



**POSITIVE SCHIZOTYPY: A PROPOSED  
ENDOPHENOTYPE FOR PSYCHOSIS IN  
NEUROLOGICAL DISORDERS**

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# ABSTRACT

In the current thesis, a model whereby the fully dimensional expression of positive schizotypal (PS) personality traits represents a psychological and biological diathesis that would predict psychotic decompensation in states of neurological stress was theoretically conceptualised and empirically validated. To our knowledge, this is the first piece of work to fully reconcile a predispositional psychological and biological susceptibility within a diathesis stress model of neurological psychosis. Whilst previous studies have assessed psychological or biological vulnerabilities to the development of psychotic symptoms in neurodegenerative and functional models, to date no individual study has theoretically or experimentally combined these features.

The predictive ability of PS for neurological psychosis was validated on interdependent neuroanatomical, psychological, emotional, cognitive and symptomatic levels. The validity of PS as an endophenotype for neurological psychosis was tested across several behavioural and neuroimaging studies. The most compelling cognitive evidence for the endophenotype's validity was the finding that PS is associated with a bias to make false positive confabulatory style memories for psychosis congruent words. This finding converges with behavioural and anatomical evidence for a relationship between confabulation and delusions in pathological populations and was supported by the neuroimaging study of the individual differences of PS traits in healthy young individuals undertaken for the current thesis. Individual differences in schizotypal traits in normal individuals were found to be reflected endophenotypically in the structure of the brain in the bilateral but predominantly right frontal regions that have been anatomically and behaviourally related to psychosis in previous studies. The endophenotype was also validated as predicting psychosis in single case studies of patients with various diagnoses and was behaviourally and anatomically associated with the psychotic reactions of patients with Parkinson's disease to Levodopa medication. The validation studies suggest that, independent of aetiology, psychosis appears to be supported by bilateral but predominantly right sided frontal and limbic regions. The majority of individuals with this non-standard but dimensional trait will not decompensate into psychosis. However, the clinical data suggests that when individuals with high PS traits are under the duress of a significant affective, neurodegenerative or neuropharmacological stressor, the prominent symptom will be psychosis.

*I would like to dedicate this thesis to Peter Charles Bruen, my father and my best friend. You will always be the rock that gives me strength and inspiration. You are the benchmark for all my standards and I will always endeavour to make you proud.*

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# CHAPTER 1

## INTRODUCTION

### *1.1 ISOLATING A VIABLE ENDOPHENOTYPE TO EXPLORE THE AETIOLOGY OF PSYCHOSIS IN NEUROLOGICAL DISORDERS*

The working hypothesis behind the current thesis arose from a prior study which investigated the neuroanatomical correlates of neuropsychiatric symptoms in a group of patients with mild Alzheimer's disease (AD; Bruen et al., 2008). The study determined some neuropsychiatric symptoms manifest in mild AD were associated with atrophy of well-defined brain structures. The findings of this study demonstrated discrete relationships between behaviour and brain structure with remarkable specificity for patients at such a mild stage of the disease. Equally striking was the convergence between the associations that were found between behaviour and brain structure and the findings from other studies utilising different brain mapping methodologies and investigating a variety of patient groups. A summary of the rationale and main findings follows.

Noncognitive neuropsychiatric alterations are ubiquitous in neurological and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Lewy body dementia and frontotemporal dementia (Mega, Cummings, Fiorello & Gornbein, 1996; Fenelon, 2008; Cummings 2003; Leroi, Voulgari, Breitner et al., 2003; Rosen et al., 2005). Compared with other symptoms of neurodegenerative

disorders, such as neuropsychological manifestations, neuropsychiatric symptoms produce disproportionate distress to both patients and care givers (Cummings, 2003). Some of the most disruptive neuropsychiatric symptoms include delusions, hallucinations, apathy, agitation, irritability and disinhibition (Cummings, 2003). Such behaviours and symptoms may also predict and exacerbate cognitive decline (Wragg, & Jeste, 1989; Scarmeas et al., 2005) and anticipate more rapid deterioration (Mega, Cummings, Fiorello & Gornbein, 1996). Furthermore, noncognitive behavioural alterations have been associated with earlier and higher rates of patient institutionalisation (Yaffe et al., 2002), and with poorer prognosis.

