difference between the response times of each hit from the median (see Betts et al., 2006).

One of the main performance indices of CPT tasks are response times. Most experimental designs rely on a single computer to administer the task. Since this is not possible in internet based studies, to compensate for potential computing related timing issues, the task was designed via HTML computing language script. This script uploaded the task on to the host (participants) computer and ran locally from the CPU. This reduced the likelihood of having a delay in the task, for example, each letter image would be stored on the local computer and uploaded from this location rather than uploaded from the website. Such methods are reliant therefore on the local computers CPU internal clock/processor for both the presentation of stimuli and collation of data. Once the task is complete the data is sent back to the host website as one data package. This allows response times to be measured accurately.

2.5.2.3 Outliers

With such a large data sample, it was again possible outliers were present. The data for each performance measure was examined.

Response time

The response times for all targets were averaged to produce a total average response time for each participant. The total sample was found to have acceptable values of skewness (0.46) and kurtosis (0.68) and was normally distributed. No outliers were identified, so no participants were excluded. See Table 7 for means (SD).
MAD values

MAD values were calculated from response times as described above. The normality of the data was assessed in the total sample \(n=994, \bar{M}=0.0586, SD=0.0239,\) skewness = 5.147 and kurtosis = 68.37), and histograms indicated extreme outliers. Participants scoring above 3 SD of the mean \(n=29\) were excluded from analyses. This produced acceptable values of skewness (0.732) and kurtosis values (0.156). See Table 7 for means (SD).

Sensitivity (d’)

For CPT d’ there was the issue with ceiling effects. Two hundred and ninety participants performed at maximal level (every target achieved with no false alarms) representing 29% of the sample. For this reason the non-parametric Spearman correlations are used. Outliers were assessed, but due to ceiling effects and the skewed data, it was unwise to select based on standard deviations from the mean. Instead number of hits and false alarms were examined. Those excluded had either 10 or more target misses or 10 or more false alarms. Ten participants were excluded. See Table 7 for means (SD).

Summary of outlier criteria for CPT

For further analyses the dataset had the following cases excluded \(n=38\)

1. Response time – no exclusions
2. MAD – beyond 3 SD of mean. Excluded 29 participants.
3. CPT d’ - those with 10 or more target misses \(n=9\), and for this with 10 or more false alarms \(n=4\). N.b. 3 participants would be excluded as MAD outliers.

Excluded 9 participants.

This led to a final CPT sample \(n=956\). There was no significant difference in age \((t(992) = 0.38, p = 0.70)\) or total SPQ \((t(992) = 0.69, p = 0.49)\) between those included and excluded.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sample size</th>
<th>Mean (SD)</th>
<th>Skewness</th>
<th>Kurtosis</th>
<th>No. at ceiling level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response time</td>
<td>956</td>
<td>0.431 (0.036)</td>
<td>0.092</td>
<td>-0.15</td>
<td>n/a</td>
</tr>
<tr>
<td>MAD</td>
<td>956</td>
<td>0.0560 (0.0166)</td>
<td>0.741</td>
<td>0.186</td>
<td>n/a</td>
</tr>
<tr>
<td>d’</td>
<td>956</td>
<td>4.82 (0.410)</td>
<td>-1.163</td>
<td>1.064</td>
<td>27.4% ((n=262))</td>
</tr>
</tbody>
</table>
2.6 Phase 2 Face-to-face testing – to be read in conjunction with Papers 3 and 4

From the initial internet sample (Phase 1), participants were invited back to compete a battery of cognitive tasks (Phase 2). The data collected is the focus of Papers 3 and 4. In this section further details beyond those of the experimental chapters will be provided. This includes detailed procedures for the data collection, along with individual task information.

2.6.1 Participants and procedure

On the website (Phase 1), participants stated whether they would be interested in taking part in further studies (Phases 2 and 3). From the 994 participants with a full dataset, 723 (73%) stated an interest in taking part in face-to-face testing. There was no significant difference in age between groups (t(992) = 1.65, p = 0.10), but those that did agree to later studies had a higher total SPQ score than those that did not (M = 28.37, SD = 13.04 Vs. M = 26.08, SD = 11.90; t(992) = 2.52, p < 0.05).

E-mails were sent to those who expressed an interest detailing Phase 2. Participants were selected if they had reported English as their first language when completing the online survey. This was to ensure that they had full comprehension of the questionnaires and task instructions. The sample was recruited (primarily) opportunistically. Although there were approximately 720 participants who stated an initial interest in completing later stages of the study, in reality, far fewer were prepared to participate when approached. There were also time and financial considerations during recruitment which limited the total size.

One hundred and nine participants were recruited for Phase 2 studies in total. In comparison to other correlational studies, the current study contains a small to average sized sample. In other studies measuring correlations between schizotypal features and cognition, sample sizes range from 90-190 (Matheson and Langdon, 2008; Park and McTigue 1997; Rawlings and Goldberg, 2001; Bergida and Lenzeweger, 2006; Tsakanikos and Claridge, 2005). The required sample size, as informed by power and effect size analyses, was suggested at approximately 60-90. This was calculated from the correlation coefficients (r: effect sizes) of the above mentioned studies ranging from 0.29-0.4 (G*Power 3.1, Faul et al., 2009). The effects sizes used to calculate the sample estimate did not cover all cognitive domains being tested in the current study, so it would be prudent to state that the estimated sample size is lower than would be expected to have
sufficient statistical power to identify all associations if they existed. Even so, the current sample did appear sufficiently powered to identify associations if they existed.

Testing took place in a purpose built test laboratory at the University of Manchester; or for younger participants from colleges outside of the area easily accessible to the University (i.e. Pendleton and St John Rigby Colleges), a psychology test laboratory. All sites were comparable and suitable for cognitive testing. All participants were tested by the same examiner (RPS). On the test day, an information sheet was presented to each participant, along with the opportunity to ask further questions. Informed consent was then obtained. The participant was administered the Mini International Neuropsychiatric Interview (MINI: Lecrubier et al., 1997). Those with a current diagnosis of psychotic disorder, current major depressive episode, or mania were excluded from the study. In total 5 participants were excluded on this basis (depressive symptoms).

The cognitive test battery took approximately 90 minutes to complete. The order of the tasks was kept consistent for each participant. The order is set out below.

Task Order. The SPQ was relevant to Papers 3 and 4, those marked * relevant to Paper 3 only, and those marked + relevant to Paper 4 only.

1. SPQ
2. WASI matrix reasoning and Vocabulary *
3. Rapid Visual Processing (RVP) *
4. Motor Dominance Demonstration Test (MDDT) +
5. Verbal Fluency (FAS) *
6. Verbal Learning - Paired word association task – immediate recall *
7. D-KEFS Trails B *
8. TEA – Telephone search *
9. TEA – Telephone search with counting *
10. Landmark Task of spatial cognition +
11. Digit Span Backward *
12. Paper Line Bisection +
13. Cross finger localisation task +
14. Verbal Learning - Paired word association task – delayed recall *

During testing, the participant was allowed to have a refreshment break. Upon completion of the test battery, the participant was debriefed and offered the opportunity to ask any questions. They were asked if they would be interested in taking part in the final study (Phase 3), and inclusion/exclusion criteria were checked for future involvement. The participant was then paid £20 for their time.
2.6.2 Measures

Further details can be found in the appropriate Paper for each measure. Additional information regarding rationale for choice of task, further description of task and sample size (including outliers) are discussed here.

For SPQ see above, section 2.1

Paper 3 Measures

The choice of task selection was based on empirical research where associations with schizotypy had been demonstrated. In addition tasks were chosen which had known brain structural correlates and were relatively quick to administer. Rather than focus specifically on tasks that tap a single cognitive domain, a choice was made to examine brain function reliant on different regions. By attempting to identify regional changes in brain function in relation to schizotypy, it would provide evidence for or against ubiquitous changes across the schizophrenia continuum. Identification of “early stage” trait markers could help in understanding aetiological and pathophysiological mechanisms.

The three domains of interest were attentional, executive and verbal learning/memory. These correspond to frontal and temporal brain regions. It is noted that for many cognitive domains there are numerous available tests. There were additional pragmatic reasons for task choice including available funds, time and resources.

2.6.2.1 WASI matrix reasoning and Vocabulary

The WASI (Weschler Abbreviated Scale of Intelligence) is a normalised and shortened form of both the WISC-III (Wechsler Intelligence Scale for Children-Third Edition: Weschler, 1991) and WAIS-III (Wechsler Adult Intelligence Scale-Third Edition: Weschler, 1997). The two subtest version was used: matrix reasoning and vocabulary (see below), which produce a full scale intelligent quotient (FSIQ-2) that is normalised to a T-score equivalent for age of participant. The FSIQ-2 score was correlated with each performance measure (Table 8). Where significant correlations existed, FSIQ-2 was added to correlational analyses where possible (i.e. Pearson product moment correlations).

Matrix reasoning is based on the Raven’s Progressive Matrices which measures abstract nonverbal reasoning ability. The participant was presented with a group of designs with a
missing picture. From a selection of alternatives, the participant selected the most appropriate design. In total there were 35 configurations to solve with increasing difficulty (first 6 were not administered unless a mistake was made on item 7, which results in items 1-6 being administered in reverse order). If the participant failed four consecutive items the test was terminated. The task was not timed.

The vocabulary subtest involved the participant provided definitions of words. The definition they provided was scored 0, 1 or 2 depending on content. In total there were 42 words to define with increasing difficulty (first 8 were not administered unless score 0 or 1 on items 9 or 10, which resulted in items 1-8 being administered in reverse order). If the participant had five consecutive scores of 0 the test was terminated. Although the task was not timed, if the participant struggled to give an answer or sat in silence for a period of 30s, the next word was administered.

2.6.2.2 Selective and Divided Attention

Two subtests from the Test of Everyday Attention (TEA) (Robertson et al., 1994) were used to measure selective and divided attention. The Test of Everyday Attention (TEA) is a battery of tests that measure the various independent attention systems. The tests were standardised on a normative sample of 154 participants aged 18-80. In the current study two subtests were used, the Telephone Search Subtest and the Telephone Search While Counting Subtest (dual task decrement). The reliability of the telephone search is excellent (0.88), although less so in the dual task (0.60) due to learning effects in task completion (Robertson et al., 1996). The tasks also have good validity as compared with other measures of attention (Robertson et al., 1996).

For Paper 3 there was the aim to examine the association between schizotypal features and various attention domains. The majority of the literature has focussed predominantly on sustained attention as measured by CPT tasks or its derivatives. Fewer studies have examined selective or divided attention, which is surprising since larger effects sizes have been found in schizophrenia patient samples (Tyson et al., 2008).

Telephone search

The Telephone Search subtest is the measure of visual selective attention. The participant was instructed to look through the list of establishments (plumbers) on a page of a simulated telephone directory, where symbols were also presented (squares, stars, circles
or crosses). The participant was instructed to mark all occurrences of a particular symbol pair (two squares). A diagram of all possible combinations of symbol pairs was placed in front of the participant during the task to minimise memory requirement. They were instructed to work as quickly as possible, whilst ignoring irrelevant symbols, until all targets were marked. There were 20 symbol pairs in total with 108 distractors. Performance measure was the time taken to complete the task divided by the number of correctly identified target pairs.

**Telephone search while counting**

The Telephone Search While Counting subtest is a measure of divided attention that also involves sustained attention. Participants performed The Telephone Search subtest whilst simultaneously counting a series of tones. Similar to the first subtest, the participant searched a list of telephone numbers (restaurants) marking the identical symbols pairs. At the same time the participant counted a series of tones played on a recording. The performance measure was a calculation based on the number of correctly circled symbol pairs, the time taken to complete the task, and the successful counting of auditory tones. This provided each participant with a dual task decrement score.

The performance measure for selective attention was normally distributed with acceptable skewness/kurtosis values (see Table 8). FSIQ-2 correlated with performance \( r(107) = -0.25, p < 0.05 \). Divided attention was not normally distributed due to some cases with low performance levels. Outliers beyond 3 SD of the mean were excluded (n=8). The resulting sample was normally distributed with acceptable skewness/kurtosis values (See Table 8). Divided attention performance was not correlated with age or FSIQ-2.

### 2.6.2.3 Rapid Visual Processing

The Rapid Visual Processing Task (RVP) (Sahakian *et al.*, 1989) is a computerised task that measures visual sustained attention. It is a modified version of the CPT-AX. The rationale for selection was based on various factors. Firstly it was an extension of the experiments of *Paper 2* investigating sustained attention. Similar to other studies, a variant CPT with greater demand on cognition was used which is reliant on selective attention and working memory. Secondly, it complemented the selective and divided attention tasks to give a basic full coverage of the major attentional system. Thirdly these types of task are relatively straightforward to design and administer on standardised testing software, as well as being quick to administer.
In this task the participant observed a sequential presentation of numbers on a computer screen at a rate of 100 digits per 60s, from a distance of approximately 70cm. The aim of the task was to identify target sequences within a stream of numbers. There were three target sequences: 3-5-7, 2-4-6 and 4-6-8. Target sequences were presented in there entirety on screen to the right of the number presentation at all times so as to minimise the memory load of the task (see Fig 1). During the task, once any target sequence had been presented the participant had up to 1800ms to respond with a keyboard press. A successful identification of a target sequence was a ‘hit’ and any non-response when a sequence was presented, recorded as a ‘miss’. In total there were 400 numbers presented in the task with task duration 4 minutes. In total there were 27 target sequences (9 of each) comprising a total of 81 numbers being a part of a target sequence. This task was presented via the software E-PRIME (York, UK).

**Fig 1:** Example of the RVP. The sequence of numbers is presented in the central box. The target sequences are always on the screen.

Detailed instructions on how to complete the task were presented onscreen. Before the main task there was a practice trial. This comprised a 120s trial in which only one target sequence was included and was highlighted in the number stream (numbers in red font and underlined) for the first 60s (see Fig 2). For the remaining 60s of the practice trial, the target sequences were not otherwise highlighted so as to replicate the test conditions. At the end of the practice the participant was provided an explanation of the main task (i.e. the sequences would not be identifiable by colour).
The performance outcome measure for this task was d’ (sensitivity). This was calculated via signal detection theory from hits, and errors of omission (missed targets) and commission (responding when no target). Data was missing for four participants due to computer hardware failure during testing. The data was normally distributed with acceptable values of skewness and kurtosis (see Table 8). FSIQ-2 and age were positively correlated with performance (FSIQ-2: \( r(103) = 0.39, p < 0.001 \); Age: \( r(103) = 0.22, p < 0.05 \)).

2.6.2.4 **Verbal Fluency (FAS)**

The verbal fluency task (FAS) (Borkowski *et al.*, 1967) is a widely used measure of phonemic fluency. It was selected as part of the executive battery of tasks as it is a well validated task that is reliant on frontal brain regions, most notably the left inferior frontal gyrus (Costafreda *et al.*, 2006). The task is widely used in both schizotypal and schizophrenia samples (e.g. Henry and Crawford, 2005; Tsakanikos and Claridge, 2005). The task is quick to complete with no specialist equipment required. For these reason it was deemed an ideal measure of frontal language function.

In this task the participant was instructed to recite as many words as possible within 60s beginning with a certain letter. The participant was informed that any word was permissible apart from proper nouns and derivatives of the same word – examples of these
were provided. The task was completed with the letters F, A and S. Performance outcome was the total number of words generated over the three trials. Total number of words was normally distributed with acceptable values of skewness and kurtosis (see Table 8). FSIQ-2 and age were positively correlated with performance (FSIQ-2: \( r(107) = 0.42, p < 0.001 \); Age: \( r(107) = 0.25, p < 0.05 \)).

### 2.6.2.5 Working memory: Digit Span Backwards (DSB)

The well known and extensively used digit span backwards subtest from the WAIS-III (Weschler, 1997) was included as a measure of working memory. In comparison to the digit span forward variant, the backwards subtest places greater demand on working memory. Again due to its ease of administration, few task instructions and quick administration time, it is well tolerated by participants. Furthermore as an extension of Paper 2 in which spatial working memory was investigated, a task that measured verbal working memory was sought. It is also used extensively in schizophrenia samples and across the continuum (e.g. Conklin et al., 2000; Warnick & Allen, 2005; Wood et al., 2007).

In this task participants were read aloud a string of numbers at a rate of approximately one number per second. At the end of the sequence the participant recites the numbers in a backwards sequence. The task increases in difficulty from three to seven numbers. For each length of numbers, the participant had two attempts to recite the correct sequence. The total number of digits recalled accurately was recorded as their score.

Data is missing for four participants due to non-completion of this task. The total score was not normally distributed as the data was negatively skewed towards maximal performance (see Table 8 for values of skewness and kurtosis). Twenty five participants (24%) performed at the maximum level (score 7). Due to non-normality Spearman Rank correlations were used in analyses. FSIQ-2 was positively correlated with performance (\( r(103) = 0.47, p < 0.001 \)).
2.6.2.6  **Cognitive Flexibility: Trails-B - Delis-Kaplan Executive Function System (D-KEFS)**

The Trails B is a well established measure of cognitive flexibility and set-shifting. The rationale for its inclusion as part of the executive function battery is due to proposed reliance on dorsolateral and medial frontal brain regions (Zakzani *et al.*, 2005), which is mainly bilateral (Shibuya-Tayoshi *et al.*, 2007). There has also been evidence of impaired performance in schizophrenia patients (Heinrichs and Zakzani, 1998) and first degree relatives (Sitskoorn *et al.*, 2004). The findings in schizotypy literature are less conclusive (see section 1.4.3.3 of the General Introduction).

The participant was instructed to connect letters and numbers in a sequential manner with pencil lines on A3 sized paper. Practice attempts were carried out firstly on connecting numbers only (1-16), and then letters only (A-P). In the test trial the participant was instructed to connect from a number to letter to number etc (i.e. 1 – A – 2 – B etc). They were asked to complete the task as quickly but accurately as possible. If during the task the participant made an incorrect connection, they were instructed immediately to return to the point where the error occurred. The performance measure was time to complete the task.

The performance measure was normally distributed with acceptable skewness/kurtosis values (see Table 8). Total time was negatively correlated with FSIQ-2 ($r(107) = -0.42$, $p < 0.001$).

2.6.2.7  **Verbal Learning/Memory: Paired Word Association Learning Task (PWALT)**

The PWALT is a subtest from the Weschler Memory Scale – Revised (Weschler, 1987). It was selected as a test of medial temporal lobe function. The immediate recall measure (see below) is a well validated measure of episodic memory which activates amongst other regions the medial temporal lobe including the hippocampus (Karlsgodt *et al.*, 2005), and has been shown to have differential activation in schizophrenia patients (Eyler *et al.*, 2008). In comparison to other similar tasks such as the California Verbal learning Test (CVLT), it is considerably shorter in administration time which had a large bearing on its selection in the current studies. For immediate recall it was a relatively good measure despite some ceiling effects. Unfortunately for delayed recall it was inadequate (see below for values). The sample were far from impaired on this task irrespective of schizotypal levels. With hindsight it would have been appropriate to select an alternative task such as
the CVLT for delayed recall even with the time and cost implications of using such an instrument. The current study would have benefited from extensive piloting of the cognitive tasks so that such issues would have been identified and subsequently corrected at an early stage of the research process.

For the PWALT, the participant was instructed to remember a list of word pairs. A list of eight word pairs were read aloud at a rate of a word pair every three seconds, with a one second gap between pairs. Once the list was completed, the first word of each pair was again read aloud and the participant instructed to recall the second word of the pair. Half of the word pairs were deemed EASY pairs (e.g. BABY-CRIES) or semantically related; and half were HARD (e.g. CRUSH-DARK) or unrelated words. If the participant recited an incorrect word pair, the correct response was provided. The list of eight word pairs and subsequent recital was repeated three times. This gave a maximum score of 24 for immediate recall (a measure of verbal learning). For delayed recall, the participant was tested again without prior knowledge after 30 minutes from the completion of the immediate recall phase. For delayed recall the participant was given the first word of each pair and asked to provide the second pair. This produced a delayed recall score (maximum 8).

Both immediate and delayed recall had ceiling effects. For immediate recall 21 participants (20%) performed at maximal level (score 24) with a negative skew in the data (see Table 8). As such non-parametric tests were used. There were no significant correlations with age or FSIQ-2. For delayed recall there were larger ceiling effects with 92 participants (84%) scoring at the maximum 8.

**Measures used in Paper 4**

Please see *Paper 4* section 2.2 (Pg. 185-186) for detailed descriptions for the Cross Finger Localisation Task and Landmark task of spatial cognition. This section reports the normality of data from these tasks, along with further details of the Paper Line Bisection.

### 2.6.2.8 Motor Dominance Demonstration Task

Full details of this task are presented in *Paper 4*. This task was selected so as to obtain a measure of degree of motor dominance. It is presumed that the initiation of actions either by hand, eye or foot, would highlight the preferred dominance of this action opposed to
asking the participant explicitly. The resultant score (-10 to 10, purely left to purely right sided dominance) was used as a covariate in analyses.

2.6.2.9 **Paper Line Bisection**

The paper line bisection is the most commonly used test of visuospatial attention. Like other measures of hemispheric specialisation, it is an ideal candidate to investigate whether increased schizotypal features are associated with changes in lateralised function. It is well validated and straightforward to administer. Deviations in performance have been found in various samples including schizophrenia patients (Michel *et al.*, 2007) and schizotypal samples (Mohr *et al.*, 2003).

The paper line bisection required the participant to judge the central position of lines presented on a sheet of paper. This involved the participant manually marking the mid-point of a series of horizontal lines. There were 20 horizontal lines in total: 7 lines were positioned towards the left side of the page, 7 in the middle, and 6 on the right side. Line length varied, ranging from 72mm to 162mm, with an average length of 115mm. Each horizontal line was separated by a 10mm gap. The paper was aligned to each participant and they were instructed not to turn the page. The participant sequentially went down the page marking the mid-point of each of the 20 lines with a small vertical pencil line. Once all the lines had been marked, another copy was placed in front of the participant and they were instructed to carry out the same task with their left hand.

Performance outcome for this task was the average deviation from the true centre of each centrally placed horizontal line for right and left hand separately. This was calculated for centrally positioned horizontal lines only (7 of the 20) as this minimises the effects of line placement which is known to impact upon performance (Jewell and McCourt, 2000). The average deviation was obtained by measuring the distance of the participant placed vertical pencil line from the left most part of the horizontal line. The difference between marked line and true centre was then calculated and converted into a percentage difference. Percentage differences could be either negative or positive representing lines marked to either the left or right of centre respectively. The percentage difference was then averaged for the 7 centrally positioned horizontal lines. This average percentage difference was calculated for both the right and left hand.
The performance measure for both left and right hand were normally distributed with acceptable values of skewness and kurtosis (see Table 8).

2.6.2.10 Landmark Task of Spatial Cognition
The rationale for task choice was to include another measure of visuospatial attentional function, but without the confounds of the manual bisection task such as motor effects, line placement etc (Jewell and McCourt, 2000). Furthermore the task was designed specifically for the current study with an aim to develop it for fMRI scanning. Since tasks of visual spatial attention are deemed markers for lateralised function, fMRI is a technique that can visualise brain activation during task performance. Therefore the collection of behavioural data would also help in the design of future studies.

The outcome measure for this task was the laterality index calculated from the judgment of the position of a bisecting vertical line on long horizontal line (See Paper 4, Pg. 185 for detailed description and equation). The performance measure was normally distributed with acceptable values of skewness/kurtosis (see Table 8). Data was collected from 106 participants due to hardware failure in 3 cases.

2.6.2.11 Crossed Finger Localisation Task
Interhemispheric transfer of somatosensory information was assessed using the Cross Finger Localisation Test (CFLT: Satomi et al., 1991). Full task description is provided in Paper 4 (Pg. 186). Paper 4 examines associations between hemispheric communication and schizotypal features, since lateralised brain function is dependent on successful neural transmission between complicit regions of each hemisphere. The CFLT is easy to administer task that provides a measure of hemispheric transfer.

The overall performance measure was score on the crossed condition of the task (maximum 32). Twenty one participants (20%) scored at maximum level. The data was negatively skewed with unacceptable values of skewness/kurtosis (see Table 8). As such non-parametric analyses were carried out. The ceiling effects found in this task are indicative that interhemispheric transfer is well functioning in normal healthy volunteers, whereas a drastic structural change such as partial or full resection of the corpus callosum is required to severely limit performance on this task (Geffen et al., 1985; Volpe et al., 1982). It would have been possible to increase the difficulty of task by including trials of three finger sequences, but this would have added an unwanted memory component to the
task. In interpreting any results, the implications of perfect or near perfect performance will be considered.

2.6.3 Normality of the variables for Papers 3 and 4
As stated in each section above, the normality of performance variables were assessed. Table 8 provides summary data for each variable in Papers 3 and 4.
Table 8: Means (SD), values of skewness/kurtosis, ceiling/floor effects, appropriate test and correlation with age/IQ for each variable for Papers 3 and 4.

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Mean (SD)</th>
<th>Skewness</th>
<th>Kurtosis</th>
<th>N at ceiling/floor</th>
<th>Correlation with IQ/Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPQ Total</td>
<td>109</td>
<td>35.52 (14.58)</td>
<td>0.12</td>
<td>-0.90</td>
<td>Pearson</td>
</tr>
<tr>
<td>IoF</td>
<td>109</td>
<td>4.46 (2.80)</td>
<td>-0.06</td>
<td>-1.12</td>
<td>Pearson Age</td>
</tr>
<tr>
<td>ESA</td>
<td>109</td>
<td>4.83 (2.49)</td>
<td>-0.24</td>
<td>-1.23</td>
<td>Spearman IQ</td>
</tr>
<tr>
<td>OBMI</td>
<td>109</td>
<td>2.01 (2.08)</td>
<td>0.88</td>
<td>-0.22</td>
<td>Spearman IQ</td>
</tr>
<tr>
<td>UPE</td>
<td>109</td>
<td>3.55 (2.35)</td>
<td>0.29</td>
<td>-0.78</td>
<td>Pearson</td>
</tr>
<tr>
<td>OEB</td>
<td>109</td>
<td>3.62 (2.56)</td>
<td>-0.08</td>
<td>-1.48</td>
<td>Spearman</td>
</tr>
<tr>
<td>NCF</td>
<td>109</td>
<td>2.83 (2.41)</td>
<td>0.54</td>
<td>-0.74</td>
<td>Spearman</td>
</tr>
<tr>
<td>OS</td>
<td>109</td>
<td>5.45 (2.27)</td>
<td>-0.26</td>
<td>-0.88</td>
<td>Pearson</td>
</tr>
<tr>
<td>CA</td>
<td>109</td>
<td>2.29 (1.89)</td>
<td>0.61</td>
<td>-0.40</td>
<td>Spearman</td>
</tr>
<tr>
<td>SU</td>
<td>109</td>
<td>3.55 (2.63)</td>
<td>0.34</td>
<td>-1.07</td>
<td>Spearman</td>
</tr>
<tr>
<td>TEA selective attention</td>
<td>109</td>
<td>2.42 (0.49)</td>
<td>0.70</td>
<td>1.21</td>
<td>Pearson IQ</td>
</tr>
<tr>
<td>TEA divided attention</td>
<td>101</td>
<td>0.26 (0.40)</td>
<td>0.82</td>
<td>0.96</td>
<td>Pearson</td>
</tr>
<tr>
<td>RVP d’</td>
<td>105</td>
<td>2.92 (0.68)</td>
<td>0.52</td>
<td>0.33</td>
<td>Pearson Age and IQ</td>
</tr>
<tr>
<td>FAS total</td>
<td>109</td>
<td>38.74 (10.71)</td>
<td>0.19</td>
<td>-0.73</td>
<td>Pearson Age and IQ</td>
</tr>
<tr>
<td>DSB</td>
<td>105</td>
<td>5.23 (1.28)</td>
<td>-0.48</td>
<td>-0.86</td>
<td>Spearman IQ</td>
</tr>
<tr>
<td>Trails B</td>
<td>109</td>
<td>55.19 (16.28)</td>
<td>0.74</td>
<td>0.37</td>
<td>Pearson IQ</td>
</tr>
<tr>
<td>Verbal Learning - Immediate</td>
<td>109</td>
<td>21.10 (3.02)</td>
<td>-1.90</td>
<td>5.27</td>
<td>21 at ceiling effect (20%) Spearman</td>
</tr>
</tbody>
</table>

Verbal Learning – Recall 92 (84%) performed at ceiling level. Analysed via group comparisons (see text)
Table 8: cont.

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Mean (SD)</th>
<th>Skewness</th>
<th>Kurtosis</th>
<th>N at ceiling/floor</th>
<th>Correlation test</th>
<th>Correlated with IQ/Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Line bisection – left hand</td>
<td>109</td>
<td>-0.82 (3.23)</td>
<td>0.23</td>
<td>0.42</td>
<td>Pearson</td>
<td></td>
</tr>
<tr>
<td>Line bisection – right hand</td>
<td>109</td>
<td>0.82 (3.25)</td>
<td>0.134</td>
<td>0.36</td>
<td>Pearson</td>
<td></td>
</tr>
<tr>
<td>Landmark task</td>
<td>106</td>
<td>0.49 (0.11)</td>
<td>-0.52</td>
<td>0.59</td>
<td>Pearson</td>
<td></td>
</tr>
<tr>
<td>CFLT</td>
<td>109</td>
<td>28.94 (3.52)</td>
<td>-2.01</td>
<td>4.81</td>
<td>Spearman</td>
<td>21 at ceiling effect (25%)</td>
</tr>
</tbody>
</table>
2.7 Diffusion imaging and probabilistic tractography

*Paper 5* sections 2.3-2.4 (Pg. 204-207) describes the imaging sequence, pre-processing and analysis of diffusion data. This section will provide further details of the procedures and the rationale in deciding on particular methods.

2.7.1 The image sequence and sources of signal distortion

To collect diffusion weighted images, the current study used a pulsed gradient spin echo (PGSE) echo planar imaging (EPI). EPI is a commonly used sequence due to extremely quick acquisition times which are necessary for diffusion imaging due to a long echo time in the MR sequence. It can however lead to coarse pixel resolution, image distortion and signal drop-out, particularly in temporal and frontal regions (Parker, 2004). Some artefactual issues are due to EPI sequences having very low image bandwidth in the phase encode of the imaging sequence. This causes problems in regions where there are multiple tissue types with different magnetic susceptibilities such as areas of bone, cerebrospinal fluid and brain tissue. Magnetic field inhomogeneities cause chemical shift and geometric and intensity distortions. Chemical shift artefacts occur in regions where fat and water are present and cause misregistration that manifests in banding in the image due to signal pile-up (Weishaupt *et al.*, 2008). The images are also susceptible to eddy currents which are induced by strong diffusion weighted gradients being rapidly switched on and off. This also causes misplacement of the signal during the phase-encode phase, causing shearing, scaling and bulk shifting in the diffusion images which are exacerbated on higher strength magnets (Jezzard *et al.*, 1998). Data quality is therefore affected by eddy currents and magnetic field inhomogeneities, as well as motion artefacts due to head movements. These problems can be solved with the use of suitable correction schemes for the data (Basser *et al.*, 2000). The current study therefore utilised a correction procedure (see below).

2.7.1.1 Multiple crossing fibre and diffusion directions

A particular issue in DTI is coping with crossing fibres within a voxel. There are regions of the brain where there are multiple crossing fibres, for example, where the corpus callosum crosses fronto-temporo association fibres. As the voxel size of interest is approximately 2mm cubed, the voxel will contain thousands of axons, although the methods will assume a single principal direction (Johansen-Berg and Behrens, 2006). These multiple fibres within a voxel can have two problematic effects. Firstly it can reduce the observed FA value due to obscuring the predominant voxel-specific diffusion direction and hence there will be lack of coherent fibre organisation within the voxel (Mori, 2007). Secondly, for tractography, consecutive voxels with a principal direction are required for tracking.
algorithms to estimate the tract (see below). In areas of crossing fibres the algorithms can sometimes terminate due to no dominant diffusion direction. To overcome the issues with multiple fibres, high angular resolution diffusion imaging (HARDI) is used (Tuch et al., 2002). This involves acquiring diffusion weighted images from many noncollinear directions (greater than 50 directions) which results in the tensor estimation being more robust (Mukherjee et al., 2008; Parker, 2004). This is in contrast to the minimum 6 noncollinear directions which are required and used extensively in studies of schizophrenia samples (see Table 5 in the General Introduction). However, due to the large number of gradient directions, the scan time can become excessively long. Such issues have been tested, with 64 directions with full brain coverage considered to be within a clinically relevant timeframe (Jones et al., 2002). The current study uses 61 diffusion gradient directions. This provides adequate data to cope with the multiple fibres which is crucial for the application of tractography methods, provides good signal-to-noise ratio, and is within an acceptable time (approximately 18 minutes per scan direction).

### 2.7.2 Pre-processing of data - diffusion distortion correction

Due to artefacts of the imaging sequence discussed earlier, it was necessary to correct images prior to analysis. This step is not always carried out in other studies. Pre-processing included the distortion correction of the datasets with methods first described (Bowtel, 1994, Chang and Fitzpatrick, 1992) with an implementation by Embleton et al (2010). For an in-depth discussion of these procedures see Embleton et al (2010). Briefly the correction process involves the acquisition of two data-sets with opposite polarity $k$-space traversal: phase encode in right-left and left-right directions. The distortion in the images due to signal pile-up and eddy currents is equal but in opposite directions, so when the images are registered together, the signal pile-up is stretched out. This correction step has been demonstrated to improve data quality both in diffusion and fMRI sequences (Embleton et al., 2010). As the tracts being investigated are close to brain regions where magnetic susceptibilities are increased (i.e. the uncinate fasciculus), the distortion correction was imperative for successful tractography.
2.7.3 Analysis methods

As mentioned in the general introduction, there are three main analysis methods:

1) regions of interest (ROI) analyses which examine diffusion parameters such as FA within a specific area, which are either operator dependent or segmented by automation;

2) whole brain voxel-based analysis (VBA) which compares all regions between groups to identify areas of difference in, for example, FA values;

3) tractography which reconstructs white matter tracts of interest with algorithms/software that utilise the diffusion information within neighbouring voxels (Basser et al., 2000). Diffusivity values can be extracted from the tract.

The pros and cons of each method are briefly detailed in Table 9.

<table>
<thead>
<tr>
<th>Type of Analysis</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VBA (Data driven analysis)</strong></td>
<td>Whole brain</td>
<td>Examination of specific regions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Good for exploratory analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ROI (hypothesis driven)</strong></td>
<td>Regional</td>
<td>Difficult to determine specificity in areas of multiple tracts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tractography (hypothesis driven)</strong></td>
<td>Specific tracts</td>
<td>Good anatomical localisation in the individual</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allows quantitative measurements of microstructural integrity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Whole tracts can be parcellated out</td>
</tr>
</tbody>
</table>

(Catani, 2006, Konrad and Winterer, 2008, Kubicki et al., 2005)
It was decided that tractography methods would be used. The reasoning was two fold. First, one of the main aims in the imaging study was to examine whether previously found differences between schizophrenia patients and controls in specific tracts would be replicated in a schizotypal sample. The tracts of interest were the uncinate (UF) and arcuate fasciculi (AF). Tractography methods are best placed in parcellating out specific tracts, whereas in ROI and VBA studies it can be difficult to differentiate these tracts from others within the same plane. ROI and VBA also assume that the tracts have similar spatial location in each individual which may not be the case. Second, the imaging was conducted in collaboration with the Imaging Science and Biomedical Engineering (ISBE) group at the University of Manchester which have extensive expertise in the field of diffusion imaging and tractography techniques. The choice of analytical method was an in-house tractography algorithm; probabilistic index of connectivity (PICo) (Parker and Alexander, 2003; 2005; Parker et al., 2003).

The type of tractography is a probabilistic technique. This method aims to reduce uncertainty in the underlying principal direction associated with noise in the data, by first producing a probability density function (PDF) which contains information from the diffusion image about the distribution of the underlying fibre structures (Haroon et al., 2009; Parker, 2004). The resultant PDF is a whole brain map in which each voxel contains information on the distribution of the fibre orientation. Constrained tracking was then carried out from seed regions of interest (see Paper 5 for placement of seed regions and details of algorithm). The only operator-dependent step was the placement of the seed regions of interest (sROI). For the current study these were defined via white mater anatomical maps (Peng et al., 2009; Wakana et al., 2004) and described methods (Wakana et al., 2007).

Probabilistic tractography has advantages over other tractography techniques as they cope better with multi-fibre voxels (Behrens et al., 2007). Confirmatory evidence for the PICo algorithm has been obtained from invasive tracer methods in a porcine brain (Dyrby et al., 2007).

2.7.4 Sample
The aim of the study was to test whether a high schizotypal group has altered FA values in the AF and UF compared to a control sample. As the participants are selected from late adolescence/early adulthood, close age matching was required due to the known changes in
white matter structures even into middle age (Bartzokis et al., 2003). Similarly due to sex differences (Lenroot et al., 2007), an attempt was made to have sex matched groups which is especially critical given a recent study demonstrating sex differences in FA values in temporal regions via DTI tractography (Choi et al., 2010).