Whilst behavioural and psychiatric symptoms are common in a number of neurodegenerative disorders, for methodological reasons, in this study the authors decided to only recruit patients with mild AD. AD, especially in the mild stage of the disease, where typical onset neuropathology is well documented and appears to be comparatively circumscribed to specific brain regions, can serve the function as a model through which the neuroanatomical regions involved in neuropsychiatric symptoms can be more readily detected and discriminated from non-related pathology. This approach is yielding valuable information about AD aetiology whereby individual symptoms and clusters of symptoms may be suggestive of specific sub-syndromes each with possible different natural histories (Cummings 2003).

In as much as neuropsychiatric research within AD patients is essential for our understanding of the disease itself, findings can also be generalised to disorders with more ambiguous neurobiological evidence, such as schizophrenia, bipolar

disorder and other neurological disorders. In terms of generalisability, such research may provide evidence for the development of more accurate structural-theoretical accounts of these symptoms and behaviours in both pathological and normal populations thus providing clarifications of the mechanisms and circuits involved in the regulation of social and emotional behaviours.

Voxel-based morphometry was used to identify those regions where lower grey matter volume correlated with higher frequency and severity of individual neuropsychiatric behaviours measured by the Neuropsychiatric Inventory (NPI; Cummings et al., 1994). Voxel-wise multiple regression analyses revealed that of the neuropsychiatric symptoms assessed in our sample, higher frequency and severity ratings of apathy, agitation and delusions were individually associated with significantly reduced grey matter in specific brain regions. Whilst each correlation converged with a priori predictions, it was the findings for delusions which have been seminal in the formation of the current thesis.

High scores for delusions were found to be significantly and discretely correlated with low grey matter volume in the right inferior parietal lobe and in bilateral inferior frontal gyri (with pronounced asymmetrical right dominance). Significant inverse correlations were also found in the medial frontal gyri and in the claustrum of the left hemisphere (please see Table 1.1 and Figure 1.1)

Table 1.1. Areas of significant correlation between GM density values and delusions

Brain area	Right/Left	Brodmann's area	Talairach Co-ordinates			Z-value at local maximum
			x	y	z	
<b>Delusions (<math>P &lt; 0.01</math>)</b>						
Inferior frontal gyrus	R	45	50	18	12	3.49
Inferior parietal lobule	R	40	34	-50	41	3.04
			42	-52	43	2.79
Inferior frontal gyrus	L	45	-55	22	15	3.14
			-51	26	21	2.88
Medial frontal gyrus	L	11	-8	61	-15	2.86
			-1	56	-15	2.66
Clastrum	L		-38	-2	4	2.75



Figure 1.1. Sagittal view of the right frontal and parietal regions where a significant correlation with the presence and severity of delusions was found.

The association between delusions and atrophy, predominantly in the right frontoparietal regions, supports findings from earlier metabolic and regional cerebral blood flow (rCBF) studies (Staff et al., 1999; Sultzer et al., 2003). Whilst there was a smaller cluster of significant correlation in the left frontal cortex, almost twice as many voxels were significantly associated with delusions in the right hemisphere. Such right/left asymmetry has previously been associated with delusions in a CT study (Forstl et al., 1991) and right fronto parietal dysfunction

has also frequently been reported in case studies of individuals with misidentification delusions (Feinberg et al., 1999; Shanks and Venneri, 2002). Such evidence suggests that a selective and severe impairment of the right anterior hemisphere, which is associated with delusional symptoms, may appear in certain patients at a relatively early disease stage.

There are two main lines of reasoning that could offer explanations concerning the co-occurrence of delusions with predominantly right anterior hemisphere damage. Firstly, this rather focal atrophy could be a manifestation of the regional variance in the onset of Alzheimer's disease neuropathology. However, based on the congruence between an association between delusional symptoms and this brain region in other neurological illnesses (Staff et al., 1999; Sultzer et al., 2003; Forstl et al., 1991; Feinberg et al., 1999; Shanks and Venneri, 2002), it seems more reasonable to suspect that such findings may reflect individual differences in structural genetic vulnerability and/or neurodevelopmental susceptibility. In this explanation, the aetiology of the early emergence of delusional psychosis in these individuals could be due to a predisposing, pre-pathological structural genetic liability which remains latent until expressed endophenotypically through neurodegeneration.

In order to empirically test the plausibility of the latter explanation, a viable endophenotype must be identified through which to explore the aetiology of positive symptoms in neurological disorders.