2.7.5 Collaboration
For this study I was guided by the ISBE team. Members of ISBE have developed the pre-processing and analytical techniques and protocols used in the current study which are published in peer reviewed journals (Embleton et al., 2010; Haroon et al., 2009; Morris et al., 2008; Parker and Alexander, 2003; 2005; Parker et al., 2003). The ISBE team helped in choice of imaging sequence and provided guidance and technical assistance in pre-processing and analytical steps. These included the following steps: creating the imaging sequence, distortion correction of the raw imaging files, the creation of the PDFs and tractography. However, I was solely responsible for implementing each process including the collection of the data, and carrying out each pre-processing and analytical step.
Data Section
Age and sex effects on schizotypal personality questionnaire (SPQ) subscale scores in an adolescent and adult cohort, with additional confirmation of a latent 4-factor structure.
Age and sex effects on schizotypal personality questionnaire (SPQ) subscale scores in an adolescent and adult cohort, with additional confirmation of a latent 4-factor structure.

Richard P. Smallman1,2, Teresa M. Rushe3, Alex M. Wood2, Shôn W. Lewis4, Emma Barkus5

1 Neuroscience and Psychiatry Unit, University of Manchester; 2 School of Psychological Sciences, University of Manchester; 3 School of Psychology, University of Ulster; 4 Community Based Medicine, University of Manchester; 5 School of Psychology, University of Wollongong.

Abstract

Introduction: The factor structure of the Schizotypal Personality Questionnaire (SPQ) has been examined in large-scale community samples. Exploratory and confirmatory factor analyses (CFA) have supported three- and four-factor models. However, most CFA studies have focused predominantly on adult samples. The current sample sought to investigate which of three well supported models would be the best fitting for a sample from late adolescence and young adulthood (ages 16-25 years). Furthermore, the effects of age and sex on SPQ subscale scores were investigated. It was hypothesised that the same demographic influences found in schizophrenia samples would be applicable to a schizotypy sample.

Methods: Participants (n=1319) completed the SPQ online. CFA was carried out on three competing models: Raine et al (1994) three-factor Disorganised model, Wuthrich and Bates (2006) modified three-factor model, and Stefanis et al (2004a) four-factor paranoid model. Additional CFAs were conducted in subgroups: adolescent (16-19 years) and young adults (20-25 years); and male and females. Scores on the 9 subscales of the SPQ were compared between adolescent and young adults, and between males and females.

Results: The Stefanis et al (2004a) model was the best fitting model for the total sample. This corresponds to cognitive-perceptual, negative, paranoid and disorganised factors. This model was also the best fitting for each subgroup. In comparison of subscales scores, male participants had significantly higher scores on subscales loading on the negative factor and ‘odd/eccentric behaviour’; whereas females had significantly higher scores on ‘odd beliefs/magical ideation’. The adolescent group had significantly higher scores on the subscales ‘unusual perceptual experiences’ and ‘odd speech’.

Conclusions: The present study supports a four-factor model in a sample of 16-25 year olds. This factor structure was also supported in subgroups of adolescents, adults, males and females. Some fit indices for this model were only considered adequate by standard conventions, suggesting improvements are possible. Males had increased negative-type
schizotypal features, whereas females had increased positive-type features. These findings match demographic patterns found in clinical samples. Possible causes for these sex differences are discussed. Higher scores in adolescence compared to adults are also discussed within the context of this dynamic developmental period.

1. Introduction
A considerable body of research has demonstrated that attenuated features of psychosis exist within the general population (Johns and van Os, 2001). These features cluster within a personality trait known as schizotypy (e.g. Raine, 2006). To assess these within the community, the Schizotypal Personality Questionnaire (SPQ: Raine, 1991) is widely used. The SPQ comprises 9 subscales that represent the DSM-III-R criteria for Schizotypal Personality Disorder. Data modelling procedures have used the 9 subscales to produce 2-, 3- and 4-factor models, reducing the subscales into easily interpretable factors, along with providing evidence for the continuity between the multidimensionality of schizotypal features and those of schizophrenia (Vollema and van den Bosch, 1995).

One of the most replicated factor models is the three-factor model of Raine et al (1994) with cognitive perceptual, interpersonal and disorganised factors (see Fig 1). This factor structure matches the three symptom clusters observed in schizophrenia: positive, negative and disorganised symptoms (Arndt et al., 1991, Liddle, 1987). The Raine model has been supported in various samples including adolescents (Fossati et al., 2003), older participants (Badcock and Dragovic, 2006), first-degree relatives of patients (Calkins et al., 2004) and psychiatric in- and outpatients (Rossi and Daneluzzo, 2002). Recently confirmatory factor analysis (CFA) has been used in community based samples to determine how well these models fit the data. This multivariate statistical technique allows the testing of the relationship between observed variables (in this case SPQ subscale scores) and latent constructs (factors), using structural equation modelling. Unlike exploratory techniques which derive structures from the data, CFA uses a priori models formed on the basis of theory. It also allows simultaneously comparison of multiple models in a given sample. The suitability of competing models can then be compared by assessing goodness of fit indices (see below). There has been interest in CFA and SPQ factor models with support coming for the Raine et al (1994) model (Reynolds et al., 2000) and variant models (i.e. Bora and Arabaci, 2009; Wuthrich and Bates, 2006). Others have proposed the addition of a fourth ‘paranoid’ factor (Stefanis et al., 2004a). See Figs 2 and 3 for Wuthrich and Bates (2006) and Stefanis et al (2004a) models. The paranoid model has recently been shown to
be the best fitting in CFA study comparing multiple models (Compton et al., 2009). One of the aims of the current study is to assess which of the three models is best fitting in a sample of late adolescents and young adults.

**Fig 1:** Factor structure of the SPQ as proposed by Raine et al (1994). The ovals are the subscales that load onto the latent factors.
- IOF – ideas of reference
- OBMG – odd beliefs/magical ideation
- UPE – unusual perceptual experiences
- SU – suspiciousness
- ESA – excessive social anxiety
- NCF – no close friends
- CA – constricted affect
- OEB – odd/eccentric behaviour
- OS – odd speech

**Fig 2:** Modified factor structure proposed by Wuthrich and Bates (2006).
- IOF – ideas of reference
- UPE – unusual perceptual experiences
- OBMG – odd beliefs/magical ideation
- SU – suspiciousness
- ESA – excessive social anxiety
- NCF – no close friends
- CA – constricted affect
- OEB – odd/eccentric behaviour
- OS – odd speech

**Fig 3:** Four-factor paranoid model proposed by Stefanis et al (2004a).
- OBMG – odd beliefs/magical ideation
- UPE – unusual perceptual experiences
- IOF – ideas of reference
- SU – suspiciousness
- ESA – excessive social anxiety
- NCF – no close friends
- CA – constricted affect
- OEB – odd/eccentric behaviour
- OS – odd speech
With a large dataset, comparisons can also be made between subscale scores to examine whether there are any changes in relations to demographic variables. Known characteristics that influence schizotypal features include age and sex. For example, age effects have been reported with adolescents producing higher SPQ scores compared to young adults (Fossati et al., 2003). Sex differences in schizotypy results are often mixed, although females tend to score higher on positive-type schizotypal features, whereas males score higher on the negative features (Fossati et al., 2003; Miller and Burns, 1995; Raine, 1992).

### 1.1 Rationale and hypotheses

The purpose of the current study is twofold. Firstly it aims to identify which model from Raine et al (1994), Wuthrich and Bates (2006), or Stefanis et al (2004a) best fits the current data: a large community sample aged 16-25 years. These three models were chosen given their support in the literature.

1. It is predicted that the Stefanis 4-factor model will best fit the data given the support from recent studies (Compton et al., 2009).

Only a few studies to date have examined the factor structure of the SPQ in adolescent samples. The current study examines whether the factor structures are equally well fitting in two different age groups: adolescents (16-19 years old) and young adults (20-25).

2. It is predicted that the model fit will be similar in adolescents and adults.

Furthermore, the factor models will also be tested in males and females separately to ensure there are no differences in relation to sex.

3. Competing models in males and females are predicted to be similar suggesting the factor structure is invariant across sex.

The second main aim of the study is to examine differences in subscale scores between age group and sex. Subscale scores will be examined in line with previous research.

4. It is predicted that the adolescent group will score higher than adult groups.
5. It is predicted that males will score higher on subscales related to negative schizotypal features, whereas females will score higher on positive-type subscales.

2. Methods

2.1. Participants

Participants were recruited from two Universities, four Colleges, two secondary schools and one business in the North-West of England. The colleges were representative of the general North-West metropolitan region (See Methodology Chapter Section 2.3 (Pg. 90) for detailed description of the sample). The total sample consisted of 1319 participants aged 16-25 years (Mean age 19.13 (SD 2.50)); 385 males (19.08 (2.59)), 934 females (19.15 (2.46)). There was no significant difference in age between males and females ($t(1317) = -0.41$, $p = 0.69$). An inclusion criterion was fluency in English to ensure comprehension of the questionnaire.

2.2. Procedure

Participants were invited by email, letter or electronic notice to visit an internet website where the study was hosted. The website consisted of questionnaires and computerised cognitive tasks. The focus of this study is the questionnaire data (Paper 2 examines the cognitive data collected at the same time).

The participant information sheet was presented on the first page of the website. Details were also provided about a prize draw in which participants would be entered into for completing the website (vouchers to the value of £50). Following on was the consent form. If participants were unclear on the consent procedure or had further questions, they were encouraged to contact a member of the research team before consenting to take part. The next webpage collected background information including age, sex, years in education, handedness (motor dominance), first language and any other languages spoken. In the original advertisement it was stated that participants should be fluent in English. Those that stated they were not fluent in English were excluded from further analysis. This was to ensure that all participants had full understanding of the instructions and questionnaire items. The next section included the Schizotypal Personality Questionnaire and cognitive tasks (Paper 2).
The databases of responses were held on a firewall protected secure section of the computer network. Ethical approval was received from the University of Manchester Senate Ethics Committee.

2.3. Schizotypal Personality Questionnaire

The SPQ (Raine, 1991) is a 74-item dichotomous (yes/no) questionnaire based on the DSM-III-R criteria for SPD (American Psychiatric Association, 1984). It is a multidimensional measure that comprises 9 subscales that cover schizotypal features as defined by DSM-III-R. The 9 subscales are Ideas of References (IoF), Excessive Social Anxiety (ESA), Odd Beliefs/Magical Ideation (OBMI), Unusual Perceptual Experiences (UPE), Odd or Eccentric Behaviour (OEB), No Close Friends (NCF), Odd Speech (OS), Constricted Affect (CA), and Suspiciousness (SU). The SPQ has high internal reliability (0.9-0.91), test-retest reliability (0.82), convergent validity (0.81 with Schizotypal Personality Scale: Claridge and Broks, 1984), and criterion validity (55% scoring in top 10% have SPD) (Raine, 1991).

2.4. Data Analysis

CFA was used to assess the factor structure of the SPQ. Three models were investigated: Raine et al (1994) disorganised (Model 1); Wuthrich and Bates (2006) modified disorganised (Model 2); and Stefanis et al (2004a) Paranoid (Model 3). CFAs for all models were carried out on the total sample and demographic subgroups: age group (16-19 and 20-25 years), and males and females. Goodness of fit indices were examined to assess how well the models fit the data.

Model fit indices (Garson, 2009)

i) Chi-Squared ($\chi^2$) values are reported, but due to $\chi^2$ being sensitive to sample size, the model can be accepted if other fit indices are within acceptable ranges.

ii) CFI (comparative fit index) (Bentler, 1990): This procedure compares the predicted and observed covariance matrices, producing a fit index on lack of fit from the null to predicted model. Suggested values of CFI $\geq 0.90$ (Bentler and Bonett, 1980).

iii) SRMR (standardised root mean-square residual) (Bentler, 1995): This index gives the average difference between observed and predicted variances and covariances in the model based on standardised residuals. Values $\leq 0.08$ are acceptable fit and $\leq 0.05$ considered good fit (Hu and Bentler, 1999).
iv) **RMSEA (Root mean square error of approximation)** (Steiger, 1990): This fit index does not rely on comparison with a null model and less affected by sample size. It is a measure of average lack of fit per degree of freedom. Values ≤ 0.05 are representative of a good fit, although ≤ 0.08 are considered adequate (Browne and Cudeck, 1993; MacCallum et al., 1996).

v) **AIC (Akaike information criterion)** (Akaike, 1987): The AIC can be used to compare models that have different number of latent factors, i.e. non-nested models. It is a goodness-of-fit measure that gives advantage to more parsimonious models. The model with the lowest AIC value is considered the best fitting (Tanaka, 1993)

Age group and sex differences in Total SPQ were assessed via student *t*-tests, whereas subscale scores were assessed via separate 2x2 factorial ANOVAs. To correct for multiple comparisons, a Bonferroni correction was applied, so significance level was set at 0.05/9, \( \alpha = 0.0056 \). Effect size eta squared \( (\eta^2) \) are reported with values of 0.01 considered small and 0.06 medium (Cohen, 1988). AMOS (v.16) was used for CFA and SPSS (v.15) for descriptive results and group comparisons.

### 3. Results.

#### 3.1 Confirmatory factor analysis

Table 1 reports the goodness of fit indices for the three factor models for total sample and the demographic groups. In all examples the \( \chi^2 \) values were significant, although unsurprising given the sample sizes. CFI values were acceptable for all models in the total sample and subgroups. SRMR values were acceptable for Model 1 in total sample and subgroups, whereas Models 2 and 3 were considered good. For RMSEA indices, only Model 3 had acceptable fit for the total sample. Similarly in female participants, Model 3 was the only one to have an acceptable RMSEA value, whereas in Males both Models 2 and 3 were acceptable. In separate age groups, only Model 3 had acceptable RMSEA values for both 16-19, and 20-25 year olds.

In comparison of models, AIC values were lowest for Model 3 in the total sample and all subgroups. This is evidence that within the current sample Model 3 (Stefanis *et al.*, 2004a) was the best fitting of the proposed models.
Table 1: CFA goodness of fit indices of each model for total sample and groups: age groups and sex.

<table>
<thead>
<tr>
<th>Group</th>
<th>Model</th>
<th>$\chi^2$</th>
<th>DF</th>
<th>CFI</th>
<th>RMSEA (90 % CI)</th>
<th>SRMR</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Sample (n=1319)</td>
<td>Model 1 (Raine et al., 1994)</td>
<td>320.62 **</td>
<td>23</td>
<td>0.93</td>
<td>0.099 (.090, .109)</td>
<td>0.0528</td>
<td>364.62</td>
</tr>
<tr>
<td></td>
<td>Model 2 (Wuthrich &amp; Bates, 2006)</td>
<td>251.06 **</td>
<td>21</td>
<td>0.946</td>
<td>0.091 (.081, .101)</td>
<td>0.0345</td>
<td>299.06</td>
</tr>
<tr>
<td></td>
<td>Model 3 (Stefanis et al., 2004a)</td>
<td>156.07 **</td>
<td>19</td>
<td>0.968</td>
<td>0.074 (.063, .085)</td>
<td>0.0380</td>
<td>208.07</td>
</tr>
<tr>
<td>Between sex comparison</td>
<td>1</td>
<td>85.16 **</td>
<td>23</td>
<td>0.949</td>
<td>0.084 (.065, .103)</td>
<td>0.0532</td>
<td>129.16</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>59.36 **</td>
<td>21</td>
<td>0.968</td>
<td>0.069 (.049, .090)</td>
<td>0.0319</td>
<td>107.36</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>34.41 *</td>
<td>19</td>
<td>0.987</td>
<td>0.046 (.019, .070)</td>
<td>0.0314</td>
<td>86.41</td>
</tr>
<tr>
<td>Female (n=914)</td>
<td>1</td>
<td>239.45 **</td>
<td>23</td>
<td>0.929</td>
<td>0.100 (.089, .112)</td>
<td>0.0512</td>
<td>283.55</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>201.20 **</td>
<td>21</td>
<td>0.941</td>
<td>0.096 (.084, .108)</td>
<td>0.0369</td>
<td>249.20</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>125.31 **</td>
<td>19</td>
<td>0.965</td>
<td>0.077 (.065, .091)</td>
<td>0.0394</td>
<td>177.31</td>
</tr>
<tr>
<td>Between age group</td>
<td>1</td>
<td>220.76 **</td>
<td>23</td>
<td>0.924</td>
<td>0.103 (.091, .116)</td>
<td>0.0552</td>
<td>264.76</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>176.28 **</td>
<td>21</td>
<td>0.94</td>
<td>0.096 (.083, .109)</td>
<td>0.0380</td>
<td>224.28</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>99.38 **</td>
<td>19</td>
<td>0.969</td>
<td>0.072 (.059, .087)</td>
<td>0.0396</td>
<td>151.38</td>
</tr>
<tr>
<td>16-19 years (n=808)</td>
<td>1</td>
<td>120.92 **</td>
<td>23</td>
<td>0.939</td>
<td>0.091 (.076, .108)</td>
<td>0.0514</td>
<td>164.92</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>98.72 **</td>
<td>21</td>
<td>0.951</td>
<td>0.085 (.069, .102)</td>
<td>0.0345</td>
<td>146.72</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>75.86 **</td>
<td>19</td>
<td>0.964</td>
<td>0.077 (.059, .095)</td>
<td>0.0387</td>
<td>127.86</td>
</tr>
</tbody>
</table>

* Sig p < 0.05, ** Sig p < 0.01

In examining the fit indices of Model 3 only, the fit indices in males and females, and adolescent and adult participants were comparable. However, RMSEA values were only considered acceptable (<0.08), so indicates improvements in model fit are possible. An interesting point is how well fitting the model was in the male sample as demonstrated by the RMSEA value (0.046 [CFI 0.019, 0.070]).

Table 2 presents the factor loadings for Model 3. The majority of factor loadings are of reasonable strength, other than the low loadings of the subscale Excessive Social Anxiety on the Paranoid factor in all samples. This could indicate some redundancy in the model. In comparison across groups, the weights of loadings are comparable providing further support for the stability of this model across demographic groups.

3.2 Comparison of SPQ scores

Fig 4 presents a plot of age versus total SPQ. There was a significant negative correlation between age and total SPQ ($r(1317) = -0.16$, $p < 0.01$). Males had significantly higher total
SPQ score compared to females (Male $M=29.44$ ($SD\ 13.73$), Female $M=27.01$ ($SD\ 12.82$), $t(1317) = 3.07, p < 0.01$).

Table 2: Factor loadings for Stefanis *et al* (2004a) model for total sample and subgroups

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Latent Factor</th>
<th>Total</th>
<th>Sex</th>
<th>Age Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odd Beliefs/Magical Thinking</td>
<td>Cognitive Perceptual</td>
<td>0.59</td>
<td>0.53</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>Perceptual</td>
<td>0.86</td>
<td>0.86</td>
<td>0.85</td>
</tr>
<tr>
<td>Unusual Perceptual Experiences</td>
<td>Cognitive Perceptual</td>
<td>0.53</td>
<td>0.86</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>Perceptual</td>
<td>0.86</td>
<td>0.86</td>
<td>0.83</td>
</tr>
<tr>
<td>Ideas of Reference</td>
<td>Paranoid</td>
<td>0.60</td>
<td>0.59</td>
<td>0.61</td>
</tr>
<tr>
<td>Suspiciousness</td>
<td>Paranoid</td>
<td>0.60</td>
<td>0.59</td>
<td>0.61</td>
</tr>
<tr>
<td>Excessive Social Anxiety</td>
<td>Paranoid</td>
<td>0.60</td>
<td>0.59</td>
<td>0.61</td>
</tr>
<tr>
<td>Suspiciousness</td>
<td>Negative</td>
<td>0.33</td>
<td>0.28</td>
<td>0.33</td>
</tr>
<tr>
<td>Excessive Social Anxiety</td>
<td>Negative</td>
<td>0.55</td>
<td>0.58</td>
<td>0.54</td>
</tr>
<tr>
<td>No Close Friends</td>
<td>Negative</td>
<td>0.83</td>
<td>0.82</td>
<td>0.81</td>
</tr>
<tr>
<td>Constricted Affect</td>
<td>Negative</td>
<td>0.83</td>
<td>0.82</td>
<td>0.81</td>
</tr>
<tr>
<td>Odd/Eccentric Behaviour</td>
<td>Disorganised</td>
<td>0.72</td>
<td>0.71</td>
<td>0.74</td>
</tr>
<tr>
<td>Odd Speech</td>
<td>Disorganised</td>
<td>0.72</td>
<td>0.71</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Fig 4: Scatter plot of age vs. total SPQ score

Table 3 presents the mean scores for SPQ subscales for the whole sample and for each subgroup along with test statistics for group comparisons. In comparison between males and females, males had higher scores on the subscales No Close Friends, Constricted Affect, Odd/Eccentric Behaviour and Odd Speech, although Odd Speech did not survive
Bonferroni correction. Females had significantly higher scores on Odd Beliefs/Magical Thinking and Excessive Social Anxiety, but only Odd Beliefs survived correction. In age group comparisons, the 16-19 year olds had higher scores on Unusual Perceptual Experiences, Ideas of Reference, Suspiciousness, Odd/Eccentric Behaviour and Odd Speech. Only Unusual Perceptual Experience and Odd Speech survived Bonferroni correction. There were also interactions between age group and sex on Ideas of Reference (F(1318) = 6.63; p = 0.009, η² = 0.005) and Suspiciousness (F(1318) = 4.43; p = 0.035, η² = 0.003), although neither survived correction for multiple comparisons.

Table 3: Subscale scores for total samples and groups categorised on sex and age group. Test statistics and effect sizes are reported for comparisons between sex and age groups.

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Total Sample</th>
<th>Male (n=385)</th>
<th>Female (n=934)</th>
<th>F</th>
<th>η²</th>
<th>Age Group</th>
<th>16-19 (n=808)</th>
<th>20-25 (n=511)</th>
<th>F</th>
<th>η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odd Beliefs/Magical Thinking</td>
<td>1.70 (1.75)</td>
<td>1.44 (1.65)</td>
<td>1.82 (1.78)</td>
<td>11.09</td>
<td>0.008</td>
<td>1.75 (1.81)</td>
<td>1.64 (1.66)</td>
<td>0.49</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Unusual Perceptual Experience</td>
<td>3.13 (2.16)</td>
<td>3.17 (2.08)</td>
<td>3.11 (2.19)</td>
<td>0.09</td>
<td>0.000</td>
<td>3.41 (2.21)</td>
<td>2.69 (2.00)</td>
<td>30.71</td>
<td>0.023</td>
<td></td>
</tr>
<tr>
<td>Ideas of Reference</td>
<td>3.80 (2.53)</td>
<td>3.75 (2.52)</td>
<td>3.83 (2.53)</td>
<td>0.00</td>
<td>0.000</td>
<td>4.03 (2.57)</td>
<td>3.45 (2.42)</td>
<td>6.78</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Suspiciousness</td>
<td>3.19 (2.44)</td>
<td>3.32 (2.48)</td>
<td>3.14 (2.43)</td>
<td>2.76</td>
<td>0.002</td>
<td>3.36 (2.49)</td>
<td>2.93 (2.34)</td>
<td>4.20</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Excessive Social Anxiety</td>
<td>4.12 (2.44)</td>
<td>3.82 (2.51)</td>
<td>4.25 (2.40)</td>
<td>6.38</td>
<td>0.005</td>
<td>4.23 (2.48)</td>
<td>3.96 (2.36)</td>
<td>1.61</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>No Close Friends</td>
<td>2.52 (2.29)</td>
<td>3.15 (2.42)</td>
<td>2.27 (2.19)</td>
<td>41.44</td>
<td>0.031</td>
<td>2.56 (2.32)</td>
<td>2.46 (2.25)</td>
<td>0.18</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Constricted Affect</td>
<td>2.15 (1.86)</td>
<td>2.70 (2.03)</td>
<td>1.92 (1.74)</td>
<td>49.43</td>
<td>0.036</td>
<td>2.21 (1.90)</td>
<td>2.05 (1.80)</td>
<td>0.88</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Odd/Eccentric Behaviour</td>
<td>2.60 (2.35)</td>
<td>3.27 (2.57)</td>
<td>2.32 (2.28)</td>
<td>46.84</td>
<td>0.034</td>
<td>2.75 (2.39)</td>
<td>2.35 (2.25)</td>
<td>5.45</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Odd Speech</td>
<td>4.42 (2.37)</td>
<td>4.61 (2.44)</td>
<td>4.34 (2.34)</td>
<td>4.02</td>
<td>0.003</td>
<td>4.61 (2.36)</td>
<td>4.11 (2.37)</td>
<td>8.81</td>
<td>0.007</td>
<td></td>
</tr>
</tbody>
</table>

* - sig at p < 0.05; ** - sig at p < 0.01; *** sig at Bonferroni corrected p < 0.0056

4. Discussion

Using confirmatory factor analysis on the SPQ it was demonstrated that the four-factor Stefanis et al (2004a) paranoid model was the best fitting for the current sample. This factor model was also the best fitting for males and females, and for adolescent and adult groups. In terms of demographic effects on schizotypy scores, adolescent participants had significantly higher scores on the subscales Unusual Perceptual Experiences and Odd Speech. In comparison across sex, males were associated with higher total SPQ scores and on subscales No Close Friends, Constricted Affect, and Odd/Eccentric Behaviour; whereas females had significantly higher scores on the Odd Beliefs/Magical Ideation subscale.
4.1 Factor Structure of the SPQ

The four-factor Stefanis et al. (2004a) paranoid model was the better fitting of the three models tested. It was the only model which adequately fit the data for each subgroup, as neither the Raine et al. (1994) nor Wuthrich and Bates (2006) had acceptable fit on some of the model fit indices for either total sample or some subgroups. Therefore, as predicted the relationship between latent factors and subscales of the SPQ are better suited to a four-factor construct. This model was also the best fitting of multiple models tested in another CFA study in a university sample (Compton et al., 2009). The other study predictions were also confirmed in that the model was suitably well fitting in younger/older groups, and males and females.

The model was devised on evidence from both schizophrenia and schizotypy literature indicating that the positive symptoms construct could be split into separate paranoid and cognitive/perceptual factors (Stefanis et al., 2004a and references therein). This paranoid factor was originally demonstrated in a three-factor model characterising a sample of SPD patients, and was a favourable model compared to the three-factor disorganised model (Bergman et al., 1996). Stefanis and colleagues (2004a) added the paranoid factor as a fourth factor to the already established disorganised model. They originally confirmed this latent structure in an all male sample aged 18-24 years. Of note, in the current study, the male subgroup was the only instance when the RMSEA goodness of fit value was considered a good fit rather than acceptable by conventional standards.

Even though the Stefanis et al. (2004a) paranoid model was the best fitting, the RMSEA fit indices were only adequate for total sample and majority of subgroups, suggesting that it could be improved upon. As previous researchers have done, modifications to the model could improve the fit indices and represent a better fitting model for an adolescent or young adult samples. However, an important consideration is that all hypothesised models are based on second-order factor structures. These second order structures presuppose that the first order structure (items loading onto subscales) are sound. To date, few studies have examined the first order structure of the SPQ. One study conducted factor analysis on items (Chmielewski and Watson, 2008), whereas another used Rasch models (Vollema and Hoijtink, 2000). Item level factor analysis on dichotomous data is not without its problems and hence the finding that the SPQ was associated with five factors must be treated with caution (Chmielewski and Watson, 2008). Using Rasch modelling (more suited to
dichotomous data) support was given for a modified Raine model with additional cross loads of Ideas of Reference onto the negative factor (Vollema and Hoijtink, 2000). Further studies utilising developed techniques such as Item Response Theory would be useful in assessing the underlying first order structure. With these structures identified, it would be then be possible to examine how these factors congregate into higher second order factors representing familiar constructs such as positive and negative symptom factors. This could provide further support for the similarities between the multidimensionality of schizotypy and schizophrenia-related disorders.

4.2 Sex and SPQ

It was hypothesised that demographic factors would have an association with schizotypal levels. This was confirmed in the current study. As predicted males scored higher on the subscales that load onto negative factors, i.e. No Close Friends and Constricted Affect, as well as having higher overall levels. This increase in negative-type features in males is replicated within the literature (Paino-Pineiro et al., 2008; Raine, 1992; Venables & Bailes, 1994; Venables et al., 1990), and mirrors the increase in negative symptoms in male schizophrenia patients (Leung and Chue, 2000).

Research is conflicting over extent of sex differences in positive schizotypal features. In the current study females had a small but significant increase on Odd Beliefs/Magical Ideation subscale that loads onto positive like symptoms similar to previous studies (Bora and Arabaci, 2009; Raine, 1992; Roth and Baribeau, 1997). These higher levels of magical ideation are still present in females in the fifth decade (Badcock and Dragovic, 2006), suggesting it is a stable increased trait in the female population. In the current study females also scored higher on Excessive Social Anxiety although this did not reach the adjusted significance level. A similar study found no increase in positive schizotypy in females when corrected for multiple comparisons (Miller and Burns, 1995). This lack of increase in positive symptoms in females was also found in a recent meta-analysis of the Chapman psychosis-proneness scales (Miettunen and Jaaskelainen, 2010). The most parsimonious conclusion is that relatively high negative type features are found in males consistently, whereas females may have subtle increases in some positive-type features as indicated by the small effect sizes when present.

Why sex differences in schizotypal levels occur is not entirely clear although may relate to developmental differences in males and females. From research carried out into other
psychopathologies, sex differences have been proposed to be related to a number of causes. These include different environmental risk factors (social roles/expectations) and different biological risk factors (gene expression, hormones, neurotransmitters, brain structure/function/circuitry, and pharmacokinetics), which lead to different thresholds for interactive processes to take place and subsequent expression of psychopathology (Zahn-Waxler et al., 2008). In addition, early maturation is associated with heightened risk for internalising disorders such as depression, anxiety and eating disorders in females (Hayward and Sanborn, 2002), as well as adolescent females being more sensitive to stresses (Bouma et al., 2008). It is likely that risk for presence of schizotypal features will also have similar factors associated with sex differences. Interactions between developmental stage and sex on schizotypal levels have been investigated (Mata et al., 2005). Females were found to have a negative correlation between age and all schizotypal features as measured by the shortened version of the SPQ (SPQ-B), whereas males were associated with a decline in negative and disorganised type symptoms only. This suggests that females may be at a particular risk for heightened expression during adolescence.

4.3 Age and SPQ

There was a negative correlation between total SPQ and age, along with significant differences in subscale scores between age groups although some did not survive correction for multiple comparisons. As predicted, the youngest group (16-19 years) had higher scores on 5 of the 9 subscales, although only Unusual Perceptual Experiences and Odd Speech remained significant. These differences in subscales scores were similar to those observed in a comparison of college and university students (Fossati et al., 2003). It has been suggested that the transition from adolescence to adulthood is critical in the reduction of attenuated psychotic-like experiences. For example, even in a relative narrow timeframe of 18-23 year olds, younger participants (18-20 years) had significantly higher delusional-like experiences compared to 21-23 year olds (Scott et al., 2008). Longitudinal studies supports the assertion of an initial decline in schizotypal features with age, and points to a reduction during the second decade followed by relative stability (Rossler et al., 2007). Furthermore, this heightened expression of schizotypal features appears specific to adolescence and not a linear decline, as evidence suggests an increase from lower levels during late childhood (Fonseca-Pedrero et al., 2008; Wigman et al., 2009). An inverted U shape in schizotypal features could be occurring from childhood through to adulthood, with adolescence the point of maximal levels which coincides with the onset of risk for psychosis development.
There are various possible explanations why late adolescence is associated with higher schizotypal levels. It is possible that maturational processes during adolescence could lead to heightened expression of particularly positive-type symptoms. The brain is going through a major period of restructuring, such as changes in grey matter density and increases in white matter connectivity (Giedd et al., 1999; Paus et al., 2001; Sowell et al., 1999; Schmithorst and Yuan 2010), along with changes in the extent of dopaminergic innervation (Spear, 2000). Before full maturity, a transient increase in expression of positive-type symptoms could be a consequence of this ongoing development.

Alternative explanations or other factors influencing expression concurrently, could be that higher schizotypal scores in younger participants are reflecting belief systems in younger groups that are considered strange or unusual (Verdoux and van Os, 2002), and/or measures of schizotypy are identifying traits that are part of normal development (DiDuca and Joseph, 1999). Other attenuated psychopathologies are also heightened during this period, for example adolescence is associated with a peak in depression rates (Hankin et al., 1998) and obsessive compulsive symptoms, which are shown to overlap with schizotypy (Fonseca-Pedrero et al., 2010). Coupled with this are naturally occurring changes in personality, such as increases in neuroticism in females (McCrae et al., 2002), along with demonstrated links between neuroticism and schizotypal levels (Barrantes-Vidal et al., 2009). Schizotypal features may be difficult to differentiate from other changes in personality or proneness to other psychopathologies during adolescence. It has been suggested specific features could be more representative of a core dimension of the extended phonotype of psychosis such as hallucinatory, delusional and paranoia, whereas magical thinking and grandiosity could be separate (Wigman et al., 2009).

4.4 Limitations

The current study does have a number of limitations. Firstly, due to convenience sampling there was an overrepresentation of people from universities and colleges. However one of the aims of the study was to determine whether the best fitting model would be appropriate for specifically an adolescent/young adult group. A higher proportion of 16-19 year olds are still in formal education, so sampling colleges will not have as much detrimental impact in terms of generalisability of the results. Secondly, similar to other studies examining the factor structure of the SPQ, there is reliance on second order factor structures based on the 9 subscales. As discussed, future studies could examine whether the
9 subscales are in fact a true representation of the 74-items of the SPQ. Thirdly, psychopathology was not screened for, so it is unclear whether participants had current or past history of psychiatric illness. Finally, the comparison of age groups was cross-sectional. Longitudinal studies would be better placed in examining the effects of developmental changes in attenuated symptoms.

4.5 Conclusions
In summary, the Stefanis et al (2004a) paranoid model of the SPQ 9 subscales was the best fitting for the current sample and this was upheld in subgroups categorised by age and by sex. Even so, the fit indices were only considered adequate indicating that improvements to the model are possible. In line with previous research, being male was associated with high subscale scores pertaining to negative schizotypal features, whereas females scored higher on Odd Beliefs, considered an attenuated positive feature. Differences in subscale scores were also noted between 16-19 and 20-25 year olds, although only Unusual Perceptual Experiences and Odd Speech survived Bonferroni correction. Possibly a younger adolescent group would be associated with even higher schizotypy scores, as individuals towards the upper boundaries of the group could have passed through the transitional period to adulthood which is characterised by sharp declines in schizotypal features. Additional examination of the interactions between sex and development stage would be useful as large population surveys indicate differences in developmental trajectories and their role in expression of attenuated positive symptoms (Spauwen et al., 2003). Longitudinal studies would be best placed to examine these trajectories and help shed light on the sex differences in risk periods for more severe clinical conditions.
Paper 2

Association between schizotypy and cognition in a large internet survey of adolescents and adults.
Association between schizotypy and cognition in a large internet survey of adolescents and adults.

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Abstract

Introduction: Presence of schizotypal features have been associated with subtle cognitive impairments similar to those observed in clinical samples, for example, deficits have been found in performance on measures of sustained attention and spatial working memory. However, the association between schizotypal features and cognitive performance is not straightforward. Whereas clinical samples are confounded by illness associated factors, schizotypy studies can be confounded by demographic factors such as age and sex. The current study aims to investigate the associations between schizotypy and performance on sustained attention and SWM in age and sex specific groups.

Methods: Data on cognitive performance from 994 participants was collected via the internet. Participants completed online versions of Schizotypal Personality Questionnaire (SPQ: Raine 1991), a spatial working memory task, and the continuous performance task (CPT-X). Correlations were explored between performance measures and SPQ total/9 subscales in the total sample and the sample divided by sex and age.

Results: In the total sample no significant correlations were found between SPQ scores and performance. In younger participants, associations were observed between increasing Odd Beliefs/Magical Ideation subscale score and SWM performance (within search, adjusted trend level $p < 0.05$; between search, adjusted significant level $p < 0.01$), whereas CPT performance was positively correlated with increased Odd/Eccentric Behaviour ($p < 0.01$) and Suspiciousness scores ($p < 0.05$). In older participants CPT performance was negatively associated with Suspiciousness scores ($p < 0.05$). Males had negative associations between CPT performance and increased schizotypal features, whilst females had decreased SWM performance associated with increased schizotypal scores.

Conclusions: There was limited association between schizotypal features and cognitive performance in a large community sample. There was no fundamental relationship between any particular schizotypal features and performance in the total sample. Associations were observed in age and sex specific groups. The presence of schizotypal features in younger
participants could be associated with delayed maturation in spatial working memory function. Male and female specific associations mirror some findings from the clinical literature. Sample composition could be a major source of heterogeneity within the schizotypy literature.

1. **Introduction**

Cognitive deficits are some of the most pervasive and debilitating aspects of schizophrenia (Heinrichs and Zakzanis, 1998). Deficits are found along the full spectrum of schizophrenia risk including Schizotypal Personality Disorder (SPD) (Voglmaier et al., 2005), relatives of patients with schizophrenia (Snitz et al., 2006), individuals at high risk for developing psychosis (Niendam et al., 2006; Wood et al., 2003), and individuals scoring highly on psychometric schizotypy (Raine, 2006). The presence of cognitive deficits in healthy volunteers who express schizotypal features provides evidence for these deficits being a stable feature of the schizophrenia/psychosis continuum. Using healthy volunteers ensures cognitive deficits can be explored without confounds such as distracting symptomatology and medication effects found in clinical samples (Hori et al., 2006).

Two cognitive domains that have been examined extensively are sustained attention and spatial working memory (see General Introduction Sections 1.4.1 and 1.4.2). Deficits in sustained attention have been found in psychometrically defined schizotypes (Chen et al., 1997), patients with schizophrenia (Cornblatt and Keilp, 1994), first-degree relatives (Sitskoorn et al., 2004) and high-risk groups (Chen et al., 1998b; Franke et al., 1994, Laurent et al., 1999). Performance deficits in otherwise healthy populations have been linked to increased positive schizotypal features in adult and adolescent samples (Chen et al., 1997; 1998a; 1998b; Lenzenweger et al., 1991). Negative schizotypal features are also associated with attentional dysfunction (Chen et al., 1997; Gooding et al., 2006), although not consistently found (Cohen et al., 2006).

Spatial working memory impairments are also well documented in schizophrenia patients (Forbes et al., 2009), relatives of patients (Barrantes-Vidal et al., 2007) and high risk groups (Smith et al., 2006). There are, however, fewer studies that have examined the association between schizotypal features and spatial working memory performance, although deficits have been shown in relation to both positive and negative features (Park et al., 1995; Park and McTigue, 1997; Tallent and Gooding, 1999). Studies in clinical
samples do indicate, however, an association more so with negative symptoms (e.g. Carter et al., 1996; Pantelis et al., 2001; Piskulic et al., 2007).

Both in sustained attention and spatial working memory research, as well as other cognitive domains, there is considerable heterogeneity in findings. Undoubtedly methodological differences such as differences in neuropsychological measures contribute to the inconsistency of findings. However, demographic variables could also be a source of variance. For instance, cognitive developmental stage could have a bearing on results. A large proportion of schizotypal research focuses on convenience samples from universities primarily aged in their early 20s. These groups will include individuals in the late stages of brain development (Giedd et al., 1999; Gogtay et al., 2004). In line with neurodevelopmental theories into the aetiology of schizophrenia (Murray and Lewis, 1987, Weinberger, 1987), late developmental stages during adolescence could be a critical phase in aberrant neurodevelopment (see Pantelis et al., 2005). The presence of schizotypal features could cause a departure from normal cognitive development, which could partially account for this period of heightened risk for serious mental illness.

Mixed findings in the literature could also be related to sex differences in cognition as demonstrated in schizophrenia (Hoff and Kremen, 2002; Leung and Chue, 2000). Few studies have directly examined sex effects in relation to schizotypy and cognition in younger samples which is surprising given the differences in brain developmental trajectories for males and females (Lenroot et al., 2007), and well documented differences in age of onset for schizophrenia (Angermeyer and Kuhn, 1988; Faraone et al., 1994). Schizotypal studies have controlled for age and sex, but given the relevance of such demographic variables in potential aetiological mechanisms in schizophrenia, their impact upon cognition with respect to presence of schizotypy is of interest. Males and females are associated with different levels of schizotypal expression (e.g. Fossati et al., 2003; Raine, 1992, Paper 1). Therefore, the interaction between sex, schizotypy and cognition in an adolescent/young adult sample warrants further research.

**Study rationale**

The aim of the current study is to examine the relationship between cognitive performance and schizotypal features in a normal healthy population. As schizotypy is considered a part of the extended phenotype of schizophrenia it is hypothesised that cognitive deficits, observed in clinical samples, will also be associated with heightened expression of
Schizotypal features. Specifically, the study aims to identify whether schizotypal features as measured by Schizotypal Personality Questionnaire (SPQ: Raine, 1991) are associated with performance deficits on measures of sustained attention and spatial working memory.

It is predicted that performance on measures of sustained attention and spatial working memory will be negatively correlated with increasing schizotypal features. Furthermore, in line with previous research, it is predicted that significant correlations will be found between SPQ subscales pertaining to measure positive type schizotypal features and impaired sustained attention; whereas increasing negative schizotypal features will be correlated with decreasing SWM performance.

Further aims are to examine the association between schizotypal features and cognitive performance in relation to age and sex. There is a degree of mixed findings in the literature, due partly to the heterogeneity of samples. By collecting a large data sample, there will be sufficient power to examine associations in age and sex specific samples. It is predicted that since males are associated with greater risk for presentation of schizotypal features, more associations will be found between heightened schizotypal features and performance on both sustained attention and SWM. In more exploratory analyses, correlations will be examined between schizotypy and performance in younger and older participants.

Summary of hypotheses/aims:

i. Schizotypal features will be positively correlated with decreasing performance on sustained attention and spatial working memory tasks.

ii. SPQ subscales scores measuring positive type features will be associated with decreasing performance on sustained attention.

iii. SPQ subscales scores measuring negative type features will be associated with decreasing performance on SWM.

iv. Males generally will have stronger correlations between impaired performance and schizotypal features compared to females.

v. Correlations between performance and schizotypy will be examined in younger and older participants separately.
2. Methods

2.1 Participants and procedure

The data collected for this study was collected at the same time as the data presented in Paper 1. See corresponding sections of Paper 1 Section 2.1-2.2 (Pg. 126).

2.2 Measures

2.2.1 SPQ

The SPQ (Raine, 1991) is a 74-item dichotomous (yes/no) questionnaire based on the DSM-III-R criteria for SPD (American Psychiatric Association, 1984). It is a multidimensional measure that comprises 9 subscales that cover schizotypal features as defined by DSM-III-R. The 9 subscales are Ideas of References (IoF), Excessive Social Anxiety (ESA), Odd Beliefs/Magical Ideation (OBMI), Unusual Perceptual Experiences (UPE), Odd or Eccentric Behaviour (OEB), No Close Friends (NCF), Odd Speech (OS), Constricted Affect (CA), and Suspiciousness (SU). The SPQ has high internal reliability (0.9-0.91), test-retest reliability (0.82), convergent validity (0.81 with Schizotypal Personality Scale: Claridge and Broks, 1984), and criterion validity (55% scoring in top 10% have SPD) (Raine, 1991).

2.2.2 Spatial Working Memory

The SWM task is a self-ordered search tasks which requires the participant to search treasure chests to find coins. Further details on the SWM found in Methodology Chapter (MC) Section 2.5.1 (Pg. 93).

Task Description

For clarity the following terms are used to describe the task: A trial is the whole process of finding all the coins for one configuration of boxes. For example, the task comprised 13 trials; a practice 3 box configuration, and 4 trials for each level of box (4, 6 and 8 boxes). Within each trial there are numerous search-sweeps. These are defined as the process of clicking individual boxes until a coin is found. Once the coin is found, another search sweep is initiated and so on until all the coins are found. Therefore within a 4 box trial there are 4 search-sweeps (to find 4 coins), 6 search-sweeps for 6 boxes (6 coins) and 8 search-sweeps for 8 boxes (8 coins). Fig 1 is an example test screenshot. The coins location changes box for each search-sweep until it has been present once in each box.
On a trial, the participant attempts to find all the coins without choosing a box they had already searched in the same search-sweep, or where they had found a coin on previous search-sweeps. Hence it is possible to make two types of error: a within-search error and a between search error. A within search error is where a box is selected more than once within the same search-sweep. A between search error is the selection of a box in which a coin was found in a previous search-sweep of that trial. Number of within-search and between-search errors were obtained and used in producing performance measures (see below).

Detailed instructions were presented onscreen prior to the task, along with a video of how to complete the task. The task comprised a practice trial of 3 boxes, followed by 12 trials which include 4 trials with 4 boxes, 4 trials with 6 boxes, and 4 trials with 8 boxes. Between each trial the configuration of the boxes was altered so as to reduce the likelihood of stereotypical searching strategies.

Performance indices
Performance indices were calculated from between and within search errors. The between search error score (BSES) represents a working memory score since this is based on the participants ability to remember coin location during the trial. The within search error score (WSES) is representative of a strategy score since a strategy of searching each box in a sequential fashion would reduce there types of errors. Further details can be found in MC Section 2.5.1.2 (Pg. 98) on how these scores are calculated from number of between and within search errors. A maximum score of 12 on either measure represents no errors were
made across all trials. These errors scores reduced the undue effect of large numbers of errors found on any given trial.

Neither BSES nor WSES were normally distributed due to a skewed distribution towards maximal performance. On WSES, 31% of the sample (n=293) scored the maximum 12. Ceiling effects were less prominent for BSES with 12% (n=115) performing at maximal level. Non-parametric tests (Spearman correlations) were used for all statistical analyses (see below).

**Outliers**

Since this was an online task it was not possible to determine whether the participant fully understood the task instructions. To minimise any possible contamination of the sample, outliers were carefully examined. Number of errors and performance on the practice trial and 4 box trials were used to determine whether the participant understood the task. Section 2.5.1.3 in the MC (Pg. 95) gives step-by-step description of the procedure used to exclude participants. From the original sample of 994 participants, 45 were excluded. There were no significant differences in age or total SPQ score between those included and excluded.

### 2.2.3 Continuous Performance Task (CPT) - sustained attention

The second online task was the CPT. This version of the task is the simplest CPT-X version. Further details on the CPT including design of the internet task and outliers can be found in MC Section 2.5.2 (Pg. 97).

A continuous stream of letters was presented on screen at a rate of 500ms. The participant was instructed to respond with a keyboard press when the target letter “e” was presented. The task was 4 minutes in duration. Performance indices for this task were sensitivity (d’), response time and MAD (mean absolute deviation from the median). Sensitivity (d’) was calculated from errors of omission (missed targets) and commission (responding when no target – false alarms). The following equation was used to calculate d’:  

\[ d' = Z_{Hit} - Z_{FA} \]

Where \( Z_{Hit} \) is the z-score of hit rate\(^2\) and \( Z_{FA} \) the z-score of false alarm rate\(^3\). This represents the ability of the participant to respond to target stimuli whilst ignoring catch trials. d’ in this sample

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\(^2\) Hit rate. This is correct hits plus 0.5. This is then divided by correct hits plus number of errors of omission plus 1.

\(^3\) False alarm rate. This is errors of commission 0.5. This is then divided by errors of commission plus number of total correct hits plus 1.
was not normally distributed.

Response time was the average time to respond to a target. The participants were instructed to respond as quickly as possible. From response times it was possible to calculate a measure of variability of response (MAD). MAD was calculated by identifying the median response time for each target and subtracting the individuals target response time from the median of all participants. These are then averaged to produce an overall MAD value for each participant (Betts, Mckay, Maruff, & Anderson, 2006). Like the standard deviation, MAD is considered a robust measure of variability but does not have undue influence from outliers (Garret & Nash, 2001).

Outliers
Section 2.5.2.3 in the MC (Pg. 98) provides step-by-step details on identification of outliers. In total 39 cases were excluded due to either MAD or number of target hits/misses outside of the normal range. This resulted in a final sample n=955. There were no significant differences in age or total SPQ score between those included or excluded.

2.3 Data analysis
Data was analysed with SPSS (v.15). The means, standard deviations, and the normality of the data distribution were examined, along with values of kurtosis and skewness. As described previously and in the MC, outliers were removed for each task. Differences in cognitive performance between age groups and sex were assessed with student t-tests or Mann-Whitney U tests depending on normality of data. The strength of associations between schizotypal features and performance measures were assessed via correlations. Pearson product moment correlations were calculated for normally distributed variables, and Spearman rank correlation for non-normally distributed data. Correlations were obtained from each of the 9 subscales of the SPQ and each of the 5 performance measures (3 measures from CPT and 2 measures from SWM task). Correlations were calculated for the total sample and in subsamples: males/females; and younger (16-19 years)/older (20-25 years).

To account for multiple correlations two methods were conducted. For the total sample, the group was split randomly\(^4\) into two separate samples – sample 1 and sample 2. The

\(^4\) This random split was carried out by entering pin numbers for each participant (these were used to anonymise data) into a random list generator (www.random.org/lists/). The list was then sorted numerically with the first half sample 1, and second half sample 2.
correlations were calculated in both samples, and where significant correlations occurred in both, were taken as genuine associations. It was possible to complete this type of analysis due to the sample size – the split samples still contained 470+ cases. This splitting of sample was not appropriate for subsamples (i.e. males/females, younger/older) due to implications on the power of the study. Instead, the second method for subsamples only was to decrease the $\alpha$ level of significance. Corrected significance levels were 0.01 for significant correlations and 0.05 for trend level correlations.

Finally, to test whether there was a statistical significance between two subsample correlation coefficients (i.e. male/female and younger/older), Fisher's r-to-z transformation test was used. The correlation coefficient ($r$) for each sample (both Pearson and Spearman) was first transformed to $r'$ (Equation 1). The transformed coefficient for each sample was then entered into separate equations: those with Pearson correlations (Equation 2), or those with Spearman correlations where a suggested modification was used (Equation 3: Fieller et al, 1957). The computed $z$ value is a standardised score which is normally distributed, so significant differences by the standard $\alpha = 0.05$ criterion equate to $z > \pm 1.96$.

$r_1'$ and $r_2'$ are transformed correlations for each sample. $N_{1,2}$ represent the different sample sizes.

\[
\begin{align*}
\text{Equation 1.} \quad z &= \frac{r_1' - r_2'}{\sqrt{\frac{1}{N_1-3} + \frac{1}{N_2-3}}} \\
\text{Equation 2.} \quad z &= \frac{1.06 r_1' - 1.06 r_2'}{\sqrt{\frac{1.06}{N_1-3} + \frac{1.06}{N_2-3}}} \\
\text{Equation 3} \quad z &= \frac{r_1' - r_2'}{\sqrt{\frac{1}{N_1-3} + \frac{1}{N_2-3}}}
\end{align*}
\]

The age groups for younger and older age groups were decided based on developmental stage. The younger age groups represent a late adolescent group that includes the period of late cognitive development (e.g. Conklin et al., 2007; Zald and Iacono, 1998). The older group represents a young adult group where it is presumed cognitive development is complete.
3. Results

3.1 Sample characteristics, SPQ scores and task performance

Table 1 lists age, total SPQ score, SPQ subscale scores and task performance for the total sample, and sample split by age group and by sex. Paper 1 investigated the associations between demographic factors and schizotypal features in a larger sample from which this sample was derived. Therefore comparison of schizotypal scores will not be made in the current study.

On the SWM task, older participants had significantly higher WSES ($U(947) = 91891, z = -4.28, p < 0.001$) and BSES ($U(947) = 95690, z = -3.29, p < 0.01$). This was also demonstrated with significant positive correlations between age and each performance measure (WSES: $\rho(947) = 0.16, p < 0.001$; and BSES: $\rho(947) = 0.15, p < 0.001$). There were no significant differences between male and female performance on either error score (WSES: $U(947) = 88298, z = -1.08, p = 0.28$; BSES: $U(947) = 89909, z = -0.63, p = 0.53$).

On the CPT, older participants had greater sensitivity compared to younger participants ($U(954) = 94210, Z = -3.96, p < 0.001$), and reduced MAD ($t(954) = 2.42, p < 0.05$) representing a less variable response. This was also demonstrated in correlational analyses with age and performance (d’: $\rho(954) = 0.13, < 0.001$; and MAD: $r(954) = -0.10, p < 0.01$). There was no difference in response time between younger and older participants ($t(954) = 0.51, p = 0.61$), with this corroborated in correlational analysis ($r(954) = 0.01, p = 0.78$). Males had a quicker response time compared to females ($t(954) = -2.18, p < 0.05$), but there were no differences in MAD ($t(954) = -0.23, p = 0.82$) or d’ ($U(954) = 90319, Z = -0.50, p = 0.62$).

3.2 Correlations between SPQ and cognitive performance

Task performance and SPQ scores were plotted for CPT RT and MAD (see Appendix 5). These plots indicated there were no obvious non-linear relationships so correlational analyses were acceptable. It was not possible to produce sensible plots for WSES, BSES, or CPT d’ versus SPQ scores since the data was not normally distributed rendering them difficult to interpret (see Appendix 5, Fig 21 for an example).
Table 1: Age, total SPQ Total/subscale scores, and task performance for total sample and subsamples (younger/older and male/female).

<table>
<thead>
<tr>
<th>Sample</th>
<th>Total</th>
<th>Younger (16-19)</th>
<th>Older (20-25)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size (n)</td>
<td>994</td>
<td>558</td>
<td>406</td>
<td>286</td>
<td>708</td>
</tr>
<tr>
<td>Age</td>
<td>19.25 (2.54)</td>
<td>17.45 (1.05)</td>
<td>21.87 (1.59)</td>
<td>19.22 (2.68)</td>
<td>19.27 (2.47)</td>
</tr>
<tr>
<td>Total SPQ</td>
<td>27.75 (12.77)</td>
<td>28.9 (12.69)</td>
<td>26.09 (12.72)</td>
<td>29.38 (12.93)</td>
<td>27.09 (12.66)</td>
</tr>
<tr>
<td>IoF</td>
<td>3.77 (2.51)</td>
<td>3.96 (2.53)</td>
<td>3.50 (2.44)</td>
<td>3.74 (2.46)</td>
<td>3.78 (2.53)</td>
</tr>
<tr>
<td>ESA</td>
<td>4.17 (2.44)</td>
<td>4.25 (2.51)</td>
<td>4.04 (2.33)</td>
<td>3.86 (2.52)</td>
<td>4.29 (2.39)</td>
</tr>
<tr>
<td>OBMG</td>
<td>1.70 (1.73)</td>
<td>1.73 (1.79)</td>
<td>1.64 (1.65)</td>
<td>1.38 (1.57)</td>
<td>1.82 (1.78)</td>
</tr>
<tr>
<td>UPE</td>
<td>3.19 (2.17)</td>
<td>3.48 (2.22)</td>
<td>2.76 (2.01)</td>
<td>3.22 (2.07)</td>
<td>3.17 (2.21)</td>
</tr>
<tr>
<td>OEB</td>
<td>2.66 (2.35)</td>
<td>2.83 (2.38)</td>
<td>2.41 (2.27)</td>
<td>3.30 (2.35)</td>
<td>2.40 (2.30)</td>
</tr>
<tr>
<td>NCF</td>
<td>2.52 (2.29)</td>
<td>2.57 (2.31)</td>
<td>2.44 (2.25)</td>
<td>3.19 (2.39)</td>
<td>2.25 (2.19)</td>
</tr>
<tr>
<td>OS</td>
<td>4.41 (2.36)</td>
<td>4.58 (2.33)</td>
<td>4.18 (2.38)</td>
<td>4.59 (2.42)</td>
<td>4.34 (2.33)</td>
</tr>
<tr>
<td>CA</td>
<td>2.15 (1.83)</td>
<td>2.19 (1.87)</td>
<td>2.08 (1.78)</td>
<td>2.74 (1.98)</td>
<td>1.91 (1.71)</td>
</tr>
<tr>
<td>SU</td>
<td>3.18 (2.43)</td>
<td>3.29 (2.47)</td>
<td>3.03 (2.37)</td>
<td>3.35 (2.46)</td>
<td>3.12 (2.42)</td>
</tr>
<tr>
<td>SWM n</td>
<td>949</td>
<td>558</td>
<td>391</td>
<td>273</td>
<td>676</td>
</tr>
<tr>
<td>WSES</td>
<td>10.53 (1.49)</td>
<td>10.38 (1.50)</td>
<td>10.74 (1.46)</td>
<td>10.60 (1.50)</td>
<td>10.50 (1.49)</td>
</tr>
<tr>
<td>BSES</td>
<td>8.94 (2.33)</td>
<td>8.73 (2.38)</td>
<td>9.23 (2.23)</td>
<td>8.84 (2.43)</td>
<td>8.98 (2.29)</td>
</tr>
<tr>
<td>CPT n</td>
<td>956</td>
<td>563</td>
<td>393</td>
<td>268</td>
<td>688</td>
</tr>
<tr>
<td>CPT d'</td>
<td>4.72 (0.47)</td>
<td>4.68 (0.47)</td>
<td>4.78 (0.46)</td>
<td>4.71 (0.46)</td>
<td>4.72 (0.47)</td>
</tr>
<tr>
<td>CPT RT</td>
<td>0.431 (0.036)</td>
<td>0.432 (0.037)</td>
<td>0.430 (0.036)</td>
<td>0.427 (0.035)</td>
<td>0.433 (0.037)</td>
</tr>
<tr>
<td>CPT MAD</td>
<td>0.056 (0.017)</td>
<td>0.057 (0.017)</td>
<td>0.054 (0.016)</td>
<td>0.056 (0.016)</td>
<td>0.056 (0.017)</td>
</tr>
</tbody>
</table>

IoF – Ideas of Reference; ESA – Excessive Social Anxiety; OBMG – Odd Beliefs/Magical Ideation; UPE – Unusual Perceptual Experiences; OEB – Odd/Eccentric Behaviour; NCF – No Close Friends; OS – Odd Speech; CA – Constricted Affect; SU – Suspiciousness; WSES – spatial working memory within search error score; BSES – spatial working memory between search error score.

3.2.1 Total sample

The total sample was randomly split into sample 1 and sample 2. Correlations were calculated between SPQ scores and task performance for each sample. Table 2 reports the
correlations for both samples. There were no significant correlations between SPQ scores and task performance that were present in both of the randomly split samples. There were significant correlations between CPT MAD and subscales scores, but since they were not replicated across samples, these are likely to represent type I errors.

Table 2: Correlations between SPQ scores and task performance for two randomly generated samples.

<table>
<thead>
<tr>
<th></th>
<th>SWM BSES</th>
<th>SWM WSES</th>
<th>CPT d'</th>
<th>CPT RT</th>
<th>CPT MAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Sample size</td>
<td>477</td>
<td>472</td>
<td>477</td>
<td>472</td>
<td>484</td>
</tr>
<tr>
<td>SPQ total</td>
<td>-0.07</td>
<td>-0.02</td>
<td>-0.01</td>
<td>-0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>IoF</td>
<td>-0.04</td>
<td>-0.03</td>
<td>0.02</td>
<td>-0.05</td>
<td>-0.06</td>
</tr>
<tr>
<td>ESA</td>
<td>-0.02</td>
<td>0.00</td>
<td>0.01</td>
<td>0.06</td>
<td>0.02</td>
</tr>
<tr>
<td>UPE</td>
<td>-0.03</td>
<td>-0.01</td>
<td>-0.01</td>
<td>-0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>OS</td>
<td>-0.08</td>
<td>0.00</td>
<td>-0.01</td>
<td>-0.03</td>
<td>-0.06</td>
</tr>
<tr>
<td>OBMI</td>
<td>-0.06</td>
<td>0.01</td>
<td>-0.06</td>
<td>0.00</td>
<td>-0.07</td>
</tr>
<tr>
<td>OEB</td>
<td>-0.03</td>
<td>0.03</td>
<td>0.02</td>
<td>0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>NCF</td>
<td>-0.03</td>
<td>-0.04</td>
<td>0.01</td>
<td>-0.01</td>
<td>0.07</td>
</tr>
<tr>
<td>CA</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>0.04</td>
<td>0.08</td>
</tr>
<tr>
<td>SU</td>
<td>-0.05</td>
<td>-0.08</td>
<td>-0.04</td>
<td>-0.05</td>
<td>-0.02</td>
</tr>
</tbody>
</table>

* *p < 0.05; ** p < 0.01

3.2.2 Sample split by age

Spatial working memory

Table 3 reports the correlations between SPQ scores and SWM performance measures for younger and older participants, and z values comparing correlation coefficients between groups.

For WSES, there was trend (corrected level) negative correlation between performance and OBMI scores in the younger sample only. There was a significant difference in group correlations coefficients between OBMI, attributable to the negative correlation in the younger sample and positive correlation in older sample.
For BSES, there was a significant (corrected level) negative correlation between performance and OBMI scores, and trend negative correlation with SU scores. There was again a significant group difference between correlation coefficients for OBMI, attributable to the negative correlation in younger participants and positive correlation in the older sample.

**Table 3:** Correlations between SWM performance and SPQ scores for younger and older participants. Fishers r-to-z transformation tests also reported.

<table>
<thead>
<tr>
<th></th>
<th>SWM WSES</th>
<th>SWM BSES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td></td>
<td>558</td>
<td>391</td>
</tr>
<tr>
<td>SPQ</td>
<td>-0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>IoF</td>
<td>-0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>ESA</td>
<td>0.03</td>
<td>0.08</td>
</tr>
<tr>
<td>UPE</td>
<td>0.00</td>
<td>0.04</td>
</tr>
<tr>
<td>OS</td>
<td>-0.01</td>
<td>-0.02</td>
</tr>
<tr>
<td>OBMI</td>
<td>-0.10 **</td>
<td>0.06</td>
</tr>
<tr>
<td>OEB</td>
<td>0.05</td>
<td>-0.02</td>
</tr>
<tr>
<td>NCF</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>CA</td>
<td>0.05</td>
<td>0.00</td>
</tr>
<tr>
<td>SU</td>
<td>-0.02</td>
<td>-0.07</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01

**Continuous Performance Task**

Table 4 reports the correlations between SPQ scores and CPT performance measures for younger and older participants, along with z values for comparison of correlation coefficients.

**Table 4:** Correlations between CPT performance and SPQ scores for younger and older participants. Fishers r-to-z transformation tests scores also reported.

<table>
<thead>
<tr>
<th></th>
<th>CPT d'</th>
<th>CPT RT</th>
<th>CPT MAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Younger</td>
<td>Older</td>
<td>z</td>
</tr>
<tr>
<td></td>
<td>563</td>
<td>393</td>
<td></td>
</tr>
<tr>
<td>SPQ</td>
<td>0.05</td>
<td>-0.01</td>
<td>0.81</td>
</tr>
<tr>
<td>IoF</td>
<td>-0.03</td>
<td>-0.04</td>
<td>0.15</td>
</tr>
<tr>
<td>ESA</td>
<td>0.04</td>
<td>0.02</td>
<td>0.22</td>
</tr>
<tr>
<td>UPE</td>
<td>-0.01</td>
<td>0.00</td>
<td>-0.09</td>
</tr>
<tr>
<td>OS</td>
<td>0.05</td>
<td>-0.03</td>
<td>1.22</td>
</tr>
<tr>
<td>OBMI</td>
<td>-0.01</td>
<td>-0.05</td>
<td>0.62</td>
</tr>
<tr>
<td>OEB</td>
<td>0.11 **</td>
<td>0.02</td>
<td>1.25</td>
</tr>
<tr>
<td>NCF</td>
<td>0.07</td>
<td>0.01</td>
<td>0.81</td>
</tr>
<tr>
<td>CA</td>
<td>0.09 *</td>
<td>0.00</td>
<td>1.24</td>
</tr>
<tr>
<td>SU</td>
<td>-0.03</td>
<td>0.02</td>
<td>-0.65</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01
For d’, there was a significant positive correlation between performance and OEB score, and trend positive correlation with CA. There were no differences in group comparison of any correlation coefficients. For response time, there were no correlations with performance on any SPQ score for younger or older participants. Furthermore there were no significant differences in coefficients between groups. For MAD, in younger participants there was a trend negative correlation between performance and CA scores, whereas in older participants there was a trend positive correlation between performance and SU scores. There were no differences in any correlation coefficient between groups.

3.2.3 Sample split by sex

Spatial working memory

Table 5 reports the correlations between SPQ scores and SWM performance measures for males and females, along with z values comparing correlation coefficients.

Table 5: Correlations between SWM performance and SPQ scores for males and females. Fishers r-to-z transformation tests also reported.

<table>
<thead>
<tr>
<th></th>
<th>SWM WSES</th>
<th></th>
<th></th>
<th>SWM BSES</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>z</td>
<td>Male</td>
<td>Female</td>
<td>z</td>
</tr>
<tr>
<td></td>
<td>273</td>
<td>676</td>
<td></td>
<td>273</td>
<td>676</td>
<td></td>
</tr>
<tr>
<td>SPQ Total</td>
<td>0.08</td>
<td>-0.06</td>
<td>1.85</td>
<td>0.01</td>
<td>-0.09</td>
<td>1.31</td>
</tr>
<tr>
<td>IoF</td>
<td>0.08</td>
<td>-0.05</td>
<td>1.79</td>
<td>-0.03</td>
<td>-0.05</td>
<td>0.23</td>
</tr>
<tr>
<td>ESA</td>
<td>0.05</td>
<td>0.04</td>
<td>0.21</td>
<td>-0.04</td>
<td>-0.03</td>
<td>-0.1</td>
</tr>
<tr>
<td>UPE</td>
<td>0.04</td>
<td>-0.03</td>
<td>0.86</td>
<td>0.01</td>
<td>-0.05</td>
<td>0.74</td>
</tr>
<tr>
<td>OS</td>
<td>0.08</td>
<td>-0.07</td>
<td>2.07 *</td>
<td>0.03</td>
<td>-0.08 *</td>
<td>1.51</td>
</tr>
<tr>
<td>OBMI</td>
<td>-0.01</td>
<td>-0.03</td>
<td>0.34</td>
<td>-0.03</td>
<td>-0.05</td>
<td>0.3</td>
</tr>
<tr>
<td>OEB</td>
<td>0.15 *</td>
<td>-0.05</td>
<td>2.72 **</td>
<td>0.16 **</td>
<td>-0.06</td>
<td>3.03 **</td>
</tr>
<tr>
<td>NCF</td>
<td>0.05</td>
<td>-0.04</td>
<td>1.16</td>
<td>-0.03</td>
<td>-0.06</td>
<td>0.41</td>
</tr>
<tr>
<td>CA</td>
<td>0.05</td>
<td>0</td>
<td>0.7</td>
<td>0.05</td>
<td>-0.02</td>
<td>0.97</td>
</tr>
<tr>
<td>SU</td>
<td>-0.01</td>
<td>-0.07</td>
<td>0.71</td>
<td>-0.06</td>
<td>-0.09 *</td>
<td>0.36</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01

For WSES there were no significant correlations between SPQ scores and performance. There was a trend level (p < 0.05) positive correlation in males between performance and OEB score. There were significant differences in correlation coefficients between males
and females on both the OS and OEB. In both instances this was due to a negative correlation in females, and a positive correlation in males.

For BSES there was a significant positive correlation between performance and OEB in males. In females there were trend (corrected level) negative correlations between performance and scores on OS and SU. There was a significant difference in correlation coefficients between sexes when performance was correlated with OEB scores. This was driven by the significant positive correlation in males and a non-significant negative correlation in females.

**Continuous Performance Task**

Table 6 reports the correlations between SPQ scores and CPT performance measures for males and females, along with $z$ values for comparison of correlation coefficients.

<table>
<thead>
<tr>
<th>SPQ</th>
<th>CPT d'</th>
<th>Male</th>
<th>Female</th>
<th>z</th>
<th>CPT RT</th>
<th>Male</th>
<th>Female</th>
<th>z</th>
<th>CPT MAD</th>
<th>Male</th>
<th>Female</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>268</td>
<td>688</td>
<td>0.07</td>
<td>0.04</td>
<td>-1.49</td>
<td>0.08</td>
<td>0.05</td>
<td>-1.81</td>
<td>-0.08</td>
<td>0.05</td>
<td>-0.08</td>
<td>0.05</td>
<td>-0.08</td>
</tr>
<tr>
<td>IoF</td>
<td>-0.1</td>
<td>-0.03</td>
<td>-0.97</td>
<td>-0.03</td>
<td>0.03</td>
<td>-0.83</td>
<td>0.04</td>
<td>-0.02</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESA</td>
<td>-0.03</td>
<td>0.05</td>
<td>-1.02</td>
<td>-0.06</td>
<td>0.04</td>
<td>-1.43</td>
<td>-0.03</td>
<td>0.05</td>
<td>-1.19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPE</td>
<td>-0.14 *</td>
<td>0.02</td>
<td>-2.12 *</td>
<td>-0.06</td>
<td>0.04</td>
<td>-1.37</td>
<td>0.11</td>
<td>0.03</td>
<td>0.99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OA</td>
<td>0.02</td>
<td>-0.01</td>
<td>0.39</td>
<td>-0.15 *</td>
<td>0.03</td>
<td>-2.39 *</td>
<td>0.06</td>
<td>0.09 *</td>
<td>-0.33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OBMI</td>
<td>-0.08</td>
<td>-0.01</td>
<td>-0.86</td>
<td>-0.07</td>
<td>-0.03</td>
<td>-0.5</td>
<td>0.03</td>
<td>0.01</td>
<td>0.31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OEB</td>
<td>0.04</td>
<td>0.07</td>
<td>-0.51</td>
<td>-0.12</td>
<td>0.04</td>
<td>-2.16 *</td>
<td>0.02</td>
<td>0.02</td>
<td>-0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCF</td>
<td>-0.03</td>
<td>0.07</td>
<td>-1.36</td>
<td>-0.02</td>
<td>0.00</td>
<td>-0.28</td>
<td>0.05</td>
<td>-0.02</td>
<td>1.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA</td>
<td>-0.05</td>
<td>0.10 *</td>
<td>-1.96 *</td>
<td>0.00</td>
<td>0.06</td>
<td>-0.81</td>
<td>-0.02</td>
<td>-0.06</td>
<td>0.61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SU</td>
<td>-0.04</td>
<td>0.00</td>
<td>-0.55</td>
<td>0.02</td>
<td>0.04</td>
<td>-0.24</td>
<td>0.17 **</td>
<td>0.06</td>
<td>1.49</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* $p < 0.05$; ** $p < 0.01$

For d', in males there was a trend negative correlation between performance and UPE scores. In females there was a trend positive correlation with CA scores. In comparison of males and females correlation coefficients, there were significant differences in UPE and CA, both attributable to negative correlations in males and positive correlations in females.

For Response Time, there was a trend negative correlation between performance and OS scores in males only. In comparison between males and females coefficients, there were
significant differences in OS and OEB, again attributable to negative correlations in males
and positive correlations in females.

For MAD, there was positive correlation between MAD and SU scores in males. There
was also a trend positive correlation with OS in females. There were no significant
differences between any male or female correlation coefficients.

4. Discussion

The main hypothesis that schizotypal features would be correlated with decreasing
performance was not supported for the total sample. There were no genuine significant
correlations between any performance measures and total SPQ score or any of the 9
subscales. It was hypothesised that males would have more detrimental association
between performance and schizotypy. This was partly supported on the CPT where males
had a negative association between performance and SU levels. Finally, younger
participants had significant correlations between SWM performance and scores on OBMI
subscale. In direct comparison of younger and older groups, correlation coefficients were
significantly different between OBMI and SWM performance (both WSES and BSES),
with younger participants showing a detrimental association between schizotypy and
performance.

4.1 Effect of age group

Age related increased performance was observed on the CPT, with the older group
possessing greater sensitivity compared to younger participants. Increased sensitivity is
first noticeable during childhood (age range 8-13) (Rebok et al., 1997), but adolescence
could be associated with a reduction in ability (Chen et al., 1998a). Therefore the current
study could be identifying this dip in performance associated with adolescence. Older
participants also had lower MAD values suggesting less variability in response times. As
the average response time was not different between age groups, this suggests that
responses in the younger age group were associated with more inattentive erratic
responses.

The older age group was also associated with better performance on both SWM indices.
Lower WSES may represent a lack of strategy and has been found in children (Barnett et
al., 2005). This decrease in errors could represent a developmental transition from
predominantly working memory to use of an optimised searching strategy which reduces within-search errors. Functional magnetic resonance imaging (fMRI) studies in adolescents show regional changes in activation (left prefrontal regions including the dorsolateral prefrontal cortex along with bilateral inferior posterior parietal regions) which could be indicative of the development of a search strategy (Schweinsburg et al., 2005). The higher BSES in adult groups could be representative of improved working memory. Adult levels of performance are thought to be reached by sixteen years (Conklin et al., 2007), although continued improvements in performance are documented up to ages 20-29 years (De Luca et al., 2003). The current sample could be highlighting some of these later refinements in performance.

4.2 Schizotypy, Age and Sex Effects on Cognition

4.2.1 Continuous Performance Task

There was limited association between schizotypy and performance on the CPT. For the total sample there were no association between SPQ scores and performance. Where associations existed, these were dependent on age or sex. It is possible the task was not suitably demanding enough to identify subtle performance differences in relation to schizotypy. Deficits in schizotypal samples have been found when adopting higher demand versions of the CPT, for instance, via the CPT-identical pairs (IP) in university samples (Chen et al., 1997; Gooding et al., 2006; Lenzenweger et al., 1991; Rawlings and Goldberg, 2001), community samples (Bedwell et al., 2006; Bergida and Lenzenweger, 2006; Chen et al., 1998a), and all male army recruits (Obiols et al., 1993). The CPT-IP requires the participant to respond when two identical digits/letters are presented, thus requiring a degree of working memory function. Whether these deficits in performance are due to an attentional or working memory deficit is often unknown, but does have implications for the research question since there is greater reliance on other cognitive processing (Borgaro et al., 2003). It has also been suggested that interview based measures (i.e. schizotypal personality disorder section from Structured Clinical Interview for DSM-IV Axis II Personality Disorders) are more sensitive to detecting differences on a degraded version of the CPT-AX compared to questionnaires (i.e. the SPQ-Brief) (Bedwell et al., 2009). It is likely that in the current study, with an even-less cognitive challenging version of the CPT, it was not possible to detect subtle performance differences.

There was a significant association between d’ and SPQ scores in the younger sample. It was predicted that increased presence of schizotypal features would be associated with
performance deficits, but in fact higher scores on OEB was associated with increased sensitivity. In factor analyses this subscale loads onto disorganised factors (Raine et al., 1994; Stefanis et al., 2004a). Disorganised symptoms of schizophrenia are sometimes found to be associated with decreased cognitive performance (O’Leary et al., 2000), although not always (Klingberg et al., 2006). Why there is an opposite association occurring in the current study poses an intriguing dilemma. A possible explanation may be the interpretation of the items in a younger sample. Items from this subscale include such examples as “other people see me as slightly eccentric”, and “I have some eccentric (odd) habits”. In a younger sample, eccentricity and divergence from the ‘normal’ could be indicative of a high-achieving enquiring mind, and hence positive correlations with cognition may represent this. In older samples such eccentricities in behaviour may become more normalised as social circles widen, so true odd behaviour reported in an older group may be qualitatively different. Further research would be required to determine if and why the phenomenology of disorganised schizotypal features change during transition from adolescence to adulthood.