## ***1.2 ENDOPHENOTYPES***

According to Waldman (2005) an endophenotype is a valid and salient intervening construct that might help to explain the relationship between genes and manifest psychotic symptoms. The concept of endophenotypes was originally described by Gottesman and Shields (1965) in relation to psychiatric disorders, in its genesis the concept was especially applied to investigations concerning the association between genes and schizophrenia. Although the construct of the endophenotype was originally limited to microscopic or biochemical markers, criteria have subsequently been expanded to include any measurable candidate providing that it is observable below the level of diagnosis (McCloskey, New, Siever et al., 2009). Due to its intermediate position between liability and actual trait or disorder, the endophenotype may reveal a previously inaccessible causal pathway from the aetiology of a disorder to its associated psychological processes and behaviours (Kuntsi, Andreou, Ma et al., 2005).

Endophenotypes are the behaviourally manifest biological markers which reside between genotype and phenotype, they have been characterised as the 'quantifiable components in the genes-to-behaviours pathways' (Gould & Gottesman, 2006). This unique position makes the concept of endophenotype especially valuable to research involving the aetiology of complex psychological and psychiatric illnesses which are inherently genetically ambiguous. Once identified, the endophenotype may distinguish vulnerability to or reveal pre-clinical signs specific to distinct psychiatric disorders (Glannon, 2003). According to Glannon, when an endophenotype is well defined it may enable enhanced understanding of a particular psychiatric illness through the extrication of its biological components. Inevitably, an endophenotype should improve diagnostic

validity and predictive ability, and guide more effective interventions and preventative actions. Savitz et al., (2006) advocate the use of endophenotypes because complex traits inevitably resist conclusive causal inferences, even where good candidate genes have been identified. Such has been the case in suicide research where identifying the genes related to suicidal ideation and behaviours is obfuscated by complex gene environment interactions and genetically heterogeneous samples. Recently, studies utilising the endophenotype concept have been achieving success in schizophrenia (Smith, Cloniger, Harms, et al., 2008), depression (Savitz, Cupido & Ramesar), ADHD (Kuntsi, Andreou, Ma et al., 2005) and suicide (Baud, 2005; Roy, 2002) research. Examples of endophenotypes for schizophrenia include working memory difficulties and impairments in prepulse inhibition (Gottesman & Gould, 2003), whereas impulsive aggressive behaviours have been identified as a possible endophenotype for completed suicide (Zouk, McGirr, Lebel et al., 2007).

Current criteria aim to distinguish the endophenotype from cognitive or biological markers through the addition that an endophenotype must obtain conclusions that are both genetically and biologically salient. Recently, the criteria necessary for the identification of endophenotypes have been tested and sophisticated (Gershon & Goldin, 1986; Lenox et al., 2002) and synthesised in Gottesman & Gould's (2003) specifications that:

- 1 An endophenotype is associated with illness, in the population.
- 2 An endophenotype is heritable.
- 3 An endophenotype is state independent (manifests in an individual whether or not illness is active) but age-normed and may need to be elicited by a challenge.

4 Within families, endophenotype and illness cosegregate.

5 An endophenotype identified in probands is found in their unaffected relatives at a higher rate than in the general population (Gottesman & Gould 2003)

In addition to the above criteria, Waldman (2005) suggests an endophenotype should also have good psychometric properties and that common genetic properties should subservise both endophenotype and disorder. Waldman argues that these specifications are essential for evaluating a possible endophenotypes' validity.

Whilst the endophenotype confers a certain genetic vulnerability for a disorder, the disorder is liable to remain unexpressed in relatives of affected probands. Furthermore, as such endophenotypes should potentially reveal pathophysiological markers of the disorder in healthy persons, investigation of these individuals ought to circumvent confounds that are inescapably introduced by treatment, chronicity and institutionalisation that may obscure results in patient studies.

Our endophenotype is therefore an elementary intermediary factor that resides between genes and phenotype on a 'developmental pathway' (Savitz, Cupido & Ramesar, 2006; Gottesman & Gould, 2003). The phenotype of interest in the current thesis is delusions, or more broadly psychosis and specifically psychosis as a manifestation of neurological disorders. Therefore if psychosis, the consequence of different and complex genetic, environmental and neurological variables, is our phenotype, the endophenotype must be a more basic trait that is

highly associated with psychosis. Compared with the phenotype, the genetic architecture of the endophenotype must be more transparent and tractable (Savitz et al., 2006) and offer simpler clues to genetic associations than disease status (Chen, Kuo & Lin, 2004).

Identification of appropriate endophenotypic genetic correlates would enhance the prospect of earlier detection of individuals who may be at risk for neurological psychosis, suggest more targeted interventions based on these individuals' specific genetic vulnerabilities and propose explanations concerning the aetiology of neuropsychiatric symptoms under certain neurological conditions.