Further age related associations were only found at the trend level of significance. There was again an unexpected increase in d’ in association with increased constricted affect (a component of negative schizotypal features) in younger participants. There was also a negative a trend association between constricted affect and MAD in this sample, suggesting that as sensitivity increases with higher levels of affect, variability in response time also decreases. Conversely there was, as predicted, an increase in variability in relation to increasing Suspiciousness in the older sample. There are no previous studies investigating MAD of response times in schizotypy samples. Research in other fields have suggested that an increase in MAD could be related to either an increase in response time indicating disinhibition and impulsiveness, and/or slower responses representing lapses in attention (Betts et al., 2006). As these are only at the adjusted trend level, it would be prudent to further test associations between schizotypy and attention performance, perhaps on higher demanding tasks.

In examining male and female performance separately, there were again mainly trend level associations between schizotypal features and CPT performance. These mainly occurred in the predicted manner, for example higher scores on UPE, a positive schizotypal feature, was associated with decreased sensitivity in males. Although this did not reach the adjusted significance level, there was a significant difference in coefficients on this subscale.
suggesting a differential effect between males and females. A significant association at the corrected level did occur between Suspiciousness and MAD, where increased variability was associated with higher scores in males. This increase in attentional dysfunction is also present in schizophrenia samples, where male patients had greater deficits compared to female patients on a battery of attention tasks (Goldstein et al., 1998). Suspiciousness loads on both positive and negative factors (Raine et al., 1994; Wuthrich and Bates, 2006), as well as possibly forming part of a separate paranoid factor (Stefanis et al., 2004a). This cross loading may partly explain some of the schizotypy literature that have found associations between CPT performance and positive/negative schizotypy (Chen et al., 1997; Chen et al., 1998a; Gooding et al., 2006).

4.2.2 Spatial Working Memory

There was no association between schizotypy and SWM performance in the total sample. When the sample was split into younger participants there was a significant association between increasing OBMI scores and decreasing BSES, and trend with decreasing WSES. The correlation coefficients were significantly different between younger and older participants for both performance measures. This indicates that some heightened positive symptom-like schizotypal features are associated with worse performance in younger adolescent samples. The younger group also had a trend correlation between SU and BSES. This supports findings where an association with negative schizotypal features have been found (Park and McTigue, 1997; Tallent and Gooding, 1999), but raises questions why it occurs only in the younger sample.

Research in clinical samples suggests patients with schizophrenia have less reliance on a searching strategy (Pantelis et al., 1997) which could be reflected by the reduced WSES in the current study. Furthermore increasing negative schizophrenia symptoms are correlated with decreased performance in patient samples (Piskulic et al., 2007). In considering the associations seen in younger participants, it is possible that heightened expression of schizotypal features could be associated with a delay in full cognitive development required for this task. Once adult levels of cognitive performance were attained, as was presumed in the older sample, the association between schizotypal features and performance was no longer evident. This is surprising given the association between spatial working memory and schizotypal features found in other studies, particularly in relation to positive symptoms (Park et al., 1995; Park and McTigue, 1997; Tallent and Gooding, 1999). To determine whether presence of schizotypal features has any longer-
term implications on SWM function, longitudinal studies spanning this developmental period could test the stability of these interactions between schizotypy and cognition. Further data from specifically selected high schizotypes on greater controlled spatial working memory tasks would help to determine whether there is a genuine effect and how developmental stage could mediate this.

In examining associations in male and female samples, there was a significant association in males OEB score and SWM performance (although corrected trend level only for WSES). This was again in the unexpected direction of higher scores associated with increased performance. There was also a significant difference between male and females performance in relation to OEB. The predicted direction of increasing schizotypal and reduced performance was observed in females where trend level associations were found between performance and the subscales Odd Speech and Suspiciousness. These associations in females were not significantly different from those found in males.

4.3 Sex Differences in the Schizophrenia-Spectrum

It was predicted that males would have performance more prone to the effects of schizotypy than females. This was partly realised on the CPT with correlations between schizotypy performance in males, and significant different between male and female coefficients. The opposite was demonstrated on SWM with females only having negative associations between performance and schizotypy. From research in schizophrenia, males tend to have greater impairment on measures of attention, executive and verbal memory (Goldstein et al., 1998). However, there are often contradictory findings related to sampling and methodological reasons (Hoff and Kremen, 2002). In SPD samples, sex differences have also been observed, with males performing lower on reasoning and verbal learning tasks (Voglmaaier et al., 2005), whilst in relatives of patients, females have greater impairments than male counterparts (Kremen et al., 1997; Faraone et al., 1999). The authors suggest this may reflect a greater resistance to transition in females, hence worse functioning females are represented in a non-psychotic first degree relative sample (Kremen et al., 1997). Specifically in spatial working memory, male patients with a diagnosis of schizophrenia have been found to perform better on a strategy component of a task compared to female patients (Lecardeur et al., 2010). There was no comparison control group to determine whether these were below expected performance levels, although evidence suggests this is likely to be the case (Piskulic et al., 2007). The current
study may partially support these finding where increased schizotypy was associated with reduced SWM performance in females only.

Factors that could play a role in such sex differences could be biologically based. For example, there is ongoing brain development during the second and third decades with declining levels of grey mater, increasing white matter and greater connectivity in the brain, all of which are highly variable and sexually dimorphic (Asato et al., 2010; Lenroot and Giedd, 2006). Similarly, hormonal changes that occur during adolescence may trigger genes that confer risk to psychosis and other mental illnesses via ongoing brain development (Walker and Walder, 2003). The interaction between an at-risk developmental stage, heightened expression of subclinical symptoms and sex could have profound implications on additive risk for transition. Studies with individuals at high risk of transition to psychosis/schizophrenia suggest that females may require an additional ‘dose’ of risk, such as baseline neurocognitive impairment, for development of psychosis (Walder et al., 2008). The current study demonstrates that even in otherwise healthy populations, subtle cognitive performance differences are demonstrated in relation to schizotypy levels and sex. This may indicate differences in developmental trajectories in males and females and could mirror those seen in behavioural changes during this period (Spauwen et al., 2003). Due to the cross sectional nature of the study, it is not possible to state definitively how these interactions and trajectories develop. Longitudinal studies examining the relationship between schizotypal features, age, sex and cognition would provide vital information about this dynamic risk period.

4.4 Limitations and conclusion
The study had a number of limitations. Firstly, by placing the tasks on the internet we were unable to control the test environment, know whether the participant understood the task, provide additional instructions if required, or to monitor task behaviour. A partial solution was to remove outliers which is a common analytical procedure. Despite these limitations, there are benefits to using online experiments in terms of large samples sizes and potential for reducing motivational confounds (Reips, 2000). A second issue relates to the self-selecting population. Such convenience samples are common in schizotypy research and the ability to generalise findings may be limited. A third issue is the measurement of schizotypy in adolescent participants which may be difficult to differentiate from other factors during this period of intense biological and social change. Most schizotypy questionnaires will undoubtedly be measuring features including normal psychological
development (DiDuca and Joseph, 1999) and potentially other attenuated psychopathologies. Therefore, the extent to which it represents psychosis proneness exclusively is debatable. Fourthly, all of the significant correlations are considered small and are at risk of being type I errors. Measures to account for this were carried out by splitting the sample into two and examining associations in the total sample; whilst subsequent analyses of age and sex specific groups had reduced $\alpha$ levels of significance. Even so, the correlations were very weak and further studies would be necessary to corroborate the current findings. Finally, it is possible that the group did not contain individuals that could be deemed schizotypes. This seems unlikely though given the large sample size and inclusions of individuals with high SPQ scores. Additionally, subtle non-linear relationships may be present in the data which are difficult to identify via correlational analyses. An example of this is from a recent study investigating working memory, where participants scoring low on schizotypal measure were also found to have performance biases (Schmidt-Hansen and Honey, 2009). Alternative methods could involve the recruitment of extreme high scoring groups and compare to controls (either low or average scoring schizotypes), to maximise potential group differences.

In summary, there appears to be limited association between schizotypy and cognition in the current sample. Where associations are found, these are specific either to age or sex. In spatial working memory there may be a slight developmental delay in relation to positive schizotypal features as represented by Odd Beliefs/Magical Ideation. Sex differences were observed with males having CPT performance correlated with increased schizotypal features. Furthermore females were found to have correlations between SWM performance measures and Suspiciousness which loads onto both positive and negative schizotypal features definitions. Such specific sample effects could go some way to explaining the heterogeneity in the schizotypal/cognition literature.
Neuropsychological function and schizotypy: associations between schizotypy and verbal learning.
Neuropsychological function and schizotypy: associations between schizotypy and verbal learning.

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Abstract

\textbf{Introduction}: Cognitive deficits in schizophrenia are prevalent and could represent subtle abnormalities in brain function. Specifically, research has demonstrated performance deficits in cognitive tasks measuring function of the prefrontal and medial temporal regions. Schizotypy is a personality trait that shares some of the characteristics of more serious mental illness. It was hypothesised that given the relationship between schizotypy and schizophrenia, associations would be found between increased schizotypal features and deficits in tasks measuring prefrontal and medial temporal lobe function.

\textbf{Methods}: Participants were selected from an internet sample that completed the Schizotypal Personality Questionnaire (SPQ). Selected participants ($n=109$) completed a battery of tests examining performance on attention, executive and verbal learning/memory function. Correlational analyses were conducted to investigate association between schizotypal levels and cognitive performance.

\textbf{Results}: Schizotypy was not significantly associated with performance on measures of attention or executive function. Higher SPQ scores were associated with reduced performance on verbal learning immediate recall.

\textbf{Conclusions}: The evidence suggests that in the current study elevated schizotypal levels are not associated with changes in prefrontal functioning. The association found between increasing schizotypy and reduced verbal learning performance could be indicative of a subtle change in medial temporal lobe function. The results are discussed within the wider literature.
1. Introduction

Cognitive deficits are a core feature of schizophrenia (Fioravanti et al., 2005; Heinrichs and Zakzanis, 1998); are present prior to the onset of the disorder (Brewer et al., 2005), and detectable in relatives of patients with schizophrenia (Sitskoorn et al., 2004; Snitz et al., 2006). Measures of cognition such as those tapping executive function and memory are reliant on prefrontal and medial temporal brain regions (e.g. Carpenter et al., 2000; Eisenberg and Berman 2010; Paller and Wagner, 2002). Along with deficits in performance, patients with schizophrenia are also found to have differences in regional brain activation (e.g. Glahn et al., 2005; Minzenberg et al., 2009). Both cognitive and functional imaging studies have helped in characterising the pathophysiology of schizophrenia, namely that medial temporal and prefrontal regions are particularly susceptible regions. Siever and Davis (2004) examined the similarities between schizotypal personality disorder (SPD) and schizophrenia. They proposed that although temporal cortical structure/function was impaired across groups, there was partial sparing of prefrontal brain volume and function in SPD groups. This suggests that ‘milder’ forms may possess biological or psychosocial protective factors that manifest in less compromised prefrontal regions (Siever and Davis, 2004).

Complimentary studies in analogue samples have shown that cognitive deficits exist further along the continuum of schizophrenia, being detectable in people from the healthy general population who express schizotypal traits (Chen et al., 1998; Park et al., 1995). Schizotypy is a normally distributed trait of psychosis liability which comprises attenuated psychotic symptoms and unusual beliefs, as well as negative like symptoms such as social withdrawal (e.g. Esterberg and Compton, 2009). Schizotypal individuals can be identified via psychometric measures in the general population; are linked to more clinical criteria such as SPD (see Raine, 2006); and represent a risk-state for schizophrenia-spectrum disorder (e.g. Gooding et al., 2005). The schizotypal trait provides a means of exploring the mechanisms underpinning risk factors for schizophrenia and psychotic symptoms (Cadenhead and Braff, 2002; Lenzenweger, 2006).

Given that cognitive deficits are found in clinical samples and along the extended phenotype, it suggests they contribute towards the risk for serious mental illness and are inextricably linked with the biological/genetic risk factors which confer vulnerability for conditions such as schizophrenia. The investigation of cognitive deficits in patients with schizophrenia is often confounded by heterogeneity of disease, antipsychotic use, multiple
and distracting symptomatology (Hori et al., 2006). These confounds, particularly exposure to antipsychotic medication, are less prevalent in schizotypal samples and hence represent a relatively ‘clean’ sample for investigation.

The effects of schizotypy have been demonstrated in various cognitive domains such as sustained attention (Chen et al., 1998; Chen et al., 1997; Lenzenweger et al., 1991), spatial working memory (Park and McTigue, 1997; Tallent and Gooding, 1999) and executive function (Bedwell et al., 2006; Lin et al., 2000; Suhr and Spitznagel, 2001), although verbal learning/memory appears to be spared (LaPorte et al., 1994; Lenzenweger and Gold, 2000, Ruíz et al., 2008). (See General Introduction Section 1.4 for further information). On the basis of this evidence, schizotypal samples may share similar deficits in prefrontal brain function to clinical samples. However, mixed findings are present in the schizotypal literature; for example sustained attention and executive function deficits are not always observed (e.g. Cohen et al., 2006; Spitznagel and Suhr, 2002).

The lack of effect of schizotypy on medial temporal function as measured by verbal learning/memory tasks is surprising given the extent of impairment in clinical samples (e.g. Rushe et al., 1999; Saykin et al., 1991). Differences in study protocol may account for these findings, since there is little continuity in studies designed to examine verbal learning/memory. For instance, experimental designs have categorised samples on either positive or negative symptoms (e.g. Jahshan and Seri, 2007; Lenzenweger and Gold, 2000), or correlational analyses have only included individuals with low levels of schizotypal features (e.g. Noguchi et al., 2008).

**Study rationale**

The current study investigates the association between schizotypal features as measured by the Schizotypal Personality Questionnaires (SPQ: Raine 1991) and a battery of cognitive tasks in 16-25 year olds. A previous study investigated the relationship between schizotypy and performance on sustained attention and spatial working memory tasks in a large internet survey (Paper 2) with limited associations found. The current study extends this research by testing a further battery of tasks in controlled laboratory conditions. We hypothesize that as schizotypy is part of the extended phenotype for schizophrenia the cognitive deficits reported in patients with schizophrenia will be mirrored by associations between increasing schizotypal features and impaired performance. We will focus on tasks
reliant on prefrontal and temporal lobe function, including measures of attention, executive function and verbal learning/memory.

As noted, mixed findings are prominent in schizotypal studies which in part could be due to the categorisation of participants by symptoms type (i.e. positive/negative). Therefore, an aim of the study is to examine the correlations between symptoms as measured by the 9 SPQ subscales and task performance. From previous literature, evidence supports an association with both positive/negative features and cognitive performance. Even in specific domains such as sustained attention an association with both positive and negative schizotypal features has been demonstrated (e.g. Bedwell et al., 2006; Chen et al., 1997; Gooding et al., 2006). Specific predictions are as follows:

**Attention: Selective, Divided and Sustained.**

1. Decreased task performance on all tasks will be correlated with schizotypal features.
2. Since there is evidence for links between both positive and negative schizotypal features and performance on attention tasks (Chen et al., 1997; Chen et al., 1998a; Gooding et al., 2006), significant correlations will be present for subscales measuring positive and negative schizotypal features.

**Executive Function: digit span backwards (DSB), Trails B, verbal fluency.** There is less evidence linking executive function and schizotypal features (Laws et al., 2008; Matheson and Langdon, 2008; Spitznagel and Suhr, 2004; Suhr and Spitznagel, 2001),

3. Therefore, significant correlations between schizotypal features and performance will be observed, but of lower magnitude than those with attention tasks.
4. In line with previous studies (Dinn et al., 2002), it is predicted that associations will be found between subscales measuring negative features and Trails B performance.
5. Similarly for verbal fluency, in line with previous studies (Tsakanikos and Claridge, 2005), reduced performance will be associated with negative schizotypal features.

**Verbal learning/memory.** Based on consistent findings in clinical studies with schizophrenia patients, it is hypothesised that schizophrenia is associated with disrupted medial temporal lobe function. Therefore it is predicted that:
Decreased performance on measures of verbal learning/memory will be associated with increased schizotypal features.

Since there are few consistencies in schizotypal studies assessing verbal learning/memory, it is unclear which schizotypal features will be associated with performance. Based on negative findings into studies examining effects of positive schizotypal features (LaPorte et al., 1994; Lenzenweger and Gold, 2000), it is predicted that any association will be found with non-positive schizotypal features.

2. Methods
2.1 Participants
Participants were recruited from a large internet sample examining the relationship between schizotypy and cognition (Paper 2). Participants were originally recruited from universities, colleges, and businesses in North West England. The colleges were representative of the general North-West metropolitan region. For detailed description of the sample see Methodology Chapter (MC) Sections 2.3-2.4 (Pg. 90). An inclusion criterion was fluency in English so as to ensure comprehension of the SPQ and cognitive task instructions.

Participants completed a cognitive test battery (current study) and measures of lateralised brain function (Paper 4). One hundred and nine participants were recruited with average age 19.07 (2.63), with 32 males.

2.2 Procedure
Further details of the procedure can be found in the MC Section 2.6 (Pg. 100).

Cognitive Testing was conducted in a purpose built test laboratory at the University of Manchester, or for college students in a psychology test laboratory on college premises. All participants were tested by the same researcher (RPS). Prior to testing, the participant was provided with the information sheet and the opportunity to ask questions. Informed consent was obtained. All participants were screened for Axis I diagnoses via the Mini International Neuropsychiatric Interview (MINI: Lecrubier et al., 1997). Any participants with current or past history of Axis I disorders were excluded. Five participants were excluded due to meeting criteria for major depressive episode. Other exclusion criterion was a history of head trauma with loss of consciousness.
The test battery took approximately 90 minutes to complete. The order of the tasks was consistent for each participant (see MC Pg.101). Once the test battery was completed the participant was debriefed and paid £20 for travel expenses. Ethical approval for the study was received from the University of Manchester Senate Ethics Committee.

2.3 Measures
For each measure, further information is provided in the MC Section 2.6.2 (Pg. 102) including rationale for task choice, task instructions/procedure, and normality of data.

Schizotypy Personality Questionnaire (SPQ)
The SPQ (Raine, 1991) is a 74-item dichotomous (yes/no) questionnaire based on the DSM-III-R criteria for SPD (American Psychiatric Association, 1984). It is a multidimensional measure that comprises 9 subscales that cover schizotypal features as defined by DSM-III-R. The 9 subscales are Ideas of References (IoF), Excessive Social Anxiety (ESA), Odd Beliefs/Magical Ideation (OBMI), Unusual Perceptual Experiences (UPE), Odd or Eccentric Behaviour (OEB), No Close Friends (NCF), Odd Speech (OS), Constricted Affect (CA), and Suspiciousness (SU). The SPQ has high internal reliability (0.9-0.91), test-retest reliability (0.82), convergent validity (0.81 with Schizotypal Personality Scale: Claridge and Broks, 1984), and criterion validity (55% scoring in top 10% have SPD) (Raine, 1991).

Weschler Abbreviated Scale of Intelligence (WASI) (see MC Section 2.6.2.1 Pg. 102)
The WASI is a normalised and shortened form of both the WISC-III (Wechsler Intelligence Scale for Children-Third Edition: Weschler, 1991) and WAIS-III (Wechsler Adult Intelligence Scale-Third Edition: Weschler, 1997). The two subtest version was used: matrix reasoning and vocabulary, which produce a full scale intelligent quotient (FSIQ-2). Correlations between FSIQ-2 and task performance are calculated and where significant added as a covariate.

Selective and Divided Attention (see MC Section 2.6.2.2 Pg. 103)
Two subtests from the Test of Everyday Attention (TEA) (Robertson et al., 1994) were employed to measure selective and divided attention: the Telephone Search Subtest and the Telephone Search While Counting subtest respectively.
In the Telephone Search subtest the participant was required to search for 20 symbol pairs amongst 108 distracters as quickly as possible. Performance measure was the time taken to complete the task divided by the number of correctly identified pairs. Lower values represent better performance. For the measure of divided attention, participants performed The Telephone Search subtest whilst simultaneously counting a series of tones. Performance measure was the dual task decrement score calculated from the number of correctly identified symbol pairs, the time taken to complete the task, and the successful counting of tones. Lower values represented better performance.

**Sustained Attention: The Rapid Visual Processing (RVP) Task (see MC Section 2.6.2.3 Pg. 104)**

The Rapid Visual Processing Task (RVP) (Sahakian et al., 1989) is a computerised task that measures visual sustained attention. It is a modified version of the continuous performance task (CPT-AX). A series of numbers are presented on screen at a rate of 100 digits per minute. When a target sequence of digits had been observed, the participant responds with a keyboard press within 1800ms. The three sequences were 3-5-7, 2-4-6 and 4-6-8. To minimise memory load, the three sequences were always displayed on screen. The participant had the opportunity to practise before the test trial. Performance measure was d’ (sensitivity), calculated from errors of omission (missed targets) and commission (responding when no target). Data is missing for four participants due to computer hardware failure during task completion.

**Verbal Fluency (FAS) (see MC Section 2.6.2.4 Pg. 106)**

The verbal fluency task (FAS) (Borkowski et al., 1967) is a measure of phonemic fluency. In this task the participant was required to name as many words beginning with either F, A or S in one minute. The only restrictions on the type of words were proper nouns and derivatives of the same word. Performance outcome was the total number of words generated over the three trials.

**Working memory: Digit Span Backwards (DSB) (see MC Section 2.6.2.5 Pg. 107)**

The well known digit span backwards subtest from the WAIS-III (Weschler, 1997) was used. In this task participants are read aloud to a string of digits (increasing in difficulty from 3-7 digits). The participant then repeats the sequence backwards. The total number of
digits recalled accurately was recorded as their score. Data is missing for four participants due to non-completion of this task.

**Cognitive Flexibility: Trails-B - Delis-Kaplan Executive Function System (D-KEFS) (see MC Section 2.6.2.6 Pg. 108)**

The Trails B is a well established measure of executive function, or more specifically, cognitive flexibility. The participant was presented with an A3 piece of paper with numbers and letters. They were required to connect up the numbers and letters in alternating sequence until reaching the end point (i.e. 1 – A – 2 – B etc). They were asked to complete the task as quickly as possible with the time to completion taken as the performance outcome.

**Verbal Learning/Memory: Paired Word Association Learning Task (PWALT) (see MC Section 2.6.2.7 Pg. 108)**

The PWALT is a subtest from the Weschler Memory Scale – Revised (Weschler, 1987). A list of 8 word pairs was read aloud to the participant, and they had to recall the second word of the pair in response to the first word. Half of the word pairs are considered EASY word pairs (e.g. BABY-CRIES) or semantically related; and half are HARD (e.g. CRUSH-DARK) or unrelated words. The first word of each word pair was then presented and the participant asked which word it was paired with. Incorrect responses were corrected. This procedure was repeated 3 times and the total score over the 3 trials (maximum = 24) was recorded as the measure of verbal learning (immediate recall). Without warning, 30 minutes later the participants were again tested for their memory of the word pairs, yielding a measure of delayed recall (max=8).

**2.4 Data analysis**

Data was analysed with SPSS (v.15). Means, standard deviations and data normality were assessed for each variable. Values of skewness and kurtosis were examined along with the distribution curves (see MC Section 2.6.3 Pg. 112 for values). The strength of associations between schizotypal features and performance measures were assessed via Pearson product-moment correlations or Spearman Rank correlations depending on normality of variables. Correlations were calculated between total SPQ/9 subscales and each task performance. In analyses where FSIQ-2 and age correlated with task performance, these were added as covariates where possible (normally distributed variables) to calculate partial correlation coefficients. Sex was also added as a covariate. In consideration of correcting for multiple correlations, the significance α level was set at 0.01, with trend
level at 0.05. Due to large ceiling effects on PWALT delayed, student $t$-tests and Mann Whitney $U$ tests were used to compare SPQ total/subscale scores between those with and without maximal task performance.

3. Results

3.1 Sample characteristics, SPQ scores and task performance

Tables 1 lists age, SPQ total/subscale scores for the total sample. Total SPQ and the subscales IoF, UPE, and OS were normally distributed, whereas ESA, OBMI, OEB, NCF, and CA were not. The sample comprised 109 participants with 77 females. There was a significant difference in age between males and females (Male $M$ 20.75 ($SD$ 2.91) Vs Female $M$ 19.56 ($SD$ 2.50); $t(107) = 1.98, p < 0.05$). There was no significant difference in total SPQ score (Male $M$ 34.72 ($SD$ 13.11) Vs Female $M$ 31.61 ($SD$ 15.14); $t(107) = 1.01, p = 0.31$), but males did have higher scores on NCF and CA ($t(107) = 3.20, p < 0.01$; and $t(107) = 2.34, p < 0.05$ respectively). Table 2 lists performance for the total sample on each cognitive task.

**Table 1:** Mean (SD) age, SPQ total and subscale score for total sample.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Total SPQ</th>
<th>IoF</th>
<th>ESA</th>
<th>OBMI</th>
<th>UPE</th>
<th>OEB</th>
<th>NCF</th>
<th>OS</th>
<th>CA</th>
<th>SU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19.91</td>
<td>32.52</td>
<td>4.46</td>
<td>4.83</td>
<td>2.01</td>
<td>3.55</td>
<td>3.62</td>
<td>2.83</td>
<td>5.45</td>
<td>2.29</td>
<td>3.55</td>
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<tr>
<td></td>
<td>(2.67)</td>
<td>(14.58)</td>
<td>(2.80)</td>
<td>(2.49)</td>
<td>(2.08)</td>
<td>(2.35)</td>
<td>(2.56)</td>
<td>(2.41)</td>
<td>(2.27)</td>
<td>(1.89)</td>
<td>(2.63)</td>
</tr>
</tbody>
</table>

**Table 2:** Cognitive task performance for the total sample

<table>
<thead>
<tr>
<th>Task</th>
<th>Total Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEA selective attention</td>
<td>n=109</td>
</tr>
<tr>
<td></td>
<td>2.42 (0.49)</td>
</tr>
<tr>
<td>TEA divided attention</td>
<td>n=101</td>
</tr>
<tr>
<td></td>
<td>0.26 (0.40)</td>
</tr>
<tr>
<td>RVP d’</td>
<td>n=105</td>
</tr>
<tr>
<td></td>
<td>2.92 (0.68)</td>
</tr>
<tr>
<td>FAS total</td>
<td>n=109</td>
</tr>
<tr>
<td></td>
<td>38.74 (10.71)</td>
</tr>
<tr>
<td>DSB</td>
<td>n=105</td>
</tr>
<tr>
<td></td>
<td>5.23 (1.28)</td>
</tr>
<tr>
<td>Trails B</td>
<td>n=109</td>
</tr>
<tr>
<td></td>
<td>55.19 (16.28)</td>
</tr>
<tr>
<td>Verbal Learning - Immediate</td>
<td>n=109</td>
</tr>
<tr>
<td></td>
<td>21.10 (3.02)</td>
</tr>
<tr>
<td>Verbal Learning – Recall</td>
<td>n=109</td>
</tr>
<tr>
<td></td>
<td>7.74 (0.71)</td>
</tr>
</tbody>
</table>
3.2 Correlations between SPQ and cognitive performance

Graphs of cognitive performance and SPQ scores were plotted to check for non-linearity in the data. See Appendix 6 for plots of TEA selective and divided attention, RVP d’, FAS total, and Trails B, against total SPQ/subscale scores. Plots were not produced for DSB or Verbal Learning/Memory Immediate or Recall due to non-normality of these performance measures. From inspection of the scatter plots, there were no obvious signs of non-linear relationships between variables thus allowing correlational analyses.

Attention

See Table 3 for all correlations between SPQ scores and attention performance measures. For selective attention, FSIQ-2 correlated with performance ($r(107) = -0.25, p < 0.05$), so therefore added as a covariate where possible. There were no associations between selective attention performance and Total SPQ or subscale scores. Partial and Spearman correlations for divided attention are reported in Table 3. There was no association between SPQ scores and divided attention. For RVP d’, both age and FSIQ-2 correlated with performance ($r(105) = 0.22, p < 0.05$; and $r(105) = 0.39, p < 0.001$ respectively) so added as covariates where possible. There was a trend level (corrected at $p < 0.05$) negative correlation between OBMI and RVP d’. This indicates higher scores on this subscale are associated with lower levels of sensitivity.

Executive Function

See Table 3 for all correlations between SPQ scores and executive performance measures. For FAS total, age and FSIQ-2 correlated with performance ($r(107) = 0.25, p < 0.01$; and $r(107) = 0.42, p < 0.001$ respectively) so were added as covariates. There was no association between SPQ scores and FAS total. There were no significant association between DSB performance and SPQ scores. Trails B performance correlated with FSIQ-2 ($r(107) = -0.40, p < 0.001$) so added as a covariate. There was no association between SPQ scores and Trails B performance.

Verbal Learning/Memory

The data was not normally distributed for immediate recall, so Spearman rank correlations were calculated. See Table 3 for Spearman correlations. Total SPQ, OS, and NCF subscales scores were all significantly (corrected at $p < 0.01$) negatively correlated with immediate recall performance. This equated to fewer words remembered being associated with higher scores on total SPQ and aforementioned subscales. There were also trend level
(\(p < 0.05\)) negative correlations between performance and OBMI, CA and SU subscale scores.

In the delayed condition the SPQ total and subscales scores were compared between those with maximum performance (\(n=92\)) and those with at least 1 error (\(n=17\)). Table 4 lists SPQ scores and group comparison test statistics. Those that did not have perfect performance on the delayed recall had lower scores on the SU subscale only.

**Table 3:** Correlation coefficients between Total SPQ and its 9 subscales and cognitive performance. Some are partial correlations (controlling age and/or FSIQ-2), and some are Spearman rank correlations (see text).

<table>
<thead>
<tr>
<th></th>
<th>Attention</th>
<th>Executive Function</th>
<th>Verbal Learning/ memory immediate recall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Selective Attention a</td>
<td>Divided Attention a</td>
<td>Sustained attention a</td>
</tr>
<tr>
<td>Sample size</td>
<td>Sample size: n=109</td>
<td>n=101</td>
<td>n=105</td>
</tr>
<tr>
<td>SPQ Total a</td>
<td>0.00</td>
<td>-0.03</td>
<td>-0.07</td>
</tr>
<tr>
<td>IOF a</td>
<td>-0.09</td>
<td>0.01</td>
<td>0.03</td>
</tr>
<tr>
<td>UPE a</td>
<td>0.03</td>
<td>-0.06</td>
<td>-0.06</td>
</tr>
<tr>
<td>OS a</td>
<td>-0.01</td>
<td>0.02</td>
<td>-0.10</td>
</tr>
<tr>
<td>ESA b</td>
<td>-0.01</td>
<td>0.06</td>
<td>0.00</td>
</tr>
<tr>
<td>OBMI b</td>
<td>0.08</td>
<td>-0.04</td>
<td>-0.21 *</td>
</tr>
<tr>
<td>OEB b</td>
<td>0.01</td>
<td>-0.07</td>
<td>-0.03</td>
</tr>
<tr>
<td>NCF b</td>
<td>-0.04</td>
<td>-0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>CA b</td>
<td>0.06</td>
<td>-0.17</td>
<td>-0.05</td>
</tr>
<tr>
<td>SU b</td>
<td>-0.03</td>
<td>0.03</td>
<td>-0.12</td>
</tr>
</tbody>
</table>

\(a\) – Normally distributed; \(b\) – Not normally distributed. For normally distributed rows and columns (a), Pearson Product Moment correlations are reported. Where either a row and/or column has non-normally distributed data (b), Spearman rank correlations are reported. \(* p < 0.05, ** p < 0.01\)
Table 4: Total SPQ/subscale scores in those that did and did not have errors on the delayed recall. Student $t$-tests and Mann Whitney $U$ tests are reported for group comparisons.

<table>
<thead>
<tr>
<th>Sample size</th>
<th>No Mistakes</th>
<th>Mistake (1-4)</th>
<th>Test statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>92</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>SPQ Total</td>
<td>31.40</td>
<td>38.59</td>
<td>$t = -1.89$</td>
</tr>
<tr>
<td></td>
<td>(14.73)</td>
<td>(12.46)</td>
<td></td>
</tr>
<tr>
<td>IOF</td>
<td>4.40</td>
<td>4.76</td>
<td>$t = 0.49$</td>
</tr>
<tr>
<td></td>
<td>(2.88)</td>
<td>(2.36)</td>
<td></td>
</tr>
<tr>
<td>UPE</td>
<td>3.46</td>
<td>4.06</td>
<td>$t = -0.97$</td>
</tr>
<tr>
<td></td>
<td>(2.37)</td>
<td>(2.22)</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>5.39</td>
<td>5.76</td>
<td>$t = 0.62$</td>
</tr>
<tr>
<td></td>
<td>(2.28)</td>
<td>(2.28)</td>
<td></td>
</tr>
<tr>
<td>ESA</td>
<td>4.66</td>
<td>5.71</td>
<td>$U = 612$</td>
</tr>
<tr>
<td></td>
<td>(2.52)</td>
<td>(2.20)</td>
<td></td>
</tr>
<tr>
<td>OBMI</td>
<td>1.95</td>
<td>2.35</td>
<td>$U = 617$</td>
</tr>
<tr>
<td></td>
<td>(2.16)</td>
<td>(1.58)</td>
<td></td>
</tr>
<tr>
<td>OEB</td>
<td>3.49</td>
<td>4.35</td>
<td>$U = 612$</td>
</tr>
<tr>
<td></td>
<td>(2.59)</td>
<td>(2.37)</td>
<td></td>
</tr>
<tr>
<td>NCF</td>
<td>2.63</td>
<td>3.94</td>
<td>$U = 554$</td>
</tr>
<tr>
<td></td>
<td>(2.34)</td>
<td>(2.59)</td>
<td></td>
</tr>
<tr>
<td>CA</td>
<td>2.18</td>
<td>2.88</td>
<td>$U = 603$</td>
</tr>
<tr>
<td></td>
<td>(1.88)</td>
<td>(1.87)</td>
<td></td>
</tr>
<tr>
<td>SU</td>
<td>3.33</td>
<td>4.76</td>
<td>$U = 528 *$</td>
</tr>
<tr>
<td></td>
<td>(2.64)</td>
<td>(2.31)</td>
<td></td>
</tr>
</tbody>
</table>

* $p < 0.05$

4. Discussion

It was hypothesised that increasing schizotypal features would be associated with impaired cognitive function. This was only partly confirmed in the current study where increased schizotypal features were associated with a slight reduction in performance on the verbal learning task. As predicted this was associated with non-positive schizotypal features. There were however, no significant associations between schizotypy and performance on attention or executive tasks.

Verbal learning/memory

There were significant associations between total SPQ score and verbal learning immediate recall. Furthermore there were significant associations between performance and the subscales Odd Speech and No Close Friends, and trend level associations with Excessive Social Anxiety and Odd Beliefs/Magical Ideation. The OS subscale exclusively loads on to disorganised dimensions in factor analyses, whereas ESA loads predominantly onto negative schizotypal dimensions (Raine et al., 1994; Stefanis et al., 2004a; Wuthrich and Bates, 2006). In addition, on the delayed component of the verbal learning task, those that did not score perfectly were found to have significantly higher scores on the Suspiciousness subscale, again tending to load onto negative factors. However, given the
ceiling effects on this performance measure, caution must be taken in terms of delayed verbal memory ability.

The association found for immediate recall appears in contrast to other studies where no effects of schizotypy have been found on verbal memory function (Jahshan and Sergi, 2007; Lenzenweger and Gold, 2000; Noguchi et al., 2008; Simons et al., 2007). As alluded to in the introduction, this discrepancy with previous literature could in part be explained by methodological heterogeneity found in the schizotypy literature. First, Noguchi and colleagues (2008) used a relatively low scoring sample in their correlation of SPQ scores with task performance. The mean SPQ score of their sample was 11 which is lower than mean values suggested in the SPQ online manual (23.5-26.4) (http://www-bcf.usc.edu/~raine/spqrel.html). The current study had a mean total SPQ score of 32, including those scoring average to high on presence of schizotypal features (See MC Section 2.4 Pg. 91 for comparison of sample SPQ scores compared to the literature). It is possible that for the detrimental effects of schizotypal features to be observed, a larger ‘dose’ is required. Secondly, other studies have focussed specifically on attenuated positive symptoms such as Lenzenweger and Gold (2000). Neither their study, nor the current study, found any significant association with positive features, although the current study did find a trend negative correlation with OBMI, a subscale that loads onto positive factors (Raine et al., 1994; Stefanis et al., 2004a). This suggests that the association between task performance and schizotypy is predominantly related to negative and disorganised features. In another study that examined negative schizotypal features as measured by the Community Assessment of Psychic Experiences (CAPE: Stefanis et al., 2002), performance on the Auditory Verbal Learning Task (AVLT) was not correlated in a large sample of twins (Simons et al., 2007). As these participants were not selected due to their heightened scores, it is again indicative that performance deficits are only associated with relatively high levels of schizotypal features. Finally, a recent study found no performance differences in group comparisons between high and low total SPQ (-Brief) scoring groups on the California Verbal Learning Task (CVLT) (Jahshan and Sergi, 2007). This could be related to the selection of a control group. For example, on working memory tasks, there is evidence that very low levels of schizotypy, particularly negative features, also have performance deficits (Schmidt-Hansen and Honey, 2009). This could suggest a non-linear relationship between schizotypy and verbal learning/memory. The current study mainly sampled individuals scoring average to high on the SPQ, so the presence of low scorers with potentially their own set of performance biases, did not impact upon the correlational
analyses. Future studies could target specific high, low and control groups, to examine this relationship further.

In summarising the schizotypal literature on verbal learning/memory, there is minimal directly comparable data to the current study. Therefore, it is not possible to state definitively whether schizotypy is associated with verbal learning/memory performance. Deficits in performance are not unexpected, however, given their prominence across the schizophrenia continuum. For instance, they have been observed in patients with a diagnosis of schizophrenia (Rushe et al., 1999; Saykin et al., 1991), adolescent patients (Landro and Ueland, 2008), relatives (Sitskoorn et al., 2004), and schizotypal personality disorder (SPD) (Bergman et al., 1998; Voglmaier et al., 2000). A recent study sought to compare performance on a battery of neuropsychological tasks between three groups: individuals at high-risk for transition to schizophrenia/psychosis; those perceived at an earlier risk stage due to presence of subtle self-reported deficits in thought, cognition and perception (basic symptoms); and controls (Fromman et al., 2010). The high-risk group were significantly impaired on the overall performance measure of the auditory verbal learning test (AVLT) compared to the earlier risk group and controls, but the early risk group also had reduced ability on the encoding stage of the task (verbal learning). The current study is reminiscent of this. Encoding ability could represent a ubiquitous marker on the schizophrenia continuum ranging from relatively severe impairment in schizophrenia, through to subtle performance biases associated with heightened schizotypal features.

Imaging studies have identified prefrontal brain regions including the dorsolateral prefrontal cortices (DLPFC) as critical in encoding and retrieval in paired-word associate tasks (Sandrini et al., 2003; Schmidt et al., 2002). These areas are functionally connected to the limbic system, including the hippocampus (Dickerson et al., 2007), via large fronto-temporal association fibre such as the uncinate fasciculus (Asato et al., 2010). In accordance, the hippocampus has also been shown to be involved in encoding (Paller and Wagner, 2002). These regions have all been shown to have altered function/structure in schizophrenia samples (Jessen et al., 2003; Karlsgodt et al., 2008; Kubicki et al., 2002; Potkin et al., 2009). The negative symptoms of schizophrenia have also been shown to correlate with decreased activation in functional imaging (Wolkin et al., 1992) and decrease in white matter connectivity (Wolkin et al., 2003). Therefore it is possible that
subtle functional and structural changes could account for both the negative symptomatology and impairments in verbal learning/memory.

**Attention**

No significant association was found between any attention measure and SPQ scores, although there was a trend level association between the Odd Beliefs/Magical Ideation and sustained attention. With respect to selective attention, this supports recent findings that have failed to find impairments on negative priming tasks (Cimino and Haywood, 2008; Moritz and Andresen, 2004), despite earlier work suggesting the presence of impairment (Beech and Claridge; 1987, Peters *et al.*, 1994). Selective attention deficits could represent a genetic marker for risk rather than being associated with schizotypal traits per se (e.g. Laurent *et al.*, 2000). Divided attentional deficits have been observed in clinical samples (Daban *et al.*, 2005), which are independent of memory impairments (Oram *et al.*, 2005), with effect sizes greater than those of sustained and selective attention (Tyson *et al.*, 2008). For successful task completion, dual processing of visual and auditory stimuli occurs at an integrative central level rather than individual processing at the peripheral visual/auditory level (Bonnel and Hafter, 1998), even though multiple brain regions are involved (Anderson *et al.*, 2007; Hein *et al.*, 2007; Szameitat *et al.*, 2002). Rather than a global deficit, the effects of schizotypy may be specific to certain regions/processes, hence cognition that is reliant on multiple brain regions could possess a degree of compensatory function.

Deficits in sustained attention as measured by various CPT versions are a relatively robust finding in the schizotypy literature; including the CPT-AX (Bedwell *et al.*, 2006; Chen *et al.*, 1997) and identical pairs (CPT-IP) (Gooding *et al.*, 2006; Lenzenweger *et al.*, 1991; Obiols *et al.*, 1993; Rawlings and Goldberg, 2001). In the current study, the RVP, a modified version of CPT-AX, was used to assess sensitivity, but only a trend association was found in relation to OBMI scores, a subscale that loads almost exclusively on positive schizotypal factors (Raine *et al.*, 1994; Stefanis *et al.*, 2004a; Wuthrich and Bates, 2006). The use of the RVP in schizotypal samples is a novel application of this task, although comparable to of the CPT-AX. In studies where significant impairments have been observed, these were utilising degraded-stimulus versions (e.g. Bedwell *et al.*, 2006), and even then, the deficit are not always found (Bedwell *et al.*, 2009; Cohen *et al.*, 2006). Impaired RVP performance is observed in pre-psychotic individuals (Bartok *et al.*, 2005) and schizophrenia patients (Cattapan-Ludewig *et al.*, 2005). Successful task completion
relies on visual processing, attention and working memory. There is the implication, therefore, that impaired working memory could account for the deficit in sustained attention (Gooding et al., 2006). In the current study, the effects of working memory were minimised by presenting the sequence on screen at all times. As working memory has been found to be dysfunctional in high schizotypy samples (Schmidt-Hansen and Honey, 2009), where associations with CPT performance has found, this could be related to working memory function. However in the current study, working memory performance as measured by the digit span was not found to be associated with schizotypal levels. Higher demand versions are known to place greater reliance on other cognitive processing (Borgaro et al., 2003). Future studies investigating sustained attention deficits via high demand CPTs could benefit by co-varying working memory function.

**Executive function**

No association was found between any executive task and SPQ scores. Executive function does appear to be relatively spared in schizotypal samples. Verbal fluency performance deficits have been demonstrated in adolescent samples categorised by positive and negative features (Barrantes-Vidal et al., 2002), but not replicated in an adult community sample (Dinn et al., 2002). In another study, a sample categorised on high negative symptoms produced fewer words, whereas high positive symptoms were in fact associated with a greater number of words produced suggesting a differential effect of type of schizotypal feature (Tsakanikos and Claridge, 2005).

No association between schizotypy and digit span backwards was found. Other studies have also failed to find an association in adolescents (Barrantes-Vidal et al., 2002) or adults (Spitznagel and Suhr, 2004), including those selected specifically on negative schizotypal features (Cohen et al., 2006). Other working memory tasks including the n-back have found an association with positive symptoms on decreased performance (Schmidt-Hansen and Honey, 2009), as well as spatial working memory performance impairments found in association with negative features (Park and McTigue, 1997; Tallent and Gooding, 1999).

Finally, evidence is limited on the association between Trails B performance and schizotypal features in adult (Matheson and Langdon, 2008; Spitznagel and Suhr, 2004) and adolescent samples (Barrantes-Vidal et al., 2002). One study which compared low, median and high negative schizotypal groups, found the low group were associated with a
quicker completion time (Dinn et al., 2002). In the current study there was a focus on average to high schizotypy scores, so non-linear relationships involving low scoring individuals may not have been captured in the analysis.

**Schizotypy and cognition**

In summarising, there is limited association between schizotypy and cognition in the current sample, disconfirming the study hypotheses. In some domains this confirms some of the wider literature, particularly executive processing. A tentative explanation for the current results is that there are perhaps specific structural/functional brain regions that are associated with schizotypal features, for example those involved in verbal learning/memory. Other cognitive processes that rely on alternate brain regions, or higher functioning processes reliant on multiple regions, could be buffered by compensatory mechanisms. Whereas the clinical disorders have a global level of impairment, schizotypes are intermediate, so only mild performance biases/deficits are observable. One possibility is that tasks that are reliant predominantly on prefrontal function (i.e. executive and attention task) are relatively spared in schizotypal samples, whereas those requiring additional medial temporal regions such as verbal learning/memory may be more compromised. Such a proposition is in line with Siever and Davis’ (2004) theory that SPD patients could have genetic or environmental protective factors that result in less compromised frontal brain function compared to schizophrenia. Psychometrically defined schizotypes represent a shift further still from serious mental illness and hence may possess even more protection from prefrontal ‘pathology.’ Siever and Davis (2004) also point to comprised temporal lobe structure and function in both SPD and schizophrenia. This could be an initial site of dysfunction which schizotypes may also show subtle evidence for.

**Limitations**

The study has a number of limitations. Firstly, the study relied on self-report measures for assessing extent of schizotypal features. Although this enabled the sampling of a large number of participants in which to select candidates from, it would have been beneficial to utilise additional measures such as interview-based instrument to check the veracity of self-reported schizotypal features. The SPQ was re-administered at the test visit, but interview measures could have been used as a further screen participants. Secondly, future studies could focus on group comparisons. Although the current study contained high scoring individuals, there may have been a dilution effect due to those scoring average or below on the SPQ, along with potential subtle non-linear relationships in the data. It may
only be those with the highest levels of schizotypal features that have mild performance deficits, and only when compared to control groups are these relationships identified. Similarly the study may be underpowered to detect significant associations with performance. However in examining the correlation coefficients between schizotypy and performance on executive and attention measures, most are extremely small so unlikely to reach significance even with much larger sample sizes. Thirdly, it would have been worthwhile employing multiple tests of function to examine in greater detail the effects of schizotypy on specific cognitive domains. Some tasks also suffered from ceiling effects (i.e. verbal learning delayed recall) which limits the interpretation of the results. Given the time constraints, only a set number of tasks were feasible. Future work will investigate certain constructs more thoroughly with multiple tasks. Complimentary techniques such as brain imaging would also allow hypothesised neural correlates of performance to be examined. For example in schizotypy groups, functional magnetic resonance imaging tasks specific to prefrontal or temporal lobe function could be applied to investigate whether changes in functional activation occur. Fourthly, is the overrepresentation of female participants, which is a general issue in schizotypy studies. Given the possibility of dissociable effects of schizotypy on cognition in males and females (see Paper 2), it would have been informative to assess whether sex differences were found in the current sample. Sex was, however, controlled for in analyses where possible.

In conclusion, there were no significant association between schizotypy and executive or attentional function. There was an association between increasing schizotypal features and reduced performance on verbal learning/memory. Examinations of the brain structure/function in schizotypal samples as part of the extended schizophrenia phenotype could give insights in the pathophysiology of symptoms and cognitive deficits that are present across the schizophrenia continuum.
Paper 4

Visuospatial attention and schizotypy
Visuospatial attention and schizotypy

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Abstract

Introduction: It is suggested that changes in functional asymmetry are present in schizophrenia and related samples such as those scoring high on schizotypal features. For instance, positive schizotypy has been shown to be associated with a greater leftward bias on visuospatial attention tasks, whereas a rightward bias is found in those with heightened negative schizotypal traits. Furthermore, clinical disorders are thought also to arise due to miscommunication between brain hemispheres. The aim of the study was to examine the relationship between schizotypal features and visuospatial attention, and between schizotypy and corpus callosum function.

Methods: Adolescents and young adults (16-25 years) were invited from a large internet sample based on Schizotypal Personality Questionnaire (SPQ) scores. Selected participants (\(n=109\)) completed two measures of spatial attention: a manual Line Bisection task (left and right hands), and computerised pre-bisected (Landmark) judgement task. Furthermore, to assess whether hemispheric transfer of information, participants completed the crossed-finger localisation task (CFLT). Correlations were calculated between SPQ subscales and performance on the three tasks.

Results: All participants were associated with pseudoneglect (leftward bias) when completing the manual line bisection task with the left hand, and rightward bias when completing with the right hand. Higher scores on the No Close Friends subscale was correlated at a tend level (corrected \(p < 0.05\)) with an erring towards the centre when completing the Line Bisection left hand. On the Landmark Task, higher schizotypal score were associated with a greater left sided bias as predicted. No association between schizotypal and CFLT was found.

Conclusions: Increased schizotypal features were shown to be associated with a leftward bias on a computerised line bisection task. This right hemispace inattention was not due to schizotypy-related changes in interhemispheric transfer. The findings are discussed in theories relating positive-type schizotypal features to proposed imbalances in hemispheric function.
1. Introduction

There is substantial evidence that schizophrenia is associated with abnormal structural and functional hemispheric lateralisation which Crow, most notably, has argued is central to the aetiology of schizophrenia (Crow, 1990; Crow et al., 1989). Similarly, schizotypy appears to be associated with indices of disturbed lateralisation of function (see Lencz et al., 1995). This association has been demonstrated in studies using left and mixed handedness as the indicator of reduced cerebral asymmetry. A shift from dextrality has been found to be associated with heightened schizotypal features (Barnett and Corballis, 2002; Chapman and Chapman, 1987; Chen and Su, 2006; Kim et al., 1992; Poreh et al., 1997; Shaw et al., 2001), although not always demonstrated (e.g. Jaspers-Fayer and Peters, 2005). A recent meta-analysis by Somers and colleagues (2008) showed that mixed handedness rather than strong left handedness was associated with higher schizotypy scores. This suggests bilateral representation of motor function rather than right hemisphere motor dominance is associated with schizotypy. Further information can be found in section 1.5.1 of the General Introduction.

The association between atypical cerebral dominance and schizotypal features is also evidenced in non-manual tasks such as linguistic processing. Leonhard and Brugger (1998) for example, reported a lack of the expected right visual field advantage when performing a lexical decision task in participants scoring high on the magical ideation scale. Kiang (2010) presents a review of the literature on schizotypy and language where it is suggested that the available studies are consistent with increased involvement of the right hemisphere and reduced lateralisation of language. Further information can be found in section 1.5.2 and 1.5.3 of the General Introduction.

To a lesser extent, visuospatial attention asymmetry has been investigated in schizotypal samples. Line bisection tasks are used to measure visuospatial attention. They require the participant to either manually bisect horizontal lines, or to decide whether pre-bisected lines are in the left or right visual plane. ‘Pseudoneglect’ refers to the tendency of neurologically normal participants to bisect horizontal lines to the left of the true centre and is interpreted as reflecting the increased involvement of the right hemisphere in visuospatial attention (Bowers and Heilman, 1980; McCourt and Jewell, 1999). This predilection for right hemispheric involvement has been demonstrated in functional magnetic resonance imaging studies, where increased activations occur in the right hemisphere during line bisection tasks (Cicek et al., 2009). Mohr et al (2003) studied line
bisection and leftward turning bias (as another indicator of bias for the left hemispace) in participants rated as high and low on the Magical Ideation Scale (MIS: Eckblad and Chapman, 1983), a measure of positive schizotypy. They found increased leftward bias was more frequent in high scoring participants. In a subsequent study they reported that negative schizotypy was associated with a rightward veering bias (Mohr et al., 2005). Brugger et al (2010) have also reported that positive schizotypy is associated with a leftward bias on a number line bisection task. The data are not consistent: a number of studies failed to replicate the association between leftward bias and positive schizotypy in visuoconstructive performance (Gooding and Braun, 2004), whereas Liouta et al (2008) found positive schizotypy was associated with a rightward bias on both the line bisection and veering tasks. The interpretation of these findings for understanding brain organisation for some authors suggest an increased leftward bias reflects right hemisphere overactivation, which could be a result of increased dopamine function (e.g. Mohr et al., 2003). An alternative, but not mutually exclusive theory, is that the leftward bias could be a consequence of a left hemisphere underactivation (e.g. Brugger and Graves, 1997). Further information can be found in section 1.5.4 in the General Introduction.

With regards to the line bisection task, a number of factors influence the direction and extent of pseudoneglect on simple line bisection tasks which undoubtedly contributes towards the contradictory findings in schizophrenia (McCourt et al., 2008), schizotypy (Liouta et al., 2008) and neurologically normal samples (Jewell and McCourt, 2000). These include age, sex, nature of the task, hand used to perform the task and direction of visual scanning (Jewell and McCourt, 2000). Hand use and direction of oculomotor scanning leads to a bias towards the side that the hand or eye movement originates. Dellatolas et al (1996) compared manual bisection with judgement of pre-bisected lines presented on a computer screen and found that the pen and paper task incurred a left sided bias (presumed right hemisphere dominance), whereas performance on the computerised task was associated with a right sided bias (presumed left hemisphere dominance). Furthermore, participants who demonstrated a leftward bias on the pen and paper task demonstrated no such bias on the judgement task. However, direct comparison of fMRI data examining both bisection and forced choice tasks indicate that although there are some differences in regional activations, there is a predominant right hemisphere involvement (Cicek et al., 2009).
The effect of hand use is thought to reflect a role for the corpus callosum in line bisection tasks (Hausmann et al., 2002; 2003a; 2003b). Greater leftward bias when the left hand is used presumably reflects right hemisphere motor control in addition to right hemisphere spatial control. When the right hand is used the left sided bias is less pronounced, because the spatial information is transferred via the corpus callosum to the left hemisphere motor control centres (Hausmann et al., 2003a). Many studies have reported functional abnormalities of the corpus callosum in patients with schizophrenia (Hulshoff Pol et al., 2004; Mohr et al., 2000), including a study by Rushe et al (2007) using the Cross Finger Localization Test (CFLT), a measure of interhemispheric transfer of somatosensory information. Rushe et al (2007) found callosal function as measured by the CFLT to be impaired in schizophrenia patients compared to controls. Such disturbances in hemispheric communication could support theories of misconnection in schizophrenia (Crow, 1998). To date interhemispheric transfer has not been investigated in relation to schizotypy. Further information can be found in section 1.5.5 in the General Introduction.

**Study Rationale**

The overall aim of the present study is to explore the association between schizotypy and visuospatial attention as a marker of functional asymmetry, and between schizotypy and callosal function. Evidence demonstrating reduced functional and structural asymmetries in schizophrenia supports theories that the syndrome is characterised by a failure of cerebral dominance. Given the relationship between schizotypy and schizophrenia, it is hypothesised that performance biases on measures of visuospatial attention will be correlated with schizotypal features. To measure functional asymmetry two tasks of visuospatial attention are employed. The first task is a simple paper line bisection task (see below) which is completed with the right and left hands. Previous studies have demonstrated that positive schizotypal features are associated with altered performance on bisection tasks (Brugger et al., 2010; Mohr et al., 2003; 2005).

1. It is predicted that an exaggerated left sided bias on the paper line bisection will be correlated with positive schizotypal features as measured by the Schizotypy Personality Questionnaire (SPQ: Raine, 1991)

2. Furthermore, negative schizotypy has been linked to a greater right sided bias on bisection tasks (Mohr et al., 2005), hence significant correlations will be found between performance and subscales measuring negative schizotypal features.
The second measure of visuospatial attention is the computerised Landmark Task (see below). This task has recently been administered to a sample of schizophrenia patients (McCourt et al., 2008). Whereas controls were found to have a left sided bias in line judgement, patients neither erred to the left or right.

3. As such, it is predicted that a negative correlation will be found between Landmark Task performance and schizotypal features. Therefore, a leftward bias will be associated with reduced schizotypal scores.

The third task is the CFLT. It has been demonstrated that schizophrenia patients have dysfunctional callosal functioning on transfer of somatosensory information (Rushe et al., 2007).

4. It is predicted that decreased performance on the CFLT will be associated with higher SPQ scores.

2. Methods
2.1 Participants and procedure
The data was collected at the same time as the data reported in Paper 3. See Paper 3 sections 2.1 and 2.2, along with the Methodology Chapter (MC) Section 2.6.2 (Pg. 102), which covers rationale of task choice, further task procedures and normality of data.

2.2 Measures
Listed below are the measures used for the current study. For each measure, further detailed descriptions can be found in MC.

Schizotypy Personality Questionnaire (SPQ)
The SPQ (Raine, 1991) is a 74-item dichotomous (yes/no) questionnaire based on the DSM-III-R criteria for SPD (American Psychiatric Association, 1984). It is a multidimensional measure that comprises 9 subscales that cover schizotypal features as defined by DSM-III-R. The 9 subscales are Ideas of References (IoF), Excessive Social Anxiety (ESA), Odd Beliefs/Magical Ideation (OBMI), Unusual Perceptual Experiences (UPE), Odd or Eccentric Behaviour (OEB), No Close Friends (NCF), Odd Speech (OS), Constricted Affect (CA), and Suspiciousness (SU). The SPQ has high internal reliability (0.9-0.91), test-retest reliability (0.82), convergent validity (0.81 with Schizotypal...
Personality Scale: Claridge and Broks, 1984), and criterion validity (55% scoring in top 10% have SPD) (Raine, 1991)

**Motor Dominance Demonstration Test (MDDT)**
In the MDDT (Seisdedos et al., 1999) the participant demonstrated to the examiner their preference for right or left side for hand actions (e.g. writing), vision (e.g. looking through telescope), and foot actions (e.g. kicking a ball). There were 10 actions in total: 5 hand, 3 ocular and 2 foot. Those with a right sided preferences scored +1, left -1 and no preference 0. This produced a range of scores from +10 to -10, from purely right sided to purely left sided.

**Line Bisection (see MC Section 2.6.2.9 Pg. 110)**
The participant was presented with a sheet of paper with a series of horizontal lines in which they had to manually mark the mid-point of each line. There were 20 horizontal lines in total: 7 lines were positioned towards the left side of the page, 7 in the middle, and 6 on the right side. Line length varied, ranging from 72mm to 162mm, with an average length of 115mm. Each horizontal line was separated by a 10mm gap. The task was completed with the right and left hand.

The performance measures for this task was the average percentage difference between the true centre and the line marked by the participant for each horizontal line for right and left hand separately. This was calculated for centrally positioned horizontal lines only (7 of the 20) due to known effects of line placement (Jewell and McCourt, 2000). Each marked line was measured from the left end of the horizontal line and subtracted from the true mid-point. Each of the seven lines were averaged and turned into a percentage difference that could be either negative or positive (i.e. a bias to the left or right respectively). The average percentage difference was calculated for both the right and left hand.

**Landmark Task of Spatial Cognition (see MC Section 2.6.2.10 Pg. 111)**
The Landmark Task was designed specifically for the present study. The participant observed a long horizontal line on a computer screen and had to decide whether a small bisecting line was left of centre, centre, or right of centre. The response was made using a single key press on the keyboard with the dominant hand. There were 60 trials in which the bisecting line was either left (20 times), centre (20), or right (20). The performance measure was the “laterality index”. This was calculated from vertical lines in the central
position only and is a quantitative measure of how much the participant erred to either the left or right of centre. The calculation:

Total correct in the central position = TCP
Error - adjudged to be left of centre = EL
Error - adjudged to be right of centre= ER

$$\text{Laterality Index} = \frac{\text{TCP}/2 + \text{EL}}{\text{TCP} + \text{EL} + \text{ER}}$$

This formula provides a figure ranging from 0-1. If the person had no left or right sided bias, their score would be 0.5. Values above 0.5 represent a preference to judging lines left of true centre, whereas scores below 0.5 represent a bias to judging the vertical line right of the true centre. Three participants’ data are missing due to hardware failure during the task.

**Crossed Finger Localisation Task (see MC Section 2.6.2.11 Pg. 111)**

Interhemispheric transfer of somatosensory information was assessed using the Cross Finger Localisation Test (CFLT: Satomi et al., 1991). In this task the examiner touched the participants’ fingertips and they indicated which finger(s) had been touched. In humans, the finger tips of each hand are represented in the contralateral somatosensory cortex (Zaidel and Sperry, 1977) so the task requires transfer of sensory information across the corpus callosum, and has been validated in patients with complete (Volpe et al., 1982) and partial resection of the corpus callosum (Geffen et al., 1985).

There were two main conditions: uncrossed and crossed. For the experimental trails the participant was blindfolded. Of interest was the crossed condition where the participant had to indicate on the opposite hand which finger(s) had been touched by the examiner. The task was carried out on both the right and left hands with all four fingers being pressed twice in a counterbalanced fashion. There were two levels of difficulty. First the participant was pressed on a single finger, and then pressed on two fingers sequentially with the participant needing to repeat the sequence. In total there were 64 trials in 8 blocks. The sequence of blocks was the uncrossed version with one finger on both hands (two blocks, left and right hands, with 8 trials each), then the same for the crossed version. The next blocks were the two finger stimuli in the uncrossed condition (right and left) and the same in the crossed condition. Performance was measured as the total score for the crossed condition (maximum 32).
2.3 Data analysis
Data was analysed with SPSS (v.15). Means, standard deviations and data normality were assessed for each variable. Values of skewness and kurtosis were examined along with the distribution curves (see MC, Section 2.6.3 Pg. 112 for values).

The strength of associations between schizotypal features and performance measures were assessed via either partial correlations or Spearman rank correlations depending on normality of variables. Where normality of the variables allowed, sex, age, and MDDT were added as covariates due to know differences on spatial attention tasks (Jewell and McCourt, 2000). Correlations were obtained between total SPQ/9 subscales and performance on each outcome measure. In consideration of multiple correlations, $p < 0.01$ was considered significant and trend level was set at $p < 0.05$.

3. Results
3.1 Sample characteristics and task performance
The sample for the current study was the same as that reported in Paper 3. Total SPQ score, SPQ subscale and age are reported in Paper 3 Table 1 (Pg. 169). Briefly, 109 participants were recruited aged 19.91 ($SD=2.67$), with 32 males.

With regards to the current study, Table 1 lists performance on each task. On the Line Bisection, there was a left sided bias when the task was performed with the left hand (negative score), and right sided bias with right hand. There was no bias to either left or right on the Landmark Task, where the laterality index was 0.49. There were sex differences on Line Bisection Right Hand only where males had a significantly greater right sided bias than females (Males $M$ 1.92 ($SD$ 3.03) Vs. Females $M$ 0.36 ($SD$ 3.25); $t(107) = 2.32, p < 0.05$).
Table 1: Mean (SD) scores for each task for the total sample

<table>
<thead>
<tr>
<th>Sample</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Line Bisection Left Hand (% diff from 0)</td>
<td>n=109</td>
</tr>
<tr>
<td>Line Bisection Right Hand (% diff from 0)</td>
<td>n=109</td>
</tr>
<tr>
<td>Landmark Task (laterality index)</td>
<td>n=106</td>
</tr>
<tr>
<td>CFLT</td>
<td>n=109</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean (SD) Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.82 (3.23)</td>
</tr>
<tr>
<td>0.82 (3.25)</td>
</tr>
<tr>
<td>0.49 (0.11)</td>
</tr>
<tr>
<td>28.94 (3.52)</td>
</tr>
</tbody>
</table>

3.3 Correlations between SPQ and task performance

Scatter plots of total SPQ/subscale scores versus task performance are presented in Appendix 7. Plots were produced for Line Bisection Left Hand and Right Hand, and Landmark Task. Due to non-normality of variables, plots were not produced for CFLT. The scatter plots indicate there were no obvious non-linear relationships between associated variables, hence correlation analyses were possible.

3.2.1 Schizotypy and Line Bisection

For the Line Bisection, age, sex, and MDDT score were added as covariates in correlational analyses where possible. Table 2 lists partial and Spearman correlations for both Left and Right hand. There was a trend level (corrected $p < 0.05$) positive correlation between Line Bisection Left hand and NCF subscale only. Fig 1 demonstrates this relationship (see Appendix 7 for scatter plots with other subscales). On the figure, the point of true centre is marked at 0, with scores below 0 representing a leftward shift in bias, and positive scores a rightward shift. The positive correlation indicates that higher scores on NCF subscale were associated with a rightward shift in line placement, although on average the sample as a whole erred to the left of true centre (total sample $M = -0.82$ ($SD 3.23$)). As Fig 1 demonstrates, lower scores on NCF tend to have the expected left-sided bias, and with increasing levels of NCF this errs towards line judgement in the central region. There was no association between schizotypy and Line Bisection Right Hand performance.
3.2.2 Landmark Task

For the Landmark Task, age, sex, and MDDT score were added as covariates where possible (Table 2 lists partial and Spearman correlations). There were significant (corrected level $p < 0.01$) positive correlations between task performance and total SPQ, and between task performance and IOF, OS, and ESA subscales. There were also positive trend correlations between task performance and subscales UPE, NCF, and SU. Fig 2 is an example scatter plot for total SPQ score and laterality index (see Appendix 7 for scatter plots between laterality index and the 9 subscales). On the figure, the point of true centre is marked at 0.5, with laterality values greater than 0.5 representing a leftward shift in bias, and scores below a rightward shift in bias. Therefore with increasing total SPQ score (also for subscales IOF, OS, ESA, UPE, NCF, and SU) there is a greater leftward bias, and with lower schizotypy scores a rightward bias.

Fig 1: Scatter plot of Line Bisection Left Hand performance Vs NCF subscale score. Dashed line represents true centre (no left or right bias).
3.2.3 CFLT

Due to non-normality of the CFLT, Spearman correlations were calculated (see Table 2). There were no significant correlations between task performance and schizotypy score.

Table 2: Correlation between total SPQ/9 subscales and performance on Line Bisection Left/Right, Landmark Task, and CFLT.

<table>
<thead>
<tr>
<th>Task</th>
<th>Line Bisection Left Hand (^a)</th>
<th>Line Bisection Right Hand (^a)</th>
<th>Landmark Task (laterality index) (^a)</th>
<th>CFLT (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>109</td>
<td>109</td>
<td>106</td>
<td>109</td>
</tr>
<tr>
<td>SPQ Total  (^a)</td>
<td>0.14</td>
<td>-0.01</td>
<td>0.30 **</td>
<td>-0.05</td>
</tr>
<tr>
<td>IOF (^a)</td>
<td>0.13</td>
<td>-0.05</td>
<td>0.29 **</td>
<td>0.04</td>
</tr>
<tr>
<td>UPE (^a)</td>
<td>0.04</td>
<td>0.06</td>
<td>0.22 *</td>
<td>-0.02</td>
</tr>
<tr>
<td>OS (^a)</td>
<td>0.09</td>
<td>-0.09</td>
<td>0.28 **</td>
<td>-0.01</td>
</tr>
<tr>
<td>ESA (^b)</td>
<td>0.10</td>
<td>-0.02</td>
<td>0.26 **</td>
<td>-0.06</td>
</tr>
<tr>
<td>OBMI (^b)</td>
<td>0.02</td>
<td>0.11</td>
<td>0.13</td>
<td>-0.01</td>
</tr>
<tr>
<td>OEB (^b)</td>
<td>0.01</td>
<td>-0.06</td>
<td>0.15</td>
<td>0.04</td>
</tr>
<tr>
<td>NCF (^b)</td>
<td>0.24 *</td>
<td>0.10</td>
<td>0.21 *</td>
<td>-0.08</td>
</tr>
<tr>
<td>CA (^b)</td>
<td>0.15</td>
<td>0.09</td>
<td>0.14</td>
<td>-0.12</td>
</tr>
<tr>
<td>SU (^b)</td>
<td>0.18</td>
<td>0.07</td>
<td>0.25 *</td>
<td>-0.05</td>
</tr>
</tbody>
</table>

\(^a\) – Normally distributed; \(^b\) – Not normally distributed. For normally distributed rows and columns (a), partial correlations are reported. Where either a row and/or column has non-normally distributed data (b), Spearman rank correlations are reported. * \(p < 0.05\); ** \(p < 0.01\).
4. **Discussion**

It was hypothesised that increasing presence of schizotypal features would be associated with a reduction in functional asymmetry and callosal function. The results of the study showed the effect of schizotypy was dependent on the nature of the task. For performance on the Line Bisection task, only a trend correlation at the corrected significance level was present between performance with the left hand and No Close Friends subscale score. On the computerised Landmark Task, however, in opposition to the prediction, increasing judgements to the left of true centre were associated with higher total SPQ scores certain subscales. Finally, there were no associations between schizotypal features and callosal function as measured by the CFLT.

The findings of an association between schizotypy and hemispatial attention asymmetry provide only partial support of the study hypotheses. In line with the findings of Mohr *et al* (2005) it was predicted that negative schizotypy would be associated with an increased rightward bias, which was demonstrated with the positive correlation between Line Bisection Left Hand performance and scores on No Close Friends. In factor analysis studies, the NCF subscale exclusively loads onto negative symptom dimensions (e.g. Raine *et al*., 1994; Stefanis *et al*., 2004a; Wuthrich and Bates, 2006). Where low scores on NCF subscale was associated with a normal left sided bias in performance, higher scores were associated with no bias to either left or right of true centre. Contrary to the study by Mohr *et al* (2003), we found no effect of positive schizotypy on either Line Bisection Left or Right hand. There were, however, positive correlations between various schizotypal features and performance on the Landmark Task with a greater leftward bias associated with increased features. This could be partial support for the effects of positive schizotypy on increased leftward bias as seen in manual bisection tasks, but in fact it is opposite to that found in a study of schizophrenia patients (McCourt *et al*., 2008) and which formed the prediction for the current study (see below).

Many factors are involved in completing manual bisection tasks including sex, handedness, spatial position of the lines and hand use (see Jewell and McCourt, 2000). Where possible (i.e. normally distributed variables) sex was controlled for in analyses. The effect of motor dominance was also not directly analysed due to small numbers of left handed participants, but was controlled for. The effect of spatial position of the lines was eliminated, as only performance on the centrally placed lines was analysed in this study. The present study showed a strong effect of hand use on the Line Bisection task. However, in contrast to
most previous studies, pseudoneglect was apparent only when bisection was conducted with the left hand. Right hand use was associated with a shift of attention to the right hemispace. This pattern of symmetrical neglect is more typical of young children, and thought to reflect immaturity of the corpus callosum (Hausmann et al., 2003b). Use of the right hand requires activation of the left hemisphere motor cortex to complete the task, whereas left hand use is associated with activation of the motor cortex in the spatially dominant right hemisphere (Hausmann et al., 2003a). Therefore, only performance of the task using the right hand is expected to invoke interhemispheric communication. It is noteworthy that performance on the callosal task was the only task that was positively correlated with age, which may reflect immaturity of the corpus callosum in some participants. The age of the present sample is younger than that of many previous studies (mean age 19 years) which report pseudoneglect with the right hand, so this may explain the pattern of symmetrical neglect found in this study.

On the computerised Landmark Task, the participants on average judged the lines to be centrally based. This finding appears inconsistent with right hemisphere involvement in the visuospatial nature of the task and the phenomenon of pseudoneglect in neurologically normal participants (Jewell and McCourt 2000). Some studies that have employed computerised tasks have reported a rightward shift of attention (Dellatolas et al., 1996; Robertson and Eglin, 1993). In the present study the motor demands of the computerised Landmark Task were minimised as only button presses were required, and these were performed with the participant’s dominant hand, which in the majority of cases was the right hand. In this respect, the performance of the Landmark Task corresponds with performance on the pen and paper task when it is conducted with the right hand, which showed a rightward bias. Dellatolas et al (1996) highlight that a major difference between computerised tasks and conventional bisection task is that the former is conducted in the peripersonal space (between the forearms), whereas the latter is performed in extrapersonal space. They cite neuropsychological evidence that the brain damage for neglect of peripersonal space is dissociable from neglect for extrapersonal space. A review of that literature is outside the scope of this study but highlights the importance of controlling for such methodological considerations across studies.

Of relevance to the main hypothesis, was the finding that increasing schizotypal levels were associated with a tendency to judge pre-bisected lines (Landmark Task) in a more leftward direction. This leftward bias as a function of schizotypy was not seen in the paper
Line Bisection task for either hand. As stated above, this could be due to differences associated with other factors such as tasks being completed in extra- or peripersonal space, and young average age of the sample. The leftward bias on the Landmark Task was however, in opposite to the prediction based on schizophrenia literature.

With reference to schizotypal studies though, this finding is consistent with previous studies which show an increase in a leftward bias as a function of mainly positive schizotypy (Brugger and Graves, 1997; Brugger et al., 2010; Luh and Gooding, 1999; Mohr et al., 2003; Taylor et al., 2002). The leftward bias in this study and others could be interpreted either as increased involvement of the right hemisphere, reduced involvement of the left hemisphere due to left hemisphere dysfunction, or disturbed communication between the two hemispheres. The latter hypothesis is not supported by the present data, since callosal function was not associated with schizotypy. A proposed mechanism for such a leftward bias was suggested by Taylor and colleagues (2002), where observations in a subset of schizophrenia patients with an inattention of the right side could be a result of right hemispheric hyperdopaminergic function and left hemisphere hypodopaminergic function (Bracha, 1989). An extension of this theory is that negative schizotypy is associated with a rightward bias (Mohr et al., 2005), again partially confirmed in the current study, and supports theories that schizophrenia and schizotypal personality could be a result of hemispheric imbalance of function (Gruzelier, 1991; Gruzelier et al., 1995). Liouta et al (2008) suggested that increased leftward bias in schizotypy could reflect an increase in dopamine activity in the right hemisphere, although hypodopaminergia in the left hemisphere has been proposed as the lead mechanism (Brugger and Graves, 1997). A more direct method would be to examine lateralised functional differences using imaging paradigms. Functional magnetic resonance imaging (fMRI) with similar bisection tasks could be used to examine regional brain activations in relation to schizotypal features. Furthermore, to test hypotheses of the lead mechanisms for both functional changes and presence of schizotypy, positron emission tomography (PET) could directly assess extent of hemispheric dopamine function.

With regard to the schizophrenia literature, the single example that employed a similar forced choice paradigm found no leftward bias in patients compared to controls (McCourt et al., 2008). With paper line bisection tasks there are conflicting results in patient samples, for example a similar lack of bias has been found (Zivotofsky et al., 2007), but also an exaggerated left-bias (hyperpseudoneglect: Michel et al., 2007). McCourt et al (2008)
study also found a deficit in callosal function in the patient sample as demonstrated by lack of correlation between right and left hand performance. This supports the functional and structural evidence for interhemispheric disturbance in patient samples (Arnone et al., 2008; Coger and Serafetinides, 1990; Rushe et al., 2007; Woodruff et al., 1995). Visuospatial attention is influenced by interhemispheric transfer of information, so where both are disrupted in clinical samples, it would be enlightening to investigate the causal route of dysfunction, i.e. is it a result of disturbed lateralisation, reduced interconnectivity or both. In the current study there was no evidence for an association between schizotypy and callosal function, so performance biases on the Landmark Task may be predominantly driven by right hemisphere function. To understand the complex interactions between hemispheric transfer and functional specialisation, further studies could utilise both forced and free-choice versions of visuospatial attention tasks across the schizophrenia spectrum. Identifying points of deviation in analogue samples such as schizotypes may inform theories of pathophysiological mechanisms associated with transition to mental illness.

**Limitations and conclusions**

The study has a number of limitations. Firstly it was not possible to assess whether motor dominance was related to expression of schizotypal symptoms given the small number of people with left sided motor dominance. As demonstrated by the MDDT scores, the majority of the sample were predominantly right handed. Only 11 of 109 participants defined themselves as left handed. Much larger sampling pools (the current study initial sample pool was n=994) would be required if recruiting a substantial number of left-sided participants. Secondly, the sample was relatively high scoring with an average SPQ slightly above published norms (see MC section 2.4 Pg. 91). It may have been the under-representation of low scoring individuals that could identify a full linear relationship between presence of schizotypy and visuospatial attention. It may be necessary to select those that score at the extreme ends (low and high schizotypes), so as to maximise groups differences which allow the identification of subtle effects of schizotypy. Finally, there is a paucity of data linking manual and computerised bisection tasks. In a sample of healthy controls, a computerised task was found to elicit a rightward bias which is opposite to those seen in paper versions (Dellatolas et al., 1996). However in the study by McCourt et al (2008), their control group had a leftward bias, and the current study on average had neither left nor right bias. Further research is required to firstly standardise computerised bisection tasks, along with the collection of normative data. This is a worthwhile pursuit.
given the tasks potential for highlighting differences in regional brain activation in clinical and analogue samples.

In summary, schizotypal features were associated with a slight alteration in visuospatial attention. A general increase in schizotypal features were associated with an erring to the left side on a forced choice paradigm, whereas some negative type features were associated with a departure from a normal left bias on a manual bisection task. These associations between lateralised function and schizotypy are likely determined solely by regional brain function rather than disturbed interhemispheric connectivity given the lack of association between schizotypy and CFLT performance. The study partially supports the schizotypal literature, but appears in contrast to clinical data, either due partly to the heterogeneity in the literature and/or a qualitative difference between related samples. Future imaging studies could identify the extent of hemispheric imbalance in association with schizotypy, along with identifying points of deviation from clinical samples that could help in understanding the role of lateralised function across the schizophrenia spectrum.
Paper 5

Diffusion tractography study in community based schizotypes
Diffusion tractography study in community based schizotypes

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Abstract

Introduction: Dysconnectivity of white matter has been implicated in schizophrenia. Diffusion tensor studies (DTI) enables the visualisation and quantification of white matter in vivo. Via measures of diffusion such as fractional anisotropy (FA), differences in white matter tract coherence have been observed in chronic and first-episode schizophrenia patients, as well as high risk groups. There is theoretical importance in examining whether changes in white matter occur prior to transition to serious mental illness. Schizotypal samples represent a group on the schizophrenia continuum that could share aetiological risk factors to clinical disorders, but do not possess the confounds of illness. In the current study, it was hypothesised that a schizotypal sample would demonstrate changes in tract coherence in comparison to a control group.

Methods: DTI was performed at 3T on 12 high schizotypes and 12 controls matched for age, sex and IQ. We examined bilaterally the uncinate and arcuate fasciculi with a probabilistic tractography algorithm (PICo). FA values were extracted from the tractography derived tracts and compared between schizotypes and controls. Partial correlations were also examined between measures of subclinical hallucinatory/delusional features and FA values.

Results: High schizotypes were found to have significantly higher FA values in the uncinate fasciculi ($F(1, 23) = 5.25, p < 0.05$). There was no significant difference in FA values in the arcuate fasciculi. In the whole sample there was a positive correlation between increasing FA values and ‘vivid daydreams’ in the right arcuate fasciculus ($r(20) = 0.64, p < 0.001$).

Conclusions: Increased FA values in bilateral uncinate fasciculi in high schizotypes could represent either: 1) increased connectivity which is either a compensatory mechanism and/or an artefact of increased dopaminergic tone; or 2) increased FA values due to reduction in crossing fibres, suggesting a decrease in diffuse connectivity in fronto-
temporal connections. Correlations between mild hallucinatory experience and increasing FA values could indicate increasing connectivity, or ‘hyperconnectivity’, is associated with symptom formation.

1. Introduction
Communication between functionally specialised brain regions is imperative for sensory, motor and cognitive processes. It has been hypothesised that schizophrenia is characterised by aberrant connections which could account for the pathophysiology of the illness, and as such is considered a disorder of dysconnectivity (Friston, 1998; Stephan et al., 2009). Continuing research has attempted to identify these structural and functional correlates of dysconnectivity, with one such example being altered white matter connectivity (see Ellison-Wright and Bullmore, 2009; Kanaan et al., 2005; Kubicki et al., 2007; Walterfang et al., 2006).

To investigate white matter structures in schizophrenia, diffusion tensor imaging (DTI) techniques are employed to visualise and quantity tracts (Basser et al., 1994). Such techniques encode the diffusivity of water molecules in white matter tracts. Diffusion anisotropy values are calculated, such as the widely used scalar measure fractional anisotropy (FA), which can give an indication of tract coherence although influenced by the integrity of the fibres, the extent of myelination, and axonal diameters (Beaulieu, 2002). Changes in FA values are often demonstrated in schizophrenia samples and could represent differences in number/diameter of axons, thinner myelin sheaths, and/or increased crossing fibres (Kubicki et al., 2005b). There is a degree of heterogeneity within the literature due to, at least in part, methodological factors including those related to the collection of data, such as image acquisition and method of analysis, and those associated with the samples being investigated. For instance, studies have investigated various sources of variance including illness duration (Mori et al., 2007), age of onset (Kyriakopoulos et al., 2009), and the extent to which medication can influence FA values (Kubicki et al., 2005a). It is also difficult to determine whether changes in white matter are occurring pre- or post-psychosis. To better understand the progression of change, related samples have been examined including first-episode (FE) patient samples (Cheung et al., 2008; Federspiel et al., 2006; Hao et al., 2006; Luck et al., 2010; Perez-Iglesias et al., 2010; Price et al., 2008; Price et al., 2007; Szaszko et al., 2005), those with genetic
Studies utilising those with at-risk mental states (ARMS) could be particularly informative in understanding aetiological mechanisms. This group are considered at-risk due to presence of intermittent or mild subthreshold psychotic experiences (i.e. ARMS or ‘ultra-high risk’ UHR) (Yung et al., 1996). With whole brain voxel-based analysis (VBA) of DTI data, a UHR sample were found to have reduced FA values in the superior longitudinal fasciculus compared to controls (Karlsgodt et al., 2009). Peters and colleagues (2008) examined FA values in various association fibres including the uncinate fasciculus, arcuate fasciculus, anterior and dorsal cingulum and corpus callosum in first/second episode patients (n=10), high risk (n=10) and healthy controls (n=10). No significant difference between any groups were found in contrast to the evidence for reductions in FA values in FE samples in other studies (Cheung et al., 2008; Luck et al., 2010; Perez-Iglesias et al., 2010). These discrepancies could indicate qualitative differences between UHR and FE in terms of underlying structural changes, although differences in methodologies between studies need to be taken into account. For instance, Peters et al (2008) utilised tractography methods to isolate and quantify specific tracts, opposed to the global region of interest (ROI) or VBA techniques. In an extension of their earlier study, Peters et al (2010) sought to investigate whether transition to psychosis at 24-month follow-up would be predicted by earlier white matter structural differences. Again, no difference in baseline FA values were found between groups (transition n=7, non-transition n=10 and controls n=10), but it is possible the sample was not sufficiently powered to detect subtle changes. Other tractography studies in FE patients have found subtle differences in tract coherence in core regions of the UF (Price et al., 2008), indicating these techniques are sensitive to changes in FA values associated with early-stage pathology across the schizophrenia/psychosis continuum.

Alterations in frontotemporal connections are proposed as key regions in schizophrenia (Friston and Frith, 1995; Lawrie and Abukmeil, 1998), with DTI studies demonstrating FA changes in patients in tracts such as the arcuate and uncinate fasciculi (Burns et al., 2003). FA values within these regions have also been found to be positively correlated with increasing clinical symptoms (Hubl et al., 2004; Rotarska-Jagiela et al., 2009). The arcuate fasciculus (AF) connects temporoparietal regions with the frontal cortex and is a key tract between the language areas: Broca’s and Wernicke’s areas. Consistent with its proposed proximity (Hoptman et al., 2008; Munoz Maniega et al., 2008) and those with ‘at-risk mental states’ (Karlsgodt et al., 2009; Peters et al., 2008; Peters et al., 2010).
role in language, there is asymmetry in the AF with greater fibre density and FA values in the left hemisphere (Nucifora et al., 2005; Parker et al., 2005; Powel et al., 2006). The uncinate fasciculus (UF) connects prefrontal and orbitofrontal cortices and is thought to be involved in reward-processing, decision making and episodic memory (Asato et al., 2010; Kubicki et al., 2005b). Again, asymmetries in this tract have been reported in tract width (Azadbakht et al., 2010) and FA values (Vernooij et al., 2007; Iturria-Medina et al., 2010). A reduction in normal asymmetry in brain function and structure is thought to characterise schizophrenia and is the central tenet of Crow’s aetiological theory on the failure of dominance in schizophrenia (Crow 1990; 1997b). DTI studies have examined the extent of reduced structural asymmetry, with a reduction in asymmetry found in the UF of patient groups (Kubicki et al., 2002).

Although to date tractography investigations in at-risk samples have failed to identify differences in coherence in the AF and UF (Peters et al., 2008; Peters et al., 2010), further research is required. Such studies are critical in determining whether the presence of white matter differences are a risk factor for transition or epiphenomenon of illness. The current study attempts to examine the extent to which white matter alterations are found in another sample along the extended phenotype of schizophrenia: community based schizotypes.

Schizotypy is a trait of psychosis liability which comprises attenuated psychotic symptoms, unusual beliefs, as well as negative like symptoms such as social withdrawal (e.g. Esterberg and Compton, 2009). Schizotypal trait provides a means of exploring the mechanisms underpinning risk factors for schizophrenia and psychotic symptoms (Cadenhead and Braff, 2002; Lenzenweger, 2006). Therefore, it is possible that high schizotypes could share similarities in white matter structures with more severe clinical manifestations. One study has examined white mater structures in a group with high psychotic-like experiences which could be considered a schizotypal group (Volpe et al., 2008). With VBA methods, they found an increase in FA values in the left AF in the high psychotic-experience groups, whereas the low psychotic-like experience group had higher FA values in the right AF, corpus callosum and fronto-parietal tracts. However, as the authors noted, there were a number of shortcomings including small sample size (total n=13) and considerable sex bias in comparison groups which limits the interpretability. Even so, this is taken as evidence for structural white matter changes in association with schizotypy in otherwise healthy volunteers.
If it is possible to identify further structural differences associated with schizotypal features, it will lend support to schizotypy as a representative model of schizophrenia with similar changes in brain structures, along with the well documented cognitive deficits and shared aetiological factors (Lenzenweger et al., 1991; Park et al., 1995; van Os et al., 2009). However, community based schizotypy samples are ‘healthy’ so could possess protective factors preventing transition to psychosis. ‘Normal’ white matter structures could be one such example.

**Study rationale**

The overall aim of the study is to investigate white matter structures and the relationship to schizotypal features. Two main white matter tracts that have been studied in clinical samples are the AF and UF. Differences have been found in the connectivity of these tracts in the schizophrenia (e.g. Burns et al., 2003), as well as having associations with psychotic experiences (e.g. Rotarska-Jagiela et al., 2009). The aim of the current study is to examine these two tracts bilaterally in a schizotype group and controls. The main hypothesis of this study is that high schizotype healthy volunteers represent part of the extended phenotype of schizophrenia and will show qualitatively similar white matter dysconnectivity.

1. It is predicted that altered tract coherence will be observed in a high schizotypal group. This will be demonstrated as significant differences in FA values in the AF and UF.

Certain tracts within the brain can have higher degrees of coherence (higher FA values) compared to their opposite hemisphere counterpart. This is partly due to the function of the brain regions which the tracts connect. In schizophrenia samples the extent of these asymmetries in tract coherence is reduced. A subsidiary hypothesis therefore is that schizotypal samples will also have reduced asymmetries in white matter tracts.

2. Normal white matter asymmetries in FA values in the AF and UF will not be present in high schizotypes. This will be most notable in the AF where there is usually a pronounced hemispheric difference (left > right FA values).

In exploratory analyses, schizotypal features and measures of psychosis proneness will be correlated with FA values in the AF and UF. This will allow the investigation into the relationship between brain structure and behaviour.
To test the hypotheses, DTI and tractography techniques will be used in the current study. From DTI data it is possible to determine how fibre tracts are connected between neighbouring voxels via diffusion tractography measures (Ciccarelli et al., 2003). Tractography techniques are better placed in identifying specific tracts (Kubicki et al., 2005b). These methods overcome some of the issues associated with ROI and VBA studies such as difficulty in co-registering diffusion images to a group template, loss of resolution via spatial smoothing, and difficulty in extrapolating tracts from user defined ROIs or from areas including multiple tracts (See Methodology Chapter (MC), Section 2.7.3 Pg. 117: Catani, 2006; Kanaan et al., 2006). To date this is the first study to utilise DTI tractography methods in a sample of community based schizotypes.

2. Methods

2.1 Participants and procedure

Participants were recruited from a previous study examining the effect of schizotypal features on cognition in late adolescence and early adulthood (Papers 3 and 4). For the current study, 24 participants were selected based on their Schizotypal Personality Questionnaire scores (SPQ: Raine, 1991): 12 controls scoring +0.5SD or below the mean total SPQ score from the larger sample (Controls); and 12 scoring +1SD above the mean (Schizotypes).

Potential participants were invited to take part in the imaging study during a previous study (Phase 2). They were provided information sheets and the opportunity to ask questions about the study before deciding whether or not they wanted to participate. Exclusion criteria were current or past history of self-reported psychiatric disorder as assessed by the Mini International Neuropsychiatric Interview (MINI: Lecrubier et al., 1997), history of head trauma with loss of consciousness, non-right motor dominance, and exclusion criteria for MRI (i.e. irremovable metal objects, pregnancy etc). Selective recruitment of participants was carried out to ensure sex ratios and ages of participants were matched for both groups as closely as possible. The recruitment procedure continued until there were sufficient participants in both the control and high schizotype group within the funds available for conducting the study (n=24).

On the day of testing the participant was provided once again with the information sheet. Prior to entering the scan room each participant completed the MINI to ensure no
development of self-reported psychiatric disorder. Participants also completed the two questionnaires: the Peters et al Delusional Inventory and Launay-Slade Hallucinatory Scale (see below). The participant was then taken to the scan room where the radiographer completed a safety checklist. In the scanner each participant had the same series of scans (see below). Once scanning was completed the participant was debriefed and paid £20 for travel expenses.

Ethical approval was received for this study from the University of Manchester Senate Ethics Committee and NHS (National Health Service) Stockport Research Ethics Committee.

2.2 Questionnaires

**Schizotypal Personality Questionnaire – SPQ (Raine, 1991)**
The SPQ is a 74 item questionnaire based on the DSM-III-R criteria for Schizotypal Personality Disorder (American Psychiatric Association, 1984). Participants respond either ‘Yes’ or ‘No’ to each of the items. The SPQ consists of 9 subscales representing the core features of SPD: Ideas of References (IoF), Excessive Social Anxiety (ESA), Odd Beliefs/Magical Ideation (OBMI), Unusual Perceptual Experiences (UPE), Odd or Eccentric Behaviour (OEB), No Close Friends (NCF), Odd Speech (OS), Constricted Affect (CA), and Suspiciousness (SU).

**Peter’s et al Delusions Inventory (PDI-21) (Peters et al., 2004)**
The PDI-21 measures various aspects of delusional thought and is considered a measure of psychosis-proneness. There are 21 probe items. If answered affirmatively, there are three subsidiary measures of the experience to reflect the complexity of the belief expression (distress, preoccupation and conviction) (Peters et al., 1999). The measure has adequate internal consistency (0.82) and test-retest reliability (scores for each belief expression 0.78-0.81) (Peters et al., 2004). The total score was the sum of the 21 probe items and subsidiary measures.

**Launay-Slade Hallucinatory Scale (LSHS) (Launay and Slade 1981; Bentall and Slade 1985)**
The LSHS is a 12-item self report instrument designed to measure predisposition to hallucinatory experiences, and again considered a measure of psychosis-proneness. The 12-items are scored on a 5-point Likert scale and can be grouped into 5 subscales: vivid thoughts, intrusive thoughts, auditory hallucinations, vivid daydreams and visual
hallucinations. The measure has adequate internal consistency (0.79) and test-retest reliability (0.84) (Bentall and Slade, 1985). Outcome measure was total score and scores on vivid thoughts, intrusive thoughts, auditory hallucinations and vivid daydreams. Only two participants endorsed visual hallucinations so this subscale was not included in further analyses.

**Motor Dominance Demonstration Test (MDDT: Seisdedos et al., 1999)**

The MDDT is a measure of motor dominance. The participant demonstrated their preference for right or left side for hand actions (e.g. writing), vision (e.g. looking through telescope), and foot actions (e.g. kicking a ball). There were 10 actions in total: 5 hand, 3 ocular and 2 foot. Those with a right sided preference scored +1, left -1 and no preference 0. This produced a range of scores from +10 to -10, from purely right sided to purely left sided.

### 2.3 Diffusion weighted imaging acquisition and pre-processing

Images were acquired on a 3-T Philips Achieva scanner (Philips Medical Systems, Best, Netherlands) using an 8-element SENSE head coil. A pulsed gradient spin echo (PGSE) echo planar imaging (EPI) sequence was used to acquire diffusion-weighted data, implemented with TE = 54ms, $G_{\text{max}} = 62$ mT/m, half scan factor = 0.679, 112 x 112 image matrix reconstructed to 128 x 128 using zero filling, reconstructed resolution 1.875 x 1.875 mm, slice thickness 2.1mm, 60 contiguous slices, 62 non-collinear diffusion sensitization directions at $b = 1200$ s/mm$^2$ ($\Delta = 29.8$ms, $\delta = 13.1$ms), 1 at $b = 0$, SENSE acceleration factor = 2.5. Each diffusion weighted volume was acquired entirely before starting the next diffusion weighting, resulting in 44 temporally spaced volumes with different direction diffusion gradients. For each diffusion gradient direction, phase encoding was performed in right-left and left-right directions, giving two sets of images with the same diffusion gradient directions but opposite polarity $k$-space traversal, and hence reversed phase and frequency encode direction. Diffusion weighted acquisitions were cardiac gated using a peripheral pulse unit on the participant’s index finger, aimed at reducing artefacts associated with pulsatile brain movements (Jones and Pierpaoli, 2005). Due to the use of cardiac gating the duration of the diffusion weighted scan was dependent on participants’ heart rates, but was approximately 2 x 18 minutes (18 minutes per polarity acquisition, R-L/L-R). A co-localised T$_{2}$ weighted turbo spin echo scan with 0.94 x 0.94mm in-plane resolution and 2.1mm slice thickness was also obtained as a structural reference scan for
use in the distortion correction procedure. For further information see MC Section 2.7.1 (Pg. 115).

Pre-processing included the distortion correction of the diffusion datasets with described methods (Bowtel, 1994; Chang and Fitzpatrick, 1992) with an implementation by Embleton et al (2010). This step corrects distortion due to magnetic susceptibility artefacts associated with the narrow bandwidth in the phase encode direction of EPI, and eddy current-induced distortion caused by rapid switching of diffusion sensitisation gradients by the scanner hardware (Jezzard et al., 1998). This correction step has been shown to improve tractography results (Embleton et al., 2010). For further information see MC Section 2.7.2 (Pg. 116).

2.4 Diffusion Data Processing

Tractography was conducted with the probabilistic index of connectivity (PICo) algorithm (Morris et al., 2008; Parker and Alexander, 2003; 2005; Parker et al., 2003). This tractography method aims to quantify the confidence in tractography measurements of connection via the diffusion MRI data. The first step in doing this involves estimating the uncertainty in the principal orientations of diffusion by producing a probability density function (PDF) which contains information from the diffusion data about the distribution of the underlying fibre structures. The PDF is created from an implementation of model-based residual bootstrapping using $g$-ball analysis of repeated diffusion data-sets (Haroon et al., 2009). Constrained tracking was carried out from seed regions of interest (ROI: see below) at sub voxel resolution (0.5 mm) using trilinear interpolation of the PDFs. One thousand streamlines were propagated from each voxel in the seed ROI. Streamlines were terminated on leaving the brain volume, when doubling back, if they reached an unrealistic length ($> 50$ cm) or when they reached the second target ROI. The process was then reversed from the second to first ROI. The result was a map of voxels between the two ROIs with values from 0-1000 assigned to each voxel depending on the number of streamlines passing through the voxel.

**Seed placement**

Seed regions of interest (ROI) were placed manually in the white matter of the tracts in the coronal plane bilaterally for each tract. For the AF, an ROI was placed in the posterior parietal region of the superior longitudinal fasciculus, and in the white matter in the posterior temporal lobe. This produced a partial section for the AF. For the UF, ROIs were
placed in coronal slices of the inferior frontal gyrus and anterior temporal lobe (Wakana et al., 2007).

**Automated tract thresholding and extraction of FA values**

Once tracts of interest had been extracted via PICo, these connectivity maps were thresholded to remove low probability pathways likely to represent false positives. Group averaged thresholding was calculated so as to reduce inter-individual bias. The thresholding algorithm (Azadbakht et al., 2010) randomly selects a tract from one participant which becomes the target tract. Via affine registration, corresponding tracts from all other participants are registered to the target tract which produces an average probability connectivity map (tract). All tracts are again registered to the average tract to remove possible bias from initial target selection. The second average tract is then used as a template for the algorithm to iteratively apply a threshold value from 0 – 1 in 0.01 steps. At each increment the algorithm compares the individual tract and group template, and produces a similarity score. The similarity scores are averaged for all participants and the highest average is identified as the optimum group threshold. The suggested thresholding values for the AF and UF tracts were 50 and 100 streamlines respectively. These values were in agreement with the suggested values for thresholding of probabilistic connection of greater than 5% (Ciccarelli et al., 2006; Price et al., 2008) (See Figs 1 and 2 for group thresholded tracts for the AF and UF respectively). Each individual participant’s probabilistic connectivity map (tract) was then thresholded accordingly. ImageJ (Rasband, 1997-2009) was used to multiply together the resultant tract with the individuals FA maps created in DTIstudio (Jiang et al., 2006). Average FA values were then extracted for each tract bilaterally for each individual.

**Fig 1:** The arcuate fasciculus at group level in the left hemisphere thresholded at $p > 0.05$ (50 streamlines)
2.5 Statistical analysis
Data was analysed with SPSS (v.15). Age, IQ (data collected from previous study – *Paper 3*), dominance, and questionnaire scores were compared across groups with independent 2-sample *t*-tests. The extent of asymmetry in AF and UF was assessed via paired sample *t*-tests in the whole sample, with follow-up analyses in each group. For group comparisons of FA differences in the tracts, two sets of repeated measures ANCOVAs were conducted. Each tract was examined bilaterally in separate analyses, with age and whole brain FA values added as covariates. Effects sizes are reported for *t*-tests (Cohen’s *d*) and repeated measures ANCOVAs (eta squared: $\eta^2$). To examine relationships between FA values and attenuated psychotic experience, Pearson partial correlations were conducted between each tract and SPQ (and subscale scores), LSHS (and subscale scores) and PDI-21 total scores, with age and total FA values added as covariates. To compensate for multiple correlations, significance was taken at $p < 0.01$ and trend level association at $p < 0.05$.

3. Results
3.1 Sample characteristics and presence of schizotypal and psychosis proneness features
Table 1 presents the sample characteristics for controls and schizotypes. There were no significant differences in age, IQ (data collected in previous study), dominance or sex ratio between groups. Table 2 presents the questionnaire scores for controls and schizotypes, along with test statistics. As expected the schizotypes had significantly higher scores on total SPQ and all subscales apart from OBMI. The schizotypy group also had higher scores on PDI-21 total, LSHS total and LSHS vivid daydreams.
Table 1: Sample characteristics for controls and schizotypes, along with test statistics.

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=12)</th>
<th>Schizotypes (n=12)</th>
<th>test statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>21.37 (3.33)</td>
<td>21.05 (2.11)</td>
<td>t = 0.28</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>6/6</td>
<td>5/7</td>
<td>χ² = 0.17</td>
</tr>
<tr>
<td>IQ</td>
<td>119.83 (9.58)</td>
<td>118.08 (13.14)</td>
<td>t = 0.37</td>
</tr>
<tr>
<td>MDDT</td>
<td>8.08 (2.35)</td>
<td>8.33 (2.06)</td>
<td>t = -0.27</td>
</tr>
</tbody>
</table>

Table 2: Questionnaire scores for controls and schizotypes, along with test statistics.

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=12)</th>
<th>Schizotypes (n=12)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPQ – Total</td>
<td>17.00 (8.46)</td>
<td>46.25 (6.12)</td>
<td>-9.70</td>
<td>0.00</td>
</tr>
<tr>
<td>SPQ IOF</td>
<td>1.67 (1.72)</td>
<td>6.67 (2.10)</td>
<td>-6.37</td>
<td>0.00</td>
</tr>
<tr>
<td>SPQ UPE</td>
<td>1.58 (1.56)</td>
<td>3.5 (1.68)</td>
<td>-2.89</td>
<td>0.01</td>
</tr>
<tr>
<td>SPQ OS</td>
<td>4.25 (1.96)</td>
<td>7.67 (2.15)</td>
<td>-4.07</td>
<td>0.00</td>
</tr>
<tr>
<td>SPQ ESA</td>
<td>3.08 (2.71)</td>
<td>7.00 (1.71)</td>
<td>-4.23</td>
<td>0.00</td>
</tr>
<tr>
<td>SPQ OBMI</td>
<td>1.00 (1.41)</td>
<td>1.17 (1.03)</td>
<td>-0.33</td>
<td>0.74</td>
</tr>
<tr>
<td>SPQ OEB</td>
<td>2.00 (2.37)</td>
<td>5.83 (1.34)</td>
<td>-4.87</td>
<td>0.00</td>
</tr>
<tr>
<td>SPQ NCF</td>
<td>1.17 (1.34)</td>
<td>5.25 (1.76)</td>
<td>-6.39</td>
<td>0.00</td>
</tr>
<tr>
<td>SPQ CA</td>
<td>1.08 (1.16)</td>
<td>4.00 (2.22)</td>
<td>-4.04</td>
<td>0.00</td>
</tr>
<tr>
<td>SPQ SU</td>
<td>1.17 (1.53)</td>
<td>5.83 (2.08)</td>
<td>-6.26</td>
<td>0.00</td>
</tr>
<tr>
<td>LSHS – Total</td>
<td>24.17 (4.95)</td>
<td>32.25 (9.52)</td>
<td>-2.61</td>
<td>0.02</td>
</tr>
<tr>
<td>LSHS – Vivid thoughts</td>
<td>4.17 (2.41)</td>
<td>6.08 (2.31)</td>
<td>-1.99</td>
<td>0.06</td>
</tr>
<tr>
<td>LSHS – Intrusive thoughts</td>
<td>3.67 (1.16)</td>
<td>4.42 (0.90)</td>
<td>-1.77</td>
<td>0.09</td>
</tr>
<tr>
<td>LSHS – Auditory hallucinations</td>
<td>7.92 (1.17)</td>
<td>9.42 (5.02)</td>
<td>-1.01</td>
<td>0.32</td>
</tr>
<tr>
<td>LSHS – Vivid daydreams</td>
<td>6.42 (3.23)</td>
<td>9.33 (2.93)</td>
<td>-2.32</td>
<td>0.03</td>
</tr>
<tr>
<td>PDI-21 – dimensions total</td>
<td>24.33 (13.79)</td>
<td>71.75 (39.49)</td>
<td>-3.93</td>
<td>0.00</td>
</tr>
</tbody>
</table>
3.2 Asymmetry

In the whole sample there was asymmetry in the AF with greater FA values in the left hemisphere ($M=0.365, SD=0.061$) compared to right ($M=0.332, SD=0.060$); $t(23) = 4.83, p < 0.001, d = 0.55$. Follow-up analyses for each group demonstrated that both groups possessed asymmetry in the AF with left greater than right values (see Table 3 for FA values in bilateral AF tracts for each group. Controls, $t(11) = 3.80, p < 0.01, d = 0.63$; schizotypes, $t(11) = 2.94, p < 0.05, d = 0.44$).

In the whole sample there was no significant difference in FA values in the UF between the left ($M=0.312, SD=0.049$) and right hemispheres ($M=0.311, SD=0.051$); $t(23) = 0.18, p = 0.86, d = 0.02$. In accordance, no asymmetry was found in either group (see Table 3 for FA values in bilateral UF tracts for each group (controls, $t(11) = -0.22, p = 0.83, d = 0.04$; schizotypes, $t(11) = 0.56, p = 0.59, d = 0.05$)).

3.3 Controls Vs. Schizotypes

To assess differences in values between schizotypes and controls, repeated measures (Left, Right hemispheres) ANCOVAs were carried out with age and whole brain FA values added as covariates. Table 3 lists the means (SD) and test statistics. For the AF there were no between or within subjects effects. For the UF there was a significant between subjects effect of group with the schizotypes having increased FA values compared to controls. Follow up ANCOVAs demonstrated a non-significant trend increase in FA values in the left UF in the schizotypy ($F(1, 23) = 3.70, p = 0.069, \eta^2 = 0.023$), whereas in the right UF the difference was less pronounced and non-significant ($F(1, 23) = 2.94, p = 0.102, \eta^2 = 0.011$).

Table 3: Means (SD) and tests statistics for comparison of FA values in the arcuate and uncinate fasciculus in both hemispheres.

<table>
<thead>
<tr>
<th>Tract</th>
<th>Hemisphere</th>
<th>Controls</th>
<th>High</th>
<th>Group</th>
<th>Between Subjects effect</th>
<th>Within subjects effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hemisphere</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x group</td>
</tr>
<tr>
<td>Arcuate</td>
<td>Left</td>
<td>0.370 (0.056)</td>
<td>0.359 (0.067)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>0.332 (0.064)</td>
<td>0.331 (0.059)</td>
<td>0.02</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>Uncinate</td>
<td>Left</td>
<td>0.307 (0.041)</td>
<td>0.317 (0.055)</td>
<td>0.325</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>0.309 (0.048)</td>
<td>0.314 (0.057)</td>
<td>5.25 *</td>
<td></td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.23</td>
</tr>
</tbody>
</table>

* $p < 0.05$
3.4 Correlations between FA values and schizotypal features

Partial correlations between FA values and schizotypy measures (controlling for age and whole brain FA values) are reported in Table 4. There were significant (at the corrected level $p < 0.01$) positive correlations between the LSHS total score and FA values in the right AF. The right AF was also significantly positively correlated with LSHS vivid daydream subscale and PDI-21 total score at a trend level ($p < 0.05$). The right UF FA value was positively correlated at a trend level with the LSHS total and auditory hallucinations subscale.

Table 4: Partial correlations between arcuate and uncinate fasciculi and questionnaire scores.

<table>
<thead>
<tr>
<th></th>
<th>Left Arcuate</th>
<th>Right Arcuate</th>
<th>Left Uncinate</th>
<th>Right Uncinate</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPQ total</td>
<td>-0.126</td>
<td>0.231</td>
<td>0.249</td>
<td>0.291</td>
</tr>
<tr>
<td>SPQ IOF</td>
<td>-0.119</td>
<td>0.242</td>
<td>0.250</td>
<td>0.171</td>
</tr>
<tr>
<td>SPQ UPE</td>
<td>0.041</td>
<td>0.157</td>
<td>-0.086</td>
<td>0.029</td>
</tr>
<tr>
<td>SPQ OS</td>
<td>-0.015</td>
<td>-0.007</td>
<td>0.385</td>
<td>0.342</td>
</tr>
<tr>
<td>SPQ ESA</td>
<td>-0.100</td>
<td>0.212</td>
<td>0.350</td>
<td>0.157</td>
</tr>
<tr>
<td>SPQ OBMI</td>
<td>0.049</td>
<td>-0.006</td>
<td>-0.201</td>
<td>0.199</td>
</tr>
<tr>
<td>SPQ OEB</td>
<td>-0.123</td>
<td>0.219</td>
<td>0.145</td>
<td>0.194</td>
</tr>
<tr>
<td>SPQ NCF</td>
<td>-0.153</td>
<td>0.296</td>
<td>0.238</td>
<td>0.212</td>
</tr>
<tr>
<td>SPQ CA</td>
<td>-0.175</td>
<td>-0.001</td>
<td>0.230</td>
<td>0.074</td>
</tr>
<tr>
<td>SPQ SU</td>
<td>-0.110</td>
<td>0.176</td>
<td>0.192</td>
<td>0.440</td>
</tr>
<tr>
<td>LSHS – Total</td>
<td>-0.064</td>
<td>0.535</td>
<td>** -0.064</td>
<td>0.389 *</td>
</tr>
<tr>
<td>LSHS – Vivid thoughts</td>
<td>0.139</td>
<td>0.226</td>
<td>0.209</td>
<td>-0.155</td>
</tr>
<tr>
<td>LSHS – Intrusive thoughts</td>
<td>-0.110</td>
<td>0.255</td>
<td>-0.109</td>
<td>0.264</td>
</tr>
<tr>
<td>LSHS – Auditory hallucinations</td>
<td>-0.022</td>
<td>0.346</td>
<td>-0.079</td>
<td>0.444 *</td>
</tr>
<tr>
<td>LSHS – Vivid daydreams</td>
<td>-0.126</td>
<td>0.642</td>
<td>*** -0.163</td>
<td>0.313</td>
</tr>
<tr>
<td>PDI-21 – dimensions total</td>
<td>-0.122</td>
<td>0.417 *</td>
<td>0.133</td>
<td>0.241</td>
</tr>
</tbody>
</table>

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (p-values are 1-way significant)
4. Discussion

4.1 Overview
Probabilistic tractography was used to examine white matter coherence in the AF and UF bilaterally in a sample of 12 schizotypes and 12 controls. There were no differences between schizotypes and controls in the extent of asymmetry in AF and UF: AF had increased FA values in the left hemisphere compared to right; whereas no significant difference in UF was found across hemispheres. Schizotypes had significantly higher FA values in the UF compared to controls. In the sample as a whole FA values were also positively correlated with attenuated hallucinatory symptoms in the right hemisphere AF.

4.2 Asymmetry
Asymmetry in FA values was observed in the AF, with left hemisphere greater than right. However there was no group difference as both controls and schizotypes had a similar pattern of left greater than right asymmetry disconfirming the study hypothesis. There was also no asymmetry in the UF in the sample as a whole or between groups. Asymmetries in white matter tracts of healthy volunteers are often reported (Iturria-Medina et al., 2010; Vernooij et al., 2007), whilst schizophrenia patients tend to have reduced asymmetry (Park et al., 2004) including the UF (Kubicki et al., 2002). Regarding the UF, the extent to which asymmetry exists in healthy controls is debated with right greater than left, left greater than right or no difference in FA values found (Hasan et al., 2009; Lebel et al., 2008; Rodrigo et al., 2007). During the age range of the participants in the current study, the UF is still developing (Lebel et al., 2008), but this is unlikely to influence degree of asymmetry given the similar patterns found in adult and children (Hasan et al., 2009). Since there is no consensus on either the extent of asymmetry of the UF in healthy volunteers or clinical groups, it is difficult to rationalise the significance of the current finding.

In the ‘healthy’ brain, the right hemisphere as a whole has a greater degree of interconnectivity and efficiency compared to the left hemisphere (Iturria-Medina et al., 2010). Even so, the left AF has increased FA values (Buchel et al., 2004; Powell et al., 2006) and fibre density (Nucifora et al., 2005). This adds weight to the notion that the left hemisphere contains large specific pathways for specialised function such as language, whereas the right hemisphere may integrate multiple systems reflecting the interconnectivity (Iturria-Medina et al., 2010). The current study supports this finding of greater FA values in the left hemisphere AF in the whole sample, as well as in controls and schizotypes separately. In the schizophrenia literature, the degree in which asymmetry is
lost in the AF is debated (Voineskos et al., 2010), although FA reductions in left AF have been found (Burns et al., 2003; Munoz Maniega et al., 2008; Phillips et al., 2009). If changes in asymmetry in tracts such as the AF are consistently demonstrated in clinical samples, it could support theories of abnormal lateralisation in schizophrenia (Crow, 1997b). As the high schizotypy groups were indistinguishable from the controls in terms of AF asymmetry, this suggests that either lateralised differences are not a cursory step in development of more serious mental illness, or that schizotypes are protected from this potential risk factor.

4.3 Increased FA in schizotypes

The schizotypy group had a significant increase in FA values in the UF, although comparisons between groups in separate hemispheres failed to reach statistical significance. This overall increase in FA values in the schizotypy group is in line with the hypothesis that schizotypy would be associated with changes in tract coherence, albeit in an unexpected manner.

The increases in FA could be indicative of increased connectivity (Dong et al., 2004), which could be related to differences in axonal number and diameter, extent of myelin sheaths, coherence of fibres and/or extent of crossing fibres (Kubicki et al., 2005). In a sample of genetic high risk participants there was a similar increase in FA in deep left frontal regions: the subgenual anterior cingulate (Hoptman et al., 2008). Hoptman suggests possible explanations including it being an artefact of altered connectivity. A ‘healthy’ frontal lobe in which the UF terminates could contain multiple crossing fibres with commissural, association (to temporal and parietal lobes) and projection fibres (to striatum and amygdala) (Croxson et al., 2005). Crossing fibres can reduce FA values by affecting the principal direction in which FA is calculated, whilst increasing diffuse connectivity. The alternative explanation involves the concept of hypertrophy of tract due to increased dopaminergic tone from mesolimbic/mesocortical pathways (Hoptman et al., 2008). They suggest that this increase in innervation and subsequent hypertrophy of surrounding network could be representative of an early vulnerability marker. Such hyperdopaminergic states could have clinical relevance as it possibly accounts for increased incentive salience to irrelevant stimuli and hence role in initial formation of delusional mood (Heinz and Schlagenhauf, 2010)
An alternative proposal could be that increases in FA in the UF (or at least no demonstrable decrease in tract coherence in individuals with other risk characteristics) could represent a protective factor against transition to serious mental illness. Schizophrenia is associated with alterations in FA values, and of particular relevance is the decrease in left UF values found in young chronic schizophrenia patients compared to controls (Voineskos et al., 2010). This may suggest that structural changes in this region are a trait marker for transition. In related samples, one study demonstrated that where schizophrenia patients were associated with frontotemporal volume loss, individuals with schizotypal personality disorder (SPD) were relatively spared (Hazlett et al., 2008). However, in other SPD samples, reduced FA values have been demonstrated in the UF bilaterally (Gurrera et al., 2007; Nakamura et al., 2005), although volume loss and reductions in FA are not necessarily a dual process as one can occur without the other (Lim et al., 1999).

In other related samples, comparisons in FA values have added to this complex picture. In those at genetic risk for schizophrenia, areas within the anterior limb of the internal capsule only were associated with reduced FA values, with relative sparing of the AF and UF (Munoz Maniega et al., 2008). Similarly, no differences in FA values were found between a high-risk group, FE patients and controls in the AF or UF (Peters et al., 2008), or even in high-risk groups that went through transition (Peters et al., 2010). However, FA differences have been noted in FE patients using VBA (Szeszko et al., 2008), along with subtle changes in tract coherence in the UF (Price et al., 2008).

Evidence from chronic schizophrenia patients demonstrates relatively wide spread differences in tract coherence, less so in FE and UHR samples, whereas in the current study an actual increase in FA values in the UF was observed in schizotypes. This suggests that there are gradations in extent of white matter ‘pathology’ along the psychosis/schizophrenia continuum. It has been suggested that transitional periods and those immediately after onset are the most toxic in terms of neurodevelopmental change (Pantelis et al., 2005).

Future work could expand on these early studies with a greater number of participants. Steps have been taken in attempting to identify white matter structural differences associated with transition both with DTI (Peters et al., 2010) and regular MRI (Walterfang et al., 2008). Longitudinal studies are ideally placed to track ongoing brain development
and the association with psychotic features and risk of transition. The current study indicates the possibility of protective factors although further studies would be required to replicate the current findings.

### 4.4 Correlations with schizotypal features

In the present study there were correlations between FA values in the right AF and UF, and measures of hallucinatory experience and delusional ideation. The right hemisphere is thought to be involved in higher order processing of language, with communicative and social functions lateralised to this hemisphere (Mitchell and Crow, 2005). The association between vivid daydreaming and FA values in the current sample could be representative of normal healthy connections, and could represent a beneficial by-product relating structure and schizotypy. Links between schizotypy and creativity have been demonstrated (Nettle, 2006; Nettle and Clegg, 2006), as well as creativity being associated with increased connectivity in various brain regions (Takeuchi et al., 2010), although not always demonstrated (Jung et al., 2010). It is possible that the creativity associated with mild forms of the schizophrenia spectrum could be underpinned by extent of white matter connectivity. There could, however, be a point of hyperconnectivity where these relationships could go awry. Even though vivid daydreaming was associated with increased FA values, these were healthy volunteers with no reported functional deficits. In clinical samples, there may be other compromised brain regions and/or interacting risk factors which could push the individual into clinical relevance.

Within the schizophrenia literature, increased FA values in specific regions have been implicated in symptom presentation. For example, patients with auditory hallucinations have been shown to have increased FA values in the AF compared to patients without hallucinations (Hubl et al., 2004). Others have similarly shown increased FA values to be correlated with severity of hallucinations (Rotarska-Jagiela et al., 2009), whilst VBA studies have demonstrated associations between auditory hallucinations and primary/secondary auditory regions in bilateral temporal lobes (Nenadic et al., 2010). Increases in white matter volume in deep temporal sagittal regions (although predominantly left hemisphere) are also positively correlated with delusions and hallucinations (Makris et al., 2010). Other white matter tracts such as the superior longitudinal fasciculus have also been found to be associated with auditory hallucinations (Shergill et al., 2007). These studies suggest that some positive type symptoms are related
to FA values, which could indicate the importance of increased connectivity in regions associated with language.

It must be noted, however, that decreases in FA values in specific regions have also been linked to symptoms, as well as cognitive performance in patient groups. In chronic schizophrenia patients, performance on working memory and executive tasks is predictive of FA values in fronto-temporal connections including the right UF (Spoletini et al., 2009), whereas negative symptoms are negatively correlated with FA values in inferior frontal regions (Wolkin et al., 2003). Decreased tract coherence and clinical correlates are well documented in adolescent early-onset schizophrenia, with hallucinations associated with FA reductions in the inferior longitudinal fasciculus (IFL) (Ashtari et al., 2007), positive symptoms with FA reductions in anterior cingulum regions (Tang et al., 2010), and negative symptoms with FA values in right UF (Szeszko et al., 2008). In SPD, reduced FA values in the right UF have been found to be correlated with ideas of reference, suspiciousness, restricted affect and social anxiety, whereas left UF values correlated with cognitive function (Nakamura et al., 2005). However, these are predominantly negative schizotypal features whereas the current study found a positive association between attenuated positive symptoms and increasing tract coherence. Therefore the study by Nakamura et al (2005) and the current study are not mutually exclusive.

In summary, it is most parsimonious to state that tract coherence as defined by FA values could be associated with symptoms. However the picture is complex and even within the clinical literature there are associations between positive symptoms and increased/decreased FA values. Within clinical samples other risk factors are present, and in combination, increased FA values could play a primary role in the formation of pathological symptoms. Therefore, what is essentially a ‘normal’ psychobiological process of increasing FA values and attenuated symptoms, could break down in more pathological states. Further confirmatory evidence would help elucidate the role of white matter in symptom formation, particularly examining this relationship progressively across more 'severe' forms, i.e. schizotypes, high-risk and first-episode samples.

In correlating symptoms and measures of white matter tract coherence, caution should be taken given the transient state-like nature of psychotic symptoms, whereas white matter are relatively stable structures (Nenadic et al., 2010). In clinical studies where psychotic symptoms have been correlated with FA values, such relationships may be contentious.
DTI techniques could be used in combination with measures of neural activation such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). If it is possible to correlate trait features such as white matter with neural activation during actual symptom experience, this would provide evidence for direct links between brain structure and function. For the current study, the largest correlation was between vivid daydreams and FA values. Unlike hallucinations, these experiences may be representative of more stable trait like features since they are considered a pre-requisite for more transient hallucinatory experiences (Launay and Slade, 1981; Slade, 1976). The presence of these sub-clinical schizotypal features may be causally related to the hyperconnectivity in language related areas. When these systems are impacted upon by stressors, then the underlying structures could, along with other functional changes, give rise to florid psychosis seen in clinical groups. There is evidence from fMRI studies to suggest continuity in brain regions giving rise to hallucinations, where similar patterns of brain activations were demonstrated during active hallucinations in non-clinical and psychotic groups (Diederen et al., 2011). Notably, activations occurred in bilateral language areas such as the inferior frontal gyrus, a region connected by the AF. If diffusion metrics are acquired in similar paradigms and subsequently found to be associated with brain activations and behavioural measures, this would provide evidence for the role of white matter structures in symptom formation.

5. Limitations and conclusions
As this study was carried out on relatively small sample sizes, future studies would benefit from increased number of participants. In addition to comparative control data, the inclusion of high-risk candidates and first-episode patients would also provide informative data on the relationship between white matter structure and increasing ‘severity’ of symptoms/features. The use of tractography methods is a positive note in the current study given its potential to derive tracts of interest (Lim, 2007), but additional exploratory whole brain analyses could help in identifying other white matter regions which differentiate schizotypes and controls.

It was demonstrated that schizotypy groups have greater tract coherence as indicated by increasing FA values in the UF compared to average schizotypes. This increase in FA could reflect increased connectivity within this region and therefore represent a possible protective structural change. Alternatively, it could be an early marker for some other pathological changes, for example, a consequent of increased hyperdopaminergic function.
FA values in the right AF and UF, both thought to be related to language function, have positive correlations with attenuated hallucinatory and delusional symptoms. This lends support to proposals that hyperconnectivity in language associated regions may have some role in symptom formation. These types of biomarkers in analogue samples provide tantalising glimpses into potential pathophysiological processes occurring throughout the schizophrenia continuum.
Chapter 4  General Discussion

This final chapter summarises and draws the findings together. The chapter also includes discussions on the implications of the research in terms of aetiological theories and clinical relevance, the limitations of the studies, and suggests future directions for research.

4.1  Summary of the papers

The main hypothesis is that since schizotypy can be considered a part of the extended phenotype of broadly defined schizophrenia, it will share similar characteristics, namely associations between extent of symptoms/features and demographics, presence of cognitive deficits and brain structural changes. This section summarises the main findings from the series of studies.

4.1.1  Phase 1

Phase 1 was the main recruitment phase of the study. By using an online survey it was possible to recruit a large sample of participants allowing 1) the investigation into the effects of demographics on schizotypal levels and identification of the underlying factor structure of the SPQ (Paper 1); 2) examination of the associations between schizotypy and measures of sustained attention and spatial working memory (SWM) (Paper 2); and 3) identification of a large sampling pool from which participants could be selected for Phase 2 studies (see below).

Paper 1

Paper 1 examined the factor structure of the SPQ via confirmatory factor analysis. Previous research had supported both 3- (Raine et al., 1994; Wuthrich and Bates, 2005) and 4-factor models (Stefanis et al., 2004a). It was demonstrated that the 4-factor model was the best fitting as determined by goodness of fit indices. This model was also the best fitting when the sample was split into subgroups by sex and by age. Some fit indices only ‘acceptable’ levels, suggesting that further improvements to the model are possible.

A secondary aim of the study was to examine the effects of demographic variables (age and sex) on schizotypal features. SPQ subscale scores were compared between an adolescent group (16-19 years) and young adult group (20-25 years), and between males and females. The adolescent group was found to have significantly higher scores on the subscale ‘Unusual Perceptual Experience’ and ‘Odd Speech’. As predicted, this equates to
adolescent participants scoring higher on some positive and disorganised features. Males scored higher on the subscales ‘No Close Friends’, ‘Constricted Affect’ and ‘Odd/Eccentric Behaviour’, whereas females scored higher on ‘Odd Beliefs/Magical Ideation’. This suggests males present increased negative features, whereas females present higher positive features.

**Paper 2**

This paper examined associations between schizotypy and cognitive performance. Previous studies have found subtle impairments in domains of sustained attention and spatial working memory (SWM), although sources of heterogeneity related to sample composition and ongoing development could influence results. In the total sample there were no significant association between SPQ scores and performance measures. When the group was split into younger (16-19 years) and older (20-25 years), there was negative correlation in the younger sample between subscale scores defined as a positive-type schizotypal feature (Odd Beliefs/Magical Ideation) and spatial working memory function. This was not present in the older sample, suggesting a potential subtle developmental delay in ability related to the presence of heightened schizotypal features. Conversely on the CPT, higher schizotypal scores (disorganised features) in younger sample were associated with higher levels of performance. In older samples there was a decrease in CPT performance in relation to higher Suspiciousness subscale scores. In examining males and females separately, males were again associated with an unexpected increase in SWM performance associated with higher Odd/Eccentric Behaviour scores, whereas higher subscale scores in females were associated with decreased performance. On the CPT, males were found to have decreased performance associated with higher scores on various subscales.

Overall the results indicate a complex relationship between schizotypy and cognition both across age, and in males and females. Why there are differences between males and females is an intriguing line of research, as well as highlighting a potential source of heterogeneity in schizotypal studies. It was considered that normal sex differences, which are more pronounced during adolescence and early adulthood, are likely mechanisms which could be exacerbated in association with schizotypy.

**4.1.2 Phase 2**

Phase 2 involved testing participants ($n=109$) scoring either high or around average on the SPQ, on a battery of cognitive tasks (*Paper 3*). Tasks assessing lateralised function were...
also completed so as to examine the association between schizotypy and brain functional asymmetry (Paper 4).

**Paper 3**

To further investigate the association between schizotypy and brain function, tasks reliant on prefrontal and medial temporal lobe function (i.e. measures of executive function, attention and verbal learning/memory) were administered. It was hypothesised that schizotypy would be associated with impaired performance. This was only partially supported. Higher schizotypal scores were associated with small performance biases on verbal learning/memory. Surprisingly, increased schizotypal features were not associated with any performance deficits on executive or attentional tasks. This appeared to be in contrast to some previous studies. From the evidence of this study and previous research, it was proposed that schizotypy is characterised by a far more attenuated cognitive deficit compared to clinical disorders. Specifically, the current data suggests relative sparing of prefrontal function. It is unclear whether this could be due to compensatory mechanisms, but warrants further research perhaps utilising functional brain imaging.

**Paper 4**

The aims of Paper 4 were to investigate whether schizotypy was associated with changes in visuospatial attention, to test the hypothesis that schizotypy would be characterised by disturbed functional asymmetry. Line bisection tasks were used as measures of visuospatial attention. Furthermore, interhemispheric transfer between hemispheres was also examined via a crossed finger localisation task. In line with some previous studies, the results demonstrated that positive schizotypal features was associated with a leftward bias on a forced choice computer line bisection (Landmark) task. Some negative type schizotypal features were associated with a rightward bias on a paper bisection task. No association between schizotypy and interhemispheric transfer was found. The results suggest that presence of schizotypal features could be associated with a slight hemispheric imbalance of function.

4.1.3 **Phase 3**

From the 109 participants of phase 2, 12 high scoring schizotypes and 12 matched controls were selected to undergo brain imaging. Diffusion tensor imaging (DTI) and tractography methods were used to: 1) examine group differences in fractional anisotropy (FA) values
between schizotypes and controls; and 2) to examine associations between FA values and schizotypal/psychosis-proneness features.

**Paper 5**

In line with dysconnectivity theories into the pathophysiology of schizophrenia/psychosis, it was hypothesised that schizotypes would have altered tract coherence compared to controls. High schizotypes did not have reduced FA values relative to controls in the bilateral arcuate or uncinate fasciculi; neither were any differences in tract asymmetry found between groups. In fact there was an increase in tract coherence in the uncinate fasciculus bilaterally in high schizotypes. Although this finding would need to be replicated, such increased coherence does demonstrate a structural difference in schizotypal group. It could be evidence of a compensatory protective factor in schizotypes and/or an artefact/early marker for increasing dopaminergic function. Alternatively, the increase in FA could be a result of changes in geometric factors in white matter architecture in this region, such as reduced crossing fibres. At this stage it is not possible to state whether the increase in FA is reflecting an increase or decrease in connectivity in high schizotypes, but it is possible to comment on the implications of either possibility. Future studies would help elucidate exact changes in the extent of white matter connectivity both generally and in relation to schizophrenia and related samples.

In more exploratory analyses, tract coherence was correlated with extent of schizotypal/psychosis-proneness features. In the total sample, increasing FA values in the right arcuate fasciculus were correlated with increasing positive type schizotypal features. This demonstrated that coherency of white matter tracts that connect regions involved in the higher processing of language could be associated with the generation of attenuated positive symptoms. This was taken as possible evidence of a brain structure that could have some role in the phenomenon of positive-type features. Within healthy individuals this is characterised by presence of subclinical attenuated hallucinatory and delusional thought, but in clinical samples other genetic, biological and/or psychosocial factors could impact this in a deleterious manner culminating in clinical significance.

### 4.1.4 Summarising the findings

In summary, the main hypothesis that schizotypy is part of the continuum of schizophrenia and would have a similar profile in terms of behavioural, cognitive and biological correlates, is partially supported. Increased schizotypal levels are associated with subtle
changes in brain function and structure similar to clinical groups, although in a more attenuated, less compromised manner. This notion of attenuated forms of more serious clinical syndromes is a common viewpoint demonstrated throughout psychological, cognitive and brain structural studies both within the schizotypal literature and other analogue samples. In examining associations between schizotypy and brain structure/function, similarities and differences with clinical groups can help in identifying pathophysiological mechanisms in more serious mental health disorders.

4.2 Two forms of schizotypy?
Raine (2006) proposed that schizotypal personality could represent two entities: ‘neuroschizotypy’ and ‘pseudoschizotypy’. Neuroschizotypy is suggested as being closer in proximity to clinical disorders due to hypothesised neurobiological and genetic factors. Pseudoschizotypy is considered as having a weaker genetic and neurobiological basis, with heightened expression of cognitive-perceptual features which are influenced by postnatal environmental and psychosocial factors. Although originally aimed at clinical schizotypes (SPD patients), Raine suggests psychometrically defined schizotypes could also fall into either of these categories. The schizotypal features in the current study are likely representing both types, although probably erring to features associated with pseudoschizotypy. Self-reported measures are often less clinically relevant and have been described as the softest expression of the extended phenotype of the schizophrenia/psychosis continuum (van Nierop et al., 2011).

Adolescence, as a period of heightened expression, is the point where psychosocial, environmental and neurobiological changes may cause transitory increases in positive-type features, potentially causing overrepresentation of pseudoschizotypy cases. Paper 1 supports this notion by demonstrating higher scores on the subscale ‘Unusual Perceptual Experiences’ in the younger group (16-19 years) compared to the older group (20-25). No age group differences in scores on subscales representing negative type features were found, which could be more indicative of neuroschizotypy. Therefore, hypothetical neuroschizotypy could be the stable trait of schizotypy, whilst the positive-type symptoms of pseudoschizotypy are transient, with higher levels during adolescence.

These distinctions in schizotypy may account for the limited cognitive findings. It is widely reported that where cognition and (attenuated) symptoms interact, it is predominantly negative type features as demonstrated in clinical samples (Nieuwenstein et
al., 2001) and schizotypal samples (Gooding et al., 2006; Park et al., 1995). In Paper 1, negative schizotypal features had limited association with cognition apart from some associations in age or sex specific groups. When participants were invited back for further testing (Phase 2) they were selected on the unitary concept of schizotypy (total SPQ) rather than in relation to any specific symptom type. The high scoring individuals that completed the testing could have included pseudoschizotypes, particularly as adolescents were included. Since associations between schizotypy and cognition may only occur in relation to hypothetical neuroschizotypy, an inadvertent mixed sample may therefore have resulted in insufficient statistical power to detect the association with cognitive deficits. Heterogeneity in schizotypy/psychosis proneness samples is a common problem. An attempt to examine common causes of heterogeneous samples such as age and sex was carried out, but the presence of different ‘types’ of schizotypy could represent another source.

4.3 Schizotypy and cognition – spared prefrontal function?

Alternatively is the possibility of a genuine lack of association between schizotypy and cognition investigated in these studies (see below). The current findings lead to some tentative conclusions on brain function. Small but significant associations were demonstrated between sustained attention/spatial working memory performance and schizotypy (see Paper 2), but follow-up testing failed to identify significant associations with executive or attention indices (see Paper 3). However, higher schizotypal scores were related to subtle performance changes in verbal learning/memory.

It was suggested in Paper 3 that cognitive deficits associated with schizotypy could be differentiated from more severe clinical disorders by the extent to which underlying brain regions are involved. For instance executive tasks are reliant on prefrontal brain function (Shallice, 1988). It is possible that schizotypy is buffered from major executive impairment due to fully functioning prefrontal regions or presence of sufficient compensatory mechanisms. In more severe illness there could be compromised function across many brain regions/networks which lead to global deficits. Evidence suggests genetic factors have a significant role in prefrontal function in both genetically high-risk individuals and schizophrenia patients (see Cannon 2005). In the current study there are presumed to be few participants associated with genetic risk (see Limitations below), so could partly explain why prefrontal functioning is less compromised.
This proposition is in line with Siever and Davis’s (2004) hypothesis on the relationship between SPD and schizophrenia. They suggest that SPD is a mild form of schizophrenia, and draw parallels based on multiple lines of evidence, including cognitive, and structural and functional imaging data (Siever and Davis, 2004). They suggest a genetic anomaly causes vulnerability in primarily the temporal cortex. However, SPD may have differences in genetic predispositions and/or environmental factors culminating in the prefrontal regions being more resilient to downstream dysfunctional processes. They go on to state that the other genetic and environmental determining factors distinct from susceptibility to schizophrenia (such as cognitive capacity and general intelligence), could act synergistically to prevent or increase the likelihood of going through transition (Siever and Davis, 2004). This model could be extended to include community based schizotypes. From the data presented, it appears that schizotypal features as measured by the SPQ are associated with subtle changes in temporal lobe function as demonstrated on the verbal learning/memory task, whereas frontal lobe functioning could be protected to an even greater degree than SPD.

Performance on prefrontal executive tasks were not associated with schizotypy in the current study, which is in partial agreement with the literature (see section 1.4.3.3 in the General Introduction). Executive deficits are present prior to illness onset in high-risk groups (e.g. Brewer et al., 2006) which could represent a more developed pathology and hence one reason they are positioned further along the continuum in terms of risk for transition. Even within gradations of high-risk, there appears to be differences in the extent of cognitive impairment. Fromman and colleagues (2010), for example, compared cognitive performance between a high-risk group, a group deemed at an earlier stage of risk (basic symptoms: self-reported deficits in thought, cognition and perception) and controls. They generally found that the early risk group had intermediary performance between controls and high risk on tasks of executive function. The high risk group were significantly impaired on overall verbal memory (Auditory Verbal Learning Task) compared to the other groups, but on the learning aspect of the task, the early risk group again had intermediary performance. This not only demonstrates increasing cognitive impairment with increasing ‘risk’ along the continuum, but mirrors the findings of Paper 3 of evidence for an altered memory encoding ability.

Referring again to Raine’s (2006) two forms of schizotypy, one can speculate that in pseudoschizotypy intact prefrontal functioning exists alongside subtle deficits in temporal
regions. Neuroschizotypy could have more pronounced temporal lobe deficits, along with the beginnings of prefrontal impairments. In support of this proposition are findings from genetic high-risk studies, which could be presumed to include cases of purported neuroschizotypes. Increased genetic proximity is associated with elevated negative features (Calkins et al., 2004), deficits in executive function (Laurent et al., 2000; Sitskoorn et al., 2004), and in combination, deficits on tasks such as the Wisconsin Card Sorting Task (Laurent et al., 2001). For prefrontal deficits to occur, a dual ‘dose’ of genetic predisposition and presence of schizotypal features could be required. This is supported by Diwadkar and colleagues (2006) who found children of schizophrenia patients with schizotypal features were impaired on tasks of spatial working memory and executive function compared to those without schizotypal features.

4.3.1 Functional imaging of prefrontal function along the continuum

Functional MRI allows direct assessment of regional brain function. Extensive fMRI data has been collected comparing between various sample types. Meta-analyses of working memory and executive function have demonstrated differences in regional brain activations in schizophrenia samples (see Glahn et al., 2009; Minzenberg et al., 2009), including regions of reduced or increased levels of activation (hypo- or hyperactivations). Hyperactivity is often present during low cognitive load versions of tasks where more effortful processing is required to produce similar levels of performance. During higher cognitive loads, however, hypoactivation has been found in association with performance deficits (Callicott et al., 1999; Manoach, 2003). Reduced functional activation is also found in relatives of patients on high load working memory tasks in the dorsolateral and ventrolateral prefrontal cortices (Meda et al., 2008). Similarly, when comparing between at-risk mental states (ARMS), FE patients and control groups, similar regions were activated during working memory and verbal fluency tasks, with ARMS groups having intermediate levels of activation (FE lower and controls higher) in many regions (Broome et al., 2009). However, in the left anterior insula the reverse in activation patterns were found. Despite this, no performance differences were observed which could be interpreted that compensatory brain activations were sufficient to maintain performance levels. These studies indicate a degree of compensatory brain activation occurring across the schizophrenia continuum. As schizotypy is the weakest expression, there is even greater likelihood that compensatory mechanisms are involved, hence this could partially account for contradictory findings prevalent in the literature. Conducting fMRI studies in schizotypal samples would directly test this. From the results of this PhD, it would be
predicted that prefrontal regions would show similar levels of activation during executive
tasks, or at least compensatory processes, that could result in similar levels of performance.
Reduced functional activation is predicted to occur on tasks reliant on temporal lobe
function such as verbal learning/memory.

4.4 DTI – Brain structure

4.4.1 Increased FA values and what they could represent

Higher FA values were found in bilateral uncinate fasciculi in a high schizotypy group.
Since reduction in FA values are often found in clinical samples (Burns et al., 2003; Hubl
et al., 2004; Kawashima et al., 2009; McIntosh et al., 2008; Mori et al., 2007; Munoz
Maniega et al., 2008; Sussmann et al., 2009; Szeszko et al., 2008), it was suggested in
Paper 5 this increase could be a protective factor.

An alternative explanation can, however, be concluded from the role of the uncinate
fasciculus and findings from Paper 3. Firstly, it could be assumed that increasing FA
values (potentially reflecting greater connectivity) are associated with increased cognitive
performance as demonstrated in correlational studies (Nagy et al., 2004; Olesen et al.,
2003). Secondly, the uncinate fasciculus connects the medial temporal lobe with inferior
medial prefrontal regions (Wakana et al., 2004); areas that are functionally active during
verbal memory tasks (Baker et al., 2001; Fletcher, 2004). Therefore it would be predicted
that increasing FA values would be associated with increased performance. The current
study found almost the exact opposite. Higher schizotypal levels were associated with
reduced verbal learning performance (Paper 3), but in a subgroup of high schizotypes,
higher FA values were found in bilateral uncinate fasciculi (Paper 4). Caution must be
taken as the comparison groups for the imaging study were not compared on cognitive
performance due to the collection of cognitive and imaging data occurring at different time
points. Therefore, no firm conclusions can be made but it is possible to comment on the
potential relationship between increased FA values and reduced verbal learning/memory.
Briefly, it could be argued that increases in FA values in this instance may not represent
increased connectivity per se, or at least the increase in tract coherence is not associated
with a functional improvement on verbal learning/memory. This apparently contradictory
finding could be related to the calculation of FA values. FA is a measure of water
molecules’ diffusivity and can be influenced by axonal density and diameter, the extent of
myelination, and geometrical factors associated with tract structures such as crossing,
curving and splaying fibres (Beaulieu, 2002; Parker, 2004). Some of these factors can have the paradoxical effect of increasing connectivity but reducing FA values. For example, crossing fibres would reduce FA values due to changes in its calculation based on the principal direction of water diffusion, but could also result in a greater diffuse pattern of connectivity which could be beneficial in processes that require integration (Iturria-Medina et al., 2010). In this instance, the lower FA values in the control group could represent increased crossing fibres, and therefore diffuse connectivity. What FA changes represent is one of the most important questions to be answered definitively in DTI research. Further research would be required to address these issues directly, with studies utilising both functional and structural imaging techniques (see below).

4.4.2 Brain structural differences across the continuum
The alternative explanation of changes in FA values is one of increased connectivity. If this is occurring in high schizotypes in the current sample, it lends support to a framework of brain structural changes along the schizophrenia continuum. Changes in grey and white matter structures could represent a relatively late phenomenon during transition to serious mental illness. Schizotypy samples may not possess these features and hence are ‘protected’ from transition.

At the clinical end of the continuum there are structural brain changes observed in chronic (see Shenton et al., 2001) and first episode patients (see Vita et al., 2006). In high-risk individuals who go through transition, decreases are found in grey matter volumes in right hemisphere insula, and inferior frontal and superior temporal regions (Borgwardt et al., 2007a; Pantelis et al., 2003), along with other subtle changes such as greater brain contraction and volume loss in the right hemisphere prefrontal region (Sun et al., 2009). Even in ARMS groups, reductions in grey matter volumes are observed compared to controls (Borgwardt et al., 2007b; Meisenzahl et al., 2008), particularly in prefrontal regions (see Wood et al., 2008). Changes in tract coherence in genetic high risk groups as measured by DTI are often mixed with decreases, no change and increases in FA values (Hoptman et al., 2008; Karlsgodt et al., 2007; Munoz Maniega et al., 2008; Peters et al., 2008).

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3 Within a voxel there are thousands of axons. If the voxel is in a region where tracts are not crossing, the principal direction of diffusion will be in one direction since all the axons are in the same direction. Voxels in regions of crossing fibres will contain axons traversing each other, so for the overall voxel there is no principal direction, and hence a lower FA value.
In summarising the literature, there is an indication that the transition period is critical in terms of structural changes. Far fewer studies have examined structural changes in schizotypal samples. A recent study has demonstrated an increase in grey matter volumes in a high positive schizotypy group in the posterior medial cortex and precuneus (Modinos et al., 2010). It is unknown what causes such an increase, although the authors cited either compensatory mechanisms for an earlier abnormality (Kawasaki et al., 2004) or a transient increase due to pathological processes (Meisenzahl et al., 2008). The increased tract coherence in Paper 5 could reflect similar processes. Schizotypy is likely to be associated with less structural changes, whereas transition to a psychotic episode or even in those at high-risk of converting may begin to show regressive neurodevelopmental changes. These aberrant processes could impact normal changes in both cellular connectivity (synaptic pruning) and white matter development which could account for the increase in psychotic experiences (Cannon, 2008). Complimentary studies in schizotypal individuals are beneficial in determining the pervasiveness of the trait-like subtle abnormalities associated with transitional risk before the period of toxicity.

4.5 Evidence for an overactive right hemisphere?

Paper 5 demonstrated a positive correlation between measures of attenuated positive symptoms and FA values in the right arcuate fasciculus. This finding can be linked to Paper 4 where increased schizotypal features were associated with a left sided bias during a forced choice line bisection task. Both of these findings could have a similar biological basis in overactive right hemispheric function.

Increased dopaminergic function in striatal regions have formed the backbone of dopamine hypotheses in psychosis (see Davis et al., 1991), with recent formulations indicating a final common pathway in striatal presynaptic hyperdopaminergia which could, in part, be a product of structural changes in fronto-temporal regions (see Howes and Kapur, 2009). Liouta and colleagues (2008) examined data on turning behaviour, hemispatial neglect and dopamine theories of psychosis, and tested the hypothesis that positive schizotypy could be a result of hyperdopaminergia in the right hemisphere. Although they failed to find an association between left sided bias (right hemispheric overactivation) and positive schizotypy as did the current with a manual line bisection task, previous studies have found this pattern (Brugger and Graves, 1997; Mohr et al., 2003; 2005), including the current study on the forced choice bisection task (although it was not exclusive to positive schizotypy). In Paper 5 an association was demonstrated between attenuated positive
symptoms and increasing FA values in the right arcuate fasciculus. It is unlikely that these two processes are directly overlapping since dopaminergic innervations do not extend into superior temporal or inferior frontal regions, although striatal hyperdopaminergia is related to structural changes in these regions (Howes and Kapur, 2009). Rather, this proposal is more theoretical in terms of structural changes that could co-occur and explain two phenomena. Therefore, overactivation and hyperconnectivity in the right hemisphere could account for the observed left sided bias in spatial attention, and the positive correlation between white matter tract coherence and positive-type symptoms.

To investigate this theory, future studies could examine regional differences in functionally active areas during fMRI visuospatial attention tasks. PET imaging could also be used to elucidate the extent of dopaminergic function across hemispheres. From additional data, models can be developed to describe attenuated symptoms and deviance from normal asymmetry in regional activation and in relation to dopamine function.

4.6 Structural evidence for attenuated hallucinatory experience?

*Paper 5* reported positive correlations between FA values and hallucinatory/delusional features, although only the correlation with LSHS vivid daydreams subscale and total LSHS survived correction for multiple correlations. Similar results have been found in clinical samples where positive symptoms have been associated with increased FA values, although these tend to be auditory hallucinatory type symptoms (Hubl *et al.*, 2004; Rotarska-Jagiela *et al.*, 2009). Vivid daydreams are considered a prerequisite condition for hallucinations (Launay and Slade, 1981; Slade, 1976) and could represent an underlying trait. This, therefore, could represent a relationship between structural and behavioural constructs that are continuous across the schizophrenia spectrum and into the healthy general population.

There is extensive evidence of structural and functional correlates of hallucinatory behaviour (see Allen *et al.*, 2008). To account for these findings, neurocognitive models have been proposed which incorporate bottom-up and top-down processes in multiple networks (Allen *et al.*, 2008). The bottom-up processes include overactivation in sensory cortices resulting in increased anomalous perceptions. Top-down processes involve regions such as the anterior cingulate, prefrontal and premotor areas, which could be involved in cognitive/psychological mechanisms in hallucination formation. Such mechanisms include an inability to discriminate between real and imagined events, arriving at hasty judgements
Examining hallucinatory behaviour in the general population is beneficial to understanding the pervasiveness of these network models. The correlations in Paper 5 demonstrated that increased tract coherence was associated with increasing attenuated features. Perhaps in the general population there is not the same extent of dysfunctional top-down processing either due to normal functioning at this level and/or connectivity to other regions. This could again be linked to prefrontal pathology; for example, evidence suggests some dysfunctional top-down processing in hallucinatory experience in schizophrenia are related to reduced frontotemporal functional connectivity from the left dorsolateral prefrontal cortex to the left temporal cortex (Lawrie et al., 2002), a region including the uncinate fasciculus. As demonstrated in Paper 5, there was a possible increase in connectivity of the uncinate in schizotypes. In clinical samples, a more global pathology, particularly affecting prefrontal regions evidenced by reductions in grey matter and changes in white matter structures (which are not seen in schizotypes or to the same extent in ARMS) could result in the destabilising of the appraisal of perceptual experiences. Therefore, what is essentially a continuous psychobiological process of increasing FA values and attenuated symptoms, could go awry due to other factors impacting prefrontal regions which are biological, genetic and/or psychosocially based.

4.7 Implications of the research

In the next section the implications of the results will be discussed in terms of aetiological theories of schizophrenia/psychosis, and clinical relevance.

4.7.1 Implications for aetiological theories

The functional or structural evidence from the current set of studies does not support Crow’s theories (Crow, 1990; Crow et al., 1989) of abnormal lateralisation being applicable to a schizotypy sample. Paper 4 examined lateralisation of visuospatial attention, which demonstrated some association with heightened schizotypal features. This was in line with other studies that have found leftward biases on measures of spatial attention and veering behaviour (e.g. Brugger and Graves, 1997; Mohr et al., 2005). However, it is unclear the extent to which this is evidence for failure of dominance. One interpretation is that an erring to the left may be due to an increase in right hemisphere
function, suggesting that schizotypy is associated with increased asymmetric function (although possibly due to a 'pathologic' increase in dopaminergic function: Liouta et al., 2008). If the alternative explanation is presumed, in that a leftward bias represents a weakening of left hemisphere function (neglecting right hemispace), then again this is not necessarily a marker of abnormal asymmetric function since the left hemisphere is not predominantly involved in processing spatial information.

Similarly, Paper 5 reported data on white matter structural asymmetry in the form of FA values in the arcuate and uncinate fasciculi in schizotypes and controls. Asymmetry was observed in FA values in the arcuate in both groups (left hemisphere FA values greater than right hemisphere), whilst no asymmetry in FA values of the uncinate was observed in either group. The extent to which ‘normal’ asymmetry occurs in the uncinate is debated (Hasan et al., 2009; Rodrigo et al., 2007), so the implications of the lack of between-group differences on asymmetric values remains uncertain. In summarising the functional/structural findings, there is no evidence from the current studies to support a failure of cerebral dominance. This could be interpreted as changes in cerebral dominance being either: 1) a characteristic of clinical samples; and/or 2) an aetiological mechanism that is applicable to serious mental illness and not schizotypy.

Theories of dysconnectivity (Friston, 1998; 1999) were supported albeit in an unexpected manner. Later formulations of the theory have stipulated that dysconnectivity does not necessarily equate to decreases in connectivity, and instead represents “abnormal” connectivity (Stephan et al., 2009). As discussed, it is not entirely clear whether the increase in FA values are indicative of an increase or decrease in connectivity, which is generally an issue with DTI studies. However, given the strong methodology used in the current study (i.e. magnet strength, number of diffusion directions, use of tractography), there is arguably a greater likelihood that the FA increase in schizotypes in the uncinate fasciculus could be representative of increased connectivity.

Therefore, what does this increase in connectivity mean in terms of theories of dysconnectivity? One proposal was that it could be evidence of a compensatory protective process, suggesting that changes in underlying white matter connectivity are important in the development of more serious illness. As these schizotypes were otherwise healthy, this evidence of an actual connectivity increase in a region which is shown to be decreased in patient groups, could be indirectly demonstrating the importance of this region in
transition. Caution must be taken however, since even in high-risk, FE and chronic patient samples, changes in tract coherence are not always found in this region. This may suggest that changes in white matter connectivity could be an epiphenomenon of other pathological processes. A second explanation in light of dysconnectivity theories is that the increase in tract coherence could represent the beginnings of a pathological process. The positive correlation between right arcuate fasciculus FA values and positive schizotypal features could destabilise beyond a threshold. Evidence linking hallucinatory experience with hyperconnectivity supports this (Hubl et al., 2004; Makris et al., 2010; Nenadic et al., 2010; Rotarska-Jagiela et al., 2008; Shergill et al., 2007). Using an attenuated form of symptoms could provide evidence of a cursory step in altered connectivity in the evolution of full blown psychosis. Longitudinal studies with high-risk samples are essential for charting structural changes throughout the transitional period. Retrospective studies comparing baseline images (i.e. before transition to psychosis: Peters et al., 2010) will also shed light on the temporal progression of white (and grey) matter changes. Further studies of this type will provide further evidence that will help elucidate the importance of white matter dysconnectivity as a pathophysiological mechanism in schizophrenia/psychosis.

4.7.2 Clinical implications

Arguably the DTI findings have most relevance in terms of clinical implications. By examining structures in related samples, it can provide baseline information that could help to predict transition in high risk studies. High risk clinics are refining prediction models by assessing rates of transition (e.g. Ruhrmann et al., 2010). Greater accuracy will enable more effective preventative measures to be taken that could stop or at least ameliorate the symptoms of full psychotic breakdown (Yung et al., 2007). Biomarkers such as structural white matter changes could help in these predictive models. A program of research has been begun to examine the extent to which white matter changes are occurring in ARMS (e.g. Karlsgodt et al., 2009; Peters et al., 2008), as well as comparing converters and non-converters (Peters et al., 2010; Walterfang et al., 2008). Studies examining white matter structures and attenuated psychotic symptoms in the general population can provide further comparative data. The most pervasive changes in brain structures appear to occur immediately preceding or after the first episode, leading to the proposal that schizophrenia-type syndromes have a late neurodevelopmental component (Pantelis et al., 2005). Therefore those individuals demonstrating reductions in grey and white matter volumes and less tract coherences could be at very high risk of transition. How this would be implemented in clinical practise is uncertain, although imaging methods are being
developed. Karlsgodt et al (2010) describes three studies that have used machine learning (pattern classification) to predict with high accuracy those with and without schizophrenia, and between converters and non-converters based on structural MRI scans.

Whether conducting brain imaging on purported high-risk groups is viable or provides useful clinical data is still open to debate. It could be argued that such techniques are impractical due to the cost, but given the expense of hospitalisation due to later illness, societal impact and most importantly the opportunity to improve the well-being of the individual, an ability to identify extreme ultra-high risk candidates would be invaluable in offering targeted treatments at a critical time. There are issues, however, in potentially identifying, labelling and treating high risk individuals even before illness is manifested which are beyond the scope of this study.

4.8 Limitations
This section discusses the limitations of the studies. Some have been discussed previously, so will only briefly be discussed.

4.8.1 Measuring schizotypy during adolescence
A possible limitation is the measurement of schizotypy in adolescent groups. Although adolescence is generally associated with heightened expression of schizotypal features, normal psychological development and emergence of psychopathologies can cloud the picture. A potential methodological step would be to incorporate measures that focus more on pathological features rather than unusual belief systems which could be over-reported in younger groups. As Wigman and colleagues (2009) suggested, there are likely two forms: those continuous with mental illness and those that are not. Targeting negative features may also identify younger participants more closely linked with risk for transition.

4.8.2 The schizotypal sample and detecting genuine schizotypes
As mentioned previously, it is possible that the sample comprises high scoring individuals on the SPQ that could be considered either neuro- or pseudoschizotypes (Raine, 2006). If as proposed only neuroschizotypes are related to clinical disorders and hence share similar phenotypes, a more concerted effort to recruit these types of participants would have been beneficial. For instance, to target the hypothetical neuroschizotypy with the proposed shared neurodevelopmental mechanisms, there could be inclusion of markers of abnormal
development such as dermatoglyphics and neurological soft signs, both of which are present in schizotypal samples (Barkus et al., 2006; Rosa et al., 2000).

The sole use of psychometric measurements of schizotypy therefore is a limitation to the study. For initial recruitment during Phase 1, questionnaire measures were a viable method to screen a large number of participants in an automated fashion. When selecting those for further investigation it would have been beneficial to conduct interview based assessments. It has been suggested that interview based measures of schizotypy are more sensitive in selecting groups with cognitive impairments (e.g. Bedwell et al., 2009). Their use would minimise problems found with self-report measures such as misinterpretation of items and normalising potential subclinical experiences (Murphy et al., 2010). Future studies could utilise both self-report questionnaires for initial selection, with follow-up interviews.

An alternative approach could be to categorise schizotypes based on biomarkers. For example, Lenzeweger et al. (2003) originally screened participants on the Perceptual Aberration Scale. This was followed by screening with two biomarkers: the Wisconsin Card Sorting Task and smooth pursuit eye-tracking. Via a statistical classification method, the sample were then categorised into false-positive and genuine schizotypes. On further cognitive tasks the genuine schizotypes had impaired performance compared to the false positives and a control group on measures of sustained attention and spatial working memory. Although such methods would be useful in reducing heterogeneity in schizotypy sample, it would have implications for the initial sample sizes required given that there would be two screening steps; one behavioural and one cognitive. If resources are available, however, this would be a prudent step to take in selecting schizotypes for studies.

4.8.3 Methodological limitations
The internet as a form of data collection was discussed in the methodology section, so will not be covered in detail again. Perhaps the greatest concern in regards to the internet as a source of participants is the generalisability of the study findings.

A limitation related to the whole sample is the extent to which they were high functioning individuals. In terms of the sociodemographics of the study, this was less problematic in the younger aged participants due to recruitment from Colleges in the North West region as demonstrated in the Methodology Chapter Section 2.3. However for the older participants,
there was an over representation of high achieving individuals, noticeable by the above average IQ. Careful consideration was required into whether it would be possible to detect the presumed subtle effects of schizotypy on cognition. To compound this was the choice of tasks, where a number of tasks suffered from ceiling effects, which in turn limits the interpretation of associations with schizotypy. Future studies would do well to both recruit more representatively and to select well validated cognitive measures not confounded by ceiling effects. One method would be to use stratified sampling. Although such methods would provide a far more representative sample, such techniques are difficult to implement particularly in the current PhD study which had limited funding, resources and time.

Another limitation was the ageing sample. One of the initial aims of the project was to examine the interaction between schizotypy and developmental stages to investigate whether there was a particularly “toxic” period for presence of schizotypal traits. To some extent this was captured during phase 1, where Paper 1 demonstrated the effects of age on schizotypal levels, and Paper 2 found age specific association between schizotypy and cognition. Notably though, the time delay between phase 1 (recruitment) and phase 2 (face-to-face testing) was between 6 and 18 months. During this dynamic period of psychological and neurodevelopment this small increase in age could have large implications, particularly when the potential social and environmental changes are also considered (i.e. some moving from college to university settings). The age increase for the adolescent group was even more noticeable by the final phase 3 (imaging). Age was controlled for in all subsequent analyses, but the aim to investigate schizotypy in an adolescent and adulthood sample was no longer feasible. With suitable time and resources, a future study would recruit and complete all stages for each participant in a short period of time, essentially controlling the age of the group. An additional practical benefit would be reduced attrition rates. As the age range 16-25 years contains college students leaving for universities in other regions, as well as university student who could be finishing their courses, it is probable that there would be a higher rate of returning participants if the study was completed in a shorter timeframe.

As is common with psychological studies, there was an overrepresentation of females in the phase 2 studies (Papers 3 and 4). Given the sex differences in association between schizotypy and cognition in Paper 2, it would have been intriguing to continue this line of research in face-to-face tasks. It is possible this not only accounts for some proportion of the heterogeneity found in schizotypy studies, but it could also provide useful information
into sex specific pathophysiological mechanisms. Unfortunately, due to time constraints and inability to sample sufficiently large numbers of males in the initial recruitment, it was not possible to select enough males to enable further investigation. This is certainly an area worthy of further research.

Information was not collected on family history of psychiatric disorders. For the internet survey it was initially deemed too intrusive and the ethics committee were uncomfortable with participants as young as 16 years being questioned about their family health. With hindsight, it would have been informative to collect family-history data. This would provide an insight into the extent of schizotypal features in relation to genetic proximity, and allow further classification of the sample on positive family history or not; in effect a basic way of attempting to categorise the sample into purported pseudo- and neuroschizotypes (Raine, 2006). As predicted in genetic-high risk studies (e.g. Diwadker et al., 2006; Laurent et al., 2001), a dual dose of risk factors may result in a greater cognitive deficit. A family-history of psychiatric disorders was not collected at the follow-up testing session either. This too could have been advantageous, so that such effects could be controlled for, or with sufficient sample size, identifying higher 'risk' groups.

Finally, there are the issues in relation to DTI imaging. The limitations of this technique are reported both in the PhD and the wider literature. A large number of these limitations relate to the multitude of protocols. In addition there are sources of heterogeneity in relation to clinical samples. The current study attempted to overcome many of these limitations; for instance the sample that did not have potential confounds of illness. Additionally it had what is considered a strong protocol in terms of: 1) field strength of magnetic (3T); 2) distortion correction to overcome artefacts that can occur in certain brain regions; 3) a large number of diffusion gradient directions to account for regions of crossing fibres; and 4) use of probabilistic tractography methods that are widely regarded as an excellent technique for identifying tracts. Even with these steps there are limitations to this technique in terms of what FA changes are actually representing, for instance, changes in myelination, axonal integrity etc. Leading experts in DTI state that despite nearly 15 years of development, DTI is still in its relative infancy (Kubicki, 2010). Even so, this is an area of research potential for further understanding the pathophysiological mechanisms in schizophrenia and related conditions.
4.9 Future directions

Beyond the areas of research that have been suggested during this discussion, other future directions of work are discussed.

It was suggested in Paper 1 that decreases in schizotypal features in relation to age could partly be explained by normative changes in personality measures. Few studies have examined the interaction between psychological maturation and schizotypal features. Longitudinal studies of personality have found certain traits declining during the transition from late adolescence to adulthood, including negative emotionality (Blonigen et al., 2008; Donnellan et al., 2007). It would be informative to examine the relation between schizotypal features and other personality traits in longitudinal studies. Even if schizotypal features are found to match ongoing normal developmental trends in personality, this would not discount the importance of this heightened period, rather it would demonstrate that due to biological and psychological development, adolescence is a particularly risky period for deviation from normal development.

To test the hypothesis that schizotypy could be an earlier representation of pathology associated with predominantly temporal lobe function and/or compensatory mechanisms, a possible line of work could be investigations into both structure and function simultaneously. As described, fMRI studies have indicated hypo- and hyperfunction in clinical samples during specific cognitive tasks. Applying similar paradigms to schizotypes would help in understanding whether functional changes exist on a continuum from normality to severe mental illness. A future imaging study could use compatible tasks (i.e. n-back task of working memory) to identify whether performance differences are accounted for by functional differences. Furthermore, the inclusion of other comparison groups would be useful in examining brain function across the continuum. For example, it could be envisioned that four groups would be recruited: controls, high schizotypes, ultra-high risk and schizophrenia first-episode patients. There could be comparisons made at baseline and after set-periods to determine the course of changes in three related groups. As Cannon (2005) states, there is a need for data in earlier phases of schizophrenia/psychosis development so that comparisons can be made between affected neural systems of those that have gone through transition and those at particular heightened risk.
With combined fMRI and DTI, it would also be possible to examine the relationship between structure and function. For instance, studies have demonstrated correlations between functional activation and measures of white matter FA values both in the general population (Olesen et al., 2003) and in schizophrenia patients (Schlosser et al., 2007). Furthermore, it is possible to use areas of fMRI activation to initiate tracking in DTI paradigms. Although there are currently technical issues in using fMRI activation as seed regions for tractography, it would serve as a guide for seed placement for initiating tractography algorithms. Using the example of working memory, it is reliant on multiple tracts including the uncinate fasciculus. It would therefore be possible to extract values of coherence from white matter structures that are connecting functionally active areas. An investigation of this type would allow a thorough examination of structure/function in schizotypy, and to determine whether there are differences, and if so, the proposed functional location and integrity of the supporting network. An example of this has recently been carried out in a sample of schizophrenia patients (Pomarol-Clotet et al., 2010). Via VBA, fMRI and DTI it was demonstrated that a region including the medial prefrontal cortex was shown to have reduced volume (VBA), hyperactivation during the n-back working memory task (fMRI) and reduced tract coherence to this region from the corpus callosum (DTI). Similar protocols could be applied to schizotypal samples to examine whether there are sites of altered brain structure/function compared to controls, as well as high-risk and patient groups.

4.10 Conclusions

In this series of linked studies there is evidence for placement of schizotypy on the extended phenotype of schizophrenia. It was shown to have similar psychological, and brain structural and functional characteristics with serious mental illness. However, this was in an attenuated form as evidenced by less prevalent and more subtle cognitive deficits, and differences in the extent of changes in white matter structures.

Increased schizotypal features were associated with subtle decreases in verbal learning/memory performance, but not with executive or attentional function. In terms of underlying brain structures, two white matter tracts that have been studied extensively in

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6 It is difficult to initiate tractography algorithms from functional activations due to the low FA values in grey matter. Functional MRI activations are mainly localized to regions of grey matter, but when these areas of used as seed regions, the low FA values represent greater uncertainty in the principal diffusion direction, and often tractography algorithms cannot initiate (Catani, 2006). Manually creating seed regions in white matter adjacent to functional activation is one method to overcome this issue.
clinical samples, were not found to have reduced FA values, rather, schizotypes had increased tract coherence in the uncinate fasciculus. It is uncertain what may cause this, although possible explanations include a compensatory protective factor, an early marker of pathology, or decreased diffuse connectivity. There was also evidence of a relationship of schizotypal features and greater tract coherence.

In summary, it was proposed that schizotypy could be associated with subtle minor changes in medial temporal lobe function, although further studies utilising functional imaging techniques would be required to confirm this. Given the sparing of executive function, it was also proposed that schizotypes could be buffered from further functional deficits via compensatory normal prefrontal function. Various aetiological and mechanistic processes suggest this region a critical in vulnerability/protection, and further lines of research could help elucidate these complex relationships. The use of schizotypy as a model has benefits in research, both as a personality trait and due to the purported links with schizophrenia. Even so, it could benefit from more rigorous selection criteria which could reduce heterogeneity in schizotypy samples.
Section 5  References


Park, CA.


**Crow, T. J.** (1997c). Temporolimbic or transcallosal connections: where is the primary lesion in schizophrenia and what is its nature? *Schizophrenia Bulletin* **23**, 521-3.


Hoff, A. L. & Kremen, W. S. (2002). Sex differences in neurocognitive functioning in


Neuropsychology 23, 315-336.


Archives of General Psychiatry 14, 323-326.


Parker, G. J. M., Luzzi, S., Alexander, D. C., Wheeler-Kingshott, C. A. M., Cleare,


Neurosciences 61, 616-21.


Suhr, J. A. & Spitznagel, M. B. (2001). Factor versus cluster models of schizotypal traits. II:


Section 6  Appendices

Appendix 1

Schizotypal Personality Questionnaire (SPQ) (Raine, 1991)

Taken from:
http://www-bcf.usc.edu/~raine/spq.htm

Please answer each item by checking Y (Yes) or N (No). Answer all items even if unsure of your answer. When you have finished, check over each one to make sure 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?

2. I sometimes avoid going to places where there will be many people because I will get anxious.

3. Have you had experiences with the supernatural?

4. Have you often mistaken objects or shadows for people, or noises for voices?

5. Other people see me as slightly eccentric (odd).

6. I have little interest in getting to know other people

7. People sometimes find it hard to understand what I am saying.

8. People sometimes find me aloof and distant.

9. I am sure I am being talked about behind my back.

10. I am aware that people notice me when I go out for a meal or to see a film.

11. I get very nervous when I have to make polite conversation.

12. Do you believe in telepathy (mind-reading)?

13. Have you ever had the sense that some person or force is around you, even though you cannot see anyone?

14. People sometimes comment on my unusual mannerisms and habits.

15. I prefer to keep to myself.

16. I sometimes jump quickly from one topic to another when speaking.
17. I am poor at expressing my true feelings by the way I talk and look.

18. Do you often feel that other people have got it in for you?

19. Do some people drop hints about you or say things with a double meaning?

20. Do you ever get nervous when someone is walking behind you?

21. Are you sometimes sure that other people can tell what you are thinking?

22. When you look at a person, or yourself in a mirror, have you ever seen the face change right before your eyes?

23. Sometimes other people think that I am a little strange.

24. I am mostly quiet when with other people.

25. I sometimes forget what I am trying to say.

26. I rarely laugh and smile.

27. Do you sometimes get concerned that friends or co-workers are not really loyal or trustworthy?

28. Have you ever noticed a common event or object that seemed to be a special sign for you?

29. I get anxious when meeting people for the first time.

30. Do you believe in clairvoyancy (psychic forces, fortune telling)?

31. I often hear a voice speaking my thoughts aloud.

32. Some people think that I am a very bizarre person.

33. I find it hard to be emotionally close to other people.

34. I often ramble on too much when speaking.

35. My "non-verbal" communication (smiling and nodding during a Y N conversation) is poor.

36. I feel I have to be on my guard even with friends.

37. Do you sometimes see special meanings in advertisements, shop windows, or in the way things are arranged around you?

38. Do you often feel nervous when you are in a group of unfamiliar people?

39. Can other people feel your feelings when they are not there?

40. Have you ever seen things invisible to other people?
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?

42. Some people find me a bit vague and elusive during a conversation.

43. I am poor at returning social courtesies and gestures.

44. Do you often pick up hidden threats or put-downs from what people say or do?

45. When shopping do you get the feeling that other people are taking notice of you?

46. I feel very uncomfortable in social situations involving unfamiliar people.

47. Have you had experiences with astrology, seeing the future, UFOs, ESP or a sixth sense?

48. Do everyday things seem unusually large or small?

49. Writing letters to friends is more trouble than it is worth.

50. I sometimes use words in unusual ways.

51. I tend to avoid eye contact when conversing with others.

52. Have you found that it is best not to let other people know too much about you?

53. When you see people talking to each other, do you often wonder if they are talking about you?

54. I would feel very anxious if I had to give a speech in front of a large group of people.

55. Have you ever felt that you are communicating with another person telepathically (by mind-reading)?

56. Does your sense of smell sometimes become unusually strong?

57. I tend to keep in the background on social occasions.

58. Do you tend to wander off the topic when having a conversation.

59. I often feel that others have it in for me.

60. Do you sometimes feel that other people are watching you?

61. Do you ever suddenly feel distracted by distant sounds that you are not normally aware of?

Y N 62. I attach little importance to having close friends.
63. Do you sometimes feel that people are talking about you?

64. Are your thoughts sometimes so strong that you can almost hear them?

65. Do you often have to keep an eye out to stop people from taking advantage of you?

66. Do you feel that you are unable to get "close" to people?

67. I am an odd, unusual person.

68. I do not have an expressive and lively way of speaking.

69. I find it hard to communicate clearly what I want to say to people.

70. I have some eccentric (odd) habits.

71. I feel very uneasy talking to people I do not know well.

72. People occasionally comment that my conversation is confusing.

73. I tend to keep my feelings to myself.

74. People sometimes stare at me because of my odd appearance.
Appendix 2

Peter’s et al. Delusions Inventory (PDI-21) (Peters et al. 2004)

This questionnaire is designed to measure beliefs and vivid mental experiences. We believe that they are much more common than has previously been supposed, and that most people have had some such experiences during their lives. There are no right or wrong answers to any of the questions. The answers to the questions will be kept confidential so be as honest as possible. We are not interested in experiences that you have had under the influence of any recreational drugs or alcohol. Please answer all the questions.

Please answer all questions

For the questions you answer YES to, we are interested in

(a) how distressing/upsetting these beliefs or experiences are;
(b) how often you think about these beliefs or experiences; and
(c) how true you believe them to be.

On the right hand side of the page we would like you circle the number which corresponds most closely to how distressing this belief is, how often you think about it, and how much you believe that it is true.

If you answer NO, please move on to the next question

Example

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<tr>
<th>Do you ever feel as if people are reading your mind?</th>
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| 2) Do you ever feel as if things in magazines or on TV were written especially for you? |
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| 3) Do you ever feel as if some people are not what they seem? |
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| Not at all | Very distressing |
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| Hardly ever | Think about it |
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| 4) Do you ever feel as if you are being persecuted in some way? |
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| 5) Do you ever feel as if there is a conspiracy against you? |
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6) Do you ever feel as if you are, or destined to be someone very important?

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7) Do you ever feel that you are a very special or unusual person?

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8) Do you ever feel that you are especially close to God?

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9) Do you ever think people can communicate telepathically?

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10) Do you ever feel as if electrical devices such as computers can influence the way you think?

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| 11) Do you ever feel as if you have been chosen by God in some way?     | Not at all
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| 12) Do you believe in the power of witchcraft, voodoo or the occult?   | Not at all
|                                                                         | Very distressing                           |
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| 13) Are you often worried that your friends are disloyal?             | Not at all
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| 14) Do you ever feel that you have sinned more than the average person? | Not at all
|                                                                         | Very distressing                           |
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|                                                                         | Believe it is absolutely true               |

| 15) Do you ever feel that people look at you oddly because of your appearance? | Not at all
|                                                                         | Very distressing                           |
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<td>16) Do you ever feel as if you had no thoughts in your head at all?</td>
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</tr>
<tr>
<td>17) Do you ever feel as if the world is about to end?</td>
<td>Not at all distressing 1  2  3  4  5</td>
</tr>
<tr>
<td>NO  YES (please circle)</td>
<td>Hardly ever think about it 1  2  3  4  5</td>
</tr>
<tr>
<td></td>
<td>Don’t believe it’s true 1  2  3  4  5</td>
</tr>
<tr>
<td>18) Do your thoughts ever feel alien to you in some way?</td>
<td>Not at all distressing 1  2  3  4  5</td>
</tr>
<tr>
<td>NO  YES (please circle)</td>
<td>Hardly ever think about it 1  2  3  4  5</td>
</tr>
<tr>
<td></td>
<td>Don’t believe it’s true 1  2  3  4  5</td>
</tr>
<tr>
<td>19) Have your thoughts ever been so vivid that you were worried other people would hear them?</td>
<td>Not at all distressing 1  2  3  4  5</td>
</tr>
<tr>
<td>NO  YES (please circle)</td>
<td>Hardly ever think about it 1  2  3  4  5</td>
</tr>
<tr>
<td></td>
<td>Don’t believe it’s true 1  2  3  4  5</td>
</tr>
<tr>
<td>20) Do you ever feel as if your own thoughts are being echoed back to you?</td>
<td>Not at all distressing 1  2  3  4  5</td>
</tr>
<tr>
<td>NO  YES (please circle)</td>
<td>Hardly ever think about it 1  2  3  4  5</td>
</tr>
<tr>
<td></td>
<td>Don’t believe it’s true 1  2  3  4  5</td>
</tr>
</tbody>
</table>
21) Do you ever feel as if you are a robot or zombie without a will of your own? (please circle)

<table>
<thead>
<tr>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not at all distressing</th>
<th>Very distressing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hardly ever think about it</th>
<th>Think about it all the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Don’t believe it’s true</th>
<th>Believe it is absolutely true</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 3

Launay-Slade Hallucinatory Scale (Launay and Slade 1981; Bentall and Slade 1985)

Instructions:
Please answer each item. It is important that you answer every item, even if you are not quite certain which is the best answer. An occasional item may refer to experiences that you have had only when taking drugs. Unless you have had the experience at other times (when not under the influence of drugs), mark it as if you have not had that experience.

Some items may sound like others, but all of them are slightly different. Answer each item individually, and don’t worry about how you answered a somewhat similar previous item.

Please circle the response that best describes you

Example

Sometimes a passing thought will seem so real that it frightens me

Certainly does not apply to me   Possibly applies to me   Unsure   Possibly does not apply to me   Certainly does not apply to me

Sometimes a passing thought will seem so real that it frightens me

Certainly does not apply to me   Possibly applies to me   Unsure   Possibly does not apply to me   Certainly does not apply to me

Sometimes my thoughts seem as real as actual events in my life

Certainly does apply to me   Possibly applies to me   Unsure   Possibly does not apply to me   Certainly does not apply to me
No matter how much I try to concentrate on my work unrelated thoughts always creep into my mind

<table>
<thead>
<tr>
<th>Certainly does apply to me</th>
<th>Possibly applies to me</th>
<th>Unsure</th>
<th>Possibly does not apply to me</th>
<th>Certainly does not apply to me</th>
</tr>
</thead>
</table>

In the past I have had the experience of hearing a person’s voice and then found that there was no-one there

<table>
<thead>
<tr>
<th>Certainly does apply to me</th>
<th>Possibly applies to me</th>
<th>Unsure</th>
<th>Possibly does not apply to me</th>
<th>Certainly does not apply to me</th>
</tr>
</thead>
</table>

The sounds I hear in my daydreams are generally clear and distinct

<table>
<thead>
<tr>
<th>Certainly does apply to me</th>
<th>Possibly applies to me</th>
<th>Unsure</th>
<th>Possibly does not apply to me</th>
<th>Certainly does not apply to me</th>
</tr>
</thead>
</table>

The people in my daydreams seem so true to life that I sometimes think they are

<table>
<thead>
<tr>
<th>Certainly does apply to me</th>
<th>Possibly applies to me</th>
<th>Unsure</th>
<th>Possibly does not apply to me</th>
<th>Certainly does not apply to me</th>
</tr>
</thead>
</table>

In my daydreams I can hear the sound of a tune almost as clearly as if I were actually listening to it

<table>
<thead>
<tr>
<th>Certainly does apply to me</th>
<th>Possibly applies to me</th>
<th>Unsure</th>
<th>Possibly does not apply to me</th>
<th>Certainly does not apply to me</th>
</tr>
</thead>
</table>

I often hear a voice speaking my thoughts aloud

<table>
<thead>
<tr>
<th>Certainly does not apply to me</th>
<th>Possibly applies to me</th>
<th>Unsure</th>
<th>Possibly does not apply to me</th>
<th>Certainly does apply to me</th>
</tr>
</thead>
</table>

I have never been troubled by hearing voices in my head

<table>
<thead>
<tr>
<th>Certainly does apply to me</th>
<th>Possibly applies to me</th>
<th>Unsure</th>
<th>Possibly does not apply to me</th>
<th>Certainly does not apply to me</th>
</tr>
</thead>
</table>

On occasions I have seen a person’s face in front of me when no-one was in fact there

<table>
<thead>
<tr>
<th>Certainly does apply to me</th>
<th>Possibly applies to me</th>
<th>Unsure</th>
<th>Possibly does not apply to me</th>
<th>Certainly does not apply to me</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have never heard the voice of the Devil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certainly does apply to me</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possibly applies to me</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unsure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possibly does not apply to me</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certainly does not apply to me</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In the past I have heard the voice of God speaking to me</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certainly does apply to me</td>
</tr>
<tr>
<td>Possibly applies to me</td>
</tr>
<tr>
<td>Unsure</td>
</tr>
<tr>
<td>Possibly does not apply to me</td>
</tr>
<tr>
<td>Certainly does not apply to me</td>
</tr>
</tbody>
</table>
Appendix 4

Sociodemographics of the Ward Areas and Local Authorities areas of the schools/colleges based on the Office for National Statistics 2001 census data. For each college the Ward area figures are presented with the higher Local authority figures in brackets. For example Pendleton college is in the Pendleton Ward, which is in the Salford Local authority. St John Rigby college is in the Pemberton Ward, but no data was available. Therefore figure are presented for the Local authority only (Wigan).

<table>
<thead>
<tr>
<th>Ward Areas (local authorities figures in brackets)</th>
<th>Local (^{10})</th>
<th>National</th>
</tr>
</thead>
<tbody>
<tr>
<td>School/College</td>
<td>Wigan</td>
<td>England</td>
</tr>
<tr>
<td>Pendleton College</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eccles College</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manchester Grammar School, Xaverian College</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheadle and Marple College</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holden Lane High School</td>
<td></td>
<td></td>
</tr>
<tr>
<td>St John Rigby College</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9,750 (216,103)</td>
<td>11,413</td>
<td>14,422 (392,819)</td>
</tr>
<tr>
<td>Employed %(^1)</td>
<td>32.0 (55.3)</td>
<td>58.6</td>
</tr>
<tr>
<td>Student %(^1)</td>
<td>10.4 (3.0)</td>
<td>2.2</td>
</tr>
<tr>
<td>Retired and other (^{1,2})</td>
<td>31.5 (32.8)</td>
<td>32.2</td>
</tr>
<tr>
<td>Unemployed %(^3)</td>
<td>4.7 (3.8)</td>
<td>3.3</td>
</tr>
<tr>
<td>Long term limiting illness(^1)</td>
<td>24.5 (22.8)</td>
<td>25.3</td>
</tr>
<tr>
<td>No qualifications (^1)</td>
<td>34.2 (35.5)</td>
<td>31.3</td>
</tr>
<tr>
<td>Level 1 qualifications (^{1,3})</td>
<td>10.6 (16.4)</td>
<td>14.3</td>
</tr>
<tr>
<td>Level 2 qualifications (^{1,4})</td>
<td>13.9 (18.6)</td>
<td>18.5</td>
</tr>
<tr>
<td>Level 3 qualifications (^{1,5})</td>
<td>25.2 (8.2)</td>
<td>7.5</td>
</tr>
<tr>
<td>Level 4/5 qualifications (^{1,6})</td>
<td>11.9 (14.4)</td>
<td>21.8</td>
</tr>
<tr>
<td>Owner occupied (^7)</td>
<td>24.1 (56.4)</td>
<td>58.5</td>
</tr>
<tr>
<td>Rented (^8)</td>
<td>19.9 (12.2)</td>
<td>14.8</td>
</tr>
<tr>
<td>Council/Housing association (^9)</td>
<td>56.0 (31.4)</td>
<td>26.7</td>
</tr>
</tbody>
</table>

\(^1\) Aged 18-74; \(^2\) These include individuals who are retired, those looking after ill relatives, those permanently sick/disabled, otherwise inactive for reasons unknown; \(^3\) e.g. GCSEs (General Certificate of Secondary Education) grades D-G, Level 1 BTEC (Business and Technology Educational Council) awards or NVQs (National Vocational Qualifications) at Level 1; \(^4\) e.g. GCSEs grades A*-C, Level 2 BTEC awards or NVQs at Level 2; \(^5\) e.g. A-Levels (Advanced Level General Certificate of Education), Level 3 BTEC awards or NVQs at Level 3; \(^6\) e.g. certificates of higher education, Higher National Certificates/Diplomas, BTEC Professional Diplomas Certificates or NVQs at Levels 4/5; \(^7\) Owner occupied includes owns outright, owned with mortgage/loan, shared ownership; \(^8\) Rented includes private landlord or letting agent; \(^9\) Local authority council housing, housing association or registered social landlords; \(^{10}\)- No data for Pemberton ward where St John Rigby college located, so presented local level data from Wigan Metropolitan Borough.
Fig 1: SPQ total score Vs CPT average response time.

Fig 2: IOF subscale score Vs CPT average response time.

Fig 3: ESA subscale score Vs CPT average response time.

Fig 4: UPE subscale score Vs CPT average response time.
Fig 5: OS subscale score Vs CPT average response time.  
Fig 6: OBMI subscale score Vs CPT average response time

Fig 7: OEB subscale score Vs CPT average response time.  
Fig 8: NCF subscale score Vs CPT average response time
Fig 9: CA subscale score Vs CPT average response time.

Fig 10: SU subscale score Vs CPT average response time

Fig 11: SPQ total score Vs CPT MAD average.

Fig 12: IOF subscale score Vs CPT MAD average
Fig 13: ESA subscale score Vs CPT MAD average.

Fig 14: UPE subscale score Vs CPT MAD average

Fig 15: OS subscale score Vs CPT MAD average.

Fig 16: OBMI subscale score Vs CPT MAD average
Fig 17: OEB subscale score Vs CPT MAD average.

Fig 18: NCF subscale score Vs CPT MAD average

Fig 19: CA subscale score Vs CPT MAD average.

Fig 20: SU subscale score Vs CPT MAD average
Fig 21: Example of scatter plot with non-normally distributed data, e.g. SPQ total vs CPT d'
Fig 1: SPQ total score Vs TEA Selective Attention Score.

Fig 2: IOF subscale score Vs TEA Selective Attention Score.

Fig 3: ESA subscale score Vs TEA Selective Attention Score.

Fig 4: UPE subscale score Vs TEA Selective Attention Score.

Appendix 6 – Scatter plots for SPQ Scores (Total and 9 subscales) Vs Attention and Executive Function performance Indices
Fig 5: OS subscale score Vs TEA Selective Attention Score.  
Fig 6: OBMI subscale score Vs TEA Selective Attention Score

Fig 7: OEB subscale score Vs TEA Selective Attention Score.  
Fig 8: NCF subscale score Vs TEA Selective Attention Score
Fig 9: CA subscale score Vs TEA Selective Attention Score.

Fig 10: SU subscale score Vs TEA Selective Attention Score

Fig 11: SPQ total score Vs TEA Divided Attention Score.

Fig 12: IOF subscale score Vs TEA Divided Attention Score.
Fig 13: ESA subscale score Vs TEA Divided Attention Score.  
Fig 14: UPE subscale score Vs TEA Divided Attention Score

Fig 15: OS subscale score Vs TEA Divided Attention Score.  
Fig 16: OBMI subscale score Vs TEA Divided Attention Score
Fig 17: OEB subscale score Vs TEA Divided Attention Score. Fig 18: NCF subscale score Vs TEA Divided Attention Score

Fig 19: CA subscale score Vs TEA Divided Attention Score. Fig 20: SU subscale score Vs TEA Divided Attention Score
**Fig 21:** SPQ total score Vs RVP d'

**Fig 22:** IOF subscale score Vs RVP d'

**Fig 23:** ESA subscale score Vs RVP d'

**Fig 24:** UPE subscale score Vs RVP d'
Fig 29: CA subscale score Vs RVP d’

Fig 30: SU subscale score Vs RVP d’

Fig 31: SPQ total score Vs FAS Total Score.

Fig 32: IOF subscale score Vs FAS Total Score.
Fig 33: ESA subscale score Vs FAS Total Score.

Fig 34: UPE subscale score Vs FAS Total Score

Fig 35: OS subscale score Vs FAS Total Score.

Fig 36: OBMI subscale score Vs FAS Total Score
Fig 37: OEB subscale score Vs FAS Total Score.

Fig 38: NCF subscale score Vs FAS Total Score

Fig 39: CA subscale score Vs FAS Total Score.

Fig 40: SU subscale score Vs FAS Total Score
Fig 41: SPQ total score Vs Trails B Time.

Fig 42: IOF subscale score Vs Trails B Time.

Fig 43: ESA subscale score Vs Trails B Time.

Fig 44: UPE subscale score Vs Trails B Time.
Fig 45: OS subscale score Vs Trails B Time.

Fig 46: OBMI subscale score Vs Trails B Time

Fig 47: OEB subscale score Vs Trails B Time.

Fig 48: NCF subscale score Vs Trails B Time
Fig 49: CA subscale score Vs Trails B Time.

Fig 50: SU subscale score Vs Trails B Time
Fig 1: SPQ total score Vs Line Bisection Left Hand.

Fig 2: IOF subscale score Vs Line Bisection Left Hand.

Fig 3: ESA subscale score Vs Line Bisection Left Hand.

Fig 4: UPE subscale score Vs Line Bisection Left Hand.
Fig 5: OS subscale score Vs Line Bisection Left Hand.

Fig 6: OBMI subscale score Vs Line Bisection Left Hand

Fig 7: OEB subscale score Vs Line Bisection Left Hand.

Fig 8: NCF subscale score Vs Line Bisection Left Hand
Fig 9: CA subscale score Vs Line Bisection Left Hand.

Fig 10: SU subscale score Vs Line Bisection Left Hand

Fig 11: SPQ total score Vs Line Bisection Right Hand

Fig 12: IOF subscale score Vs Line Bisection Right Hand
Fig 13: ESA subscale score Vs Line Bisection Right Hand

Fig 14: UPE subscale score Vs Line Bisection Right Hand

Fig 15: OS subscale score Vs Line Bisection Right Hand

Fig 16: OBMI subscale score Vs Line Bisection Right Hand
Fig 17: OEB subscale score Vs Line Bisection Right Hand

Fig 18: NCF subscale score Vs Line Bisection Right Hand

Fig 19: CA subscale score Vs Line Bisection Right Hand

Fig 20: SU subscale score Vs Line Bisection Right Hand
Fig 21: SPQ total score Vs Landmark Task

Fig 22: IOF subscale score Vs Landmark Task

Fig 23: ESA subscale score Vs Landmark Task

Fig 24: UPE subscale score Vs Landmark Task
Fig 25: OS subscale score Vs Landmark Task

Fig 26: OBMI subscale score Vs Landmark Task

Fig 27: OEB subscale score Vs Landmark Task

Fig 28: NCF subscale score Vs Landmark Task