### ***1.3 ALZHEIMER'S DISEASE AS A PSYCHOSIS PHENOTYPE***

The primary objective of this thesis is to identify an endophenotype that will advance explanations of the emergence of psychosis in various neurodegenerative and neurological disorders. However, at present it may be useful to narrow the focus onto the research supporting the theory that Alzheimer's disease with psychosis (AD+P) is a distinct phenotype. This approach may suggest candidate endophenotypes that are generalisable to other neurological disorders as well as AD. Moreover, the method of constructing endophenotypes from well defined phenotypes has proven successful in studies of other complex diseases (Gottesman & Gould, 2003; Chen, Kuo, Lin et al., 2004).

Currently, AD is the most common cause of dementia, and in the general population its incidence is reported to be between 2.5 and 5 percent (Cummings, 2003). AD is a neurodegenerative brain disease in which the cerebral cortex is extensively damaged. The progressive damage to the cerebral cortex results in the

gradual loss of higher cognitive functions (Lopez & Becker, 2004) and changes in personality and behaviour (Rosen et al, 2005; Cummings 2003). The aetiology of AD remains unknown, and its natural history is heterogeneous across patients, whilst many symptoms are common to all patients, clinical and neuropathological dissociations are apparent. Within the central nervous system, neurological and physiological changes are progressive (Hart & Semple, 1994) and at a microscopic level, senile/ neuritic plaques (accumulation of beta-amyloid in toxic form; Hashimoto, Rockenstein, Crews, & Masliah, 2003), and neurofibrillary tangles (accumulations of Tau protein; Goedert, Klug & Crowther, 2006) are evidence of the effects of AD on brain cells. Another primary feature of AD is a neurotransmitter deficit in the cholinergic system and reduction in the levels of acetylcholine which has been especially implicated in the memory deficits that characterise AD (Morris, 2004).

As previously discussed, psychosis has frequently been observed in a large proportion of patients with AD (Hirono, Mori, Yasuda et al., 1998). This vulnerability towards psychosis, in combination with the prevalence of AD in the population has established AD as the second largest source of psychotic states after schizophrenia (White & Cummings, 1996). Recent neuroanatomical evidence suggests AD, especially in its mild stage, provides a valuable model through which to investigate the genetic and anatomical contributions to the emergence of psychosis (Bruen, McGeown, Shanks & Venneri, 2008).

Despite considerable gene mapping efforts, the genetic basis of AD is still unspecified and only some of the genes that contribute to AD risk have been identified (Sweet et al., 2003). It is increasingly becoming practice to conduct

gene mapping liability investigations on more homogeneously defined subgroups of AD. According to Sweet et al., (2003), AD with the presence of psychosis, namely delusions and/or hallucinations, represents a suitable AD subgroup for genetic investigation. This has led to the identification of Alzheimer's disease with psychosis (AD+P) as a putative distinct phenotype (Erer et al., 2005; Sweet et al., 2002). The AD+P phenotype has already proven useful for genetic analysis and evidence suggests that psychotic symptoms in AD may be familial (Sweet et al., 2002; Tunstall et al., 2000). In UK and US samples, significant associations between the occurrence of AD+P and proband psychotic status have been found in siblings (Erer, Lopez, Dekosky, & Sweet, 2005; Hollingworth, Hamshere, Holmans et al., 2007; Sweet et al., 2002) and the heritability for psychosis in AD has been estimated to be between 30 and 61 percent (Bacanu et al., 2005).

Evidence suggests that as a prodrome of AD, psychotic symptoms are rare (Rubin & Kinscherf., 1989) and in the early stage of the disease delusions and hallucinations are quite infrequent (Lykestos et al., 2000). In terms of prevalence, psychotic manifestations appear to increase linearly as the disease progresses from mild to moderate stages (Sweet et al., 2003). Although most frequently associated with more moderate and severe disease stages, these symptoms can emerge early in the course of the disease, are sometimes evident before cognitive decline is detected (Bidzan et al., 2008) and in some cases, neuropsychiatric symptoms and behaviours actually define central diagnostic features of the illness (Cummings, 2003). Recently, further evidence for the appearance of psychosis in the minimal stage of AD has been established by studies specifically assessing mild AD (Bruen et al., 2008) and from case studies (Venneri, Shanks, Staff et al., 2000; Shanks & Venneri, 2002).

Despite these recent efforts, it is still difficult to ascertain the true prevalence of AD+P across AD disease stages as there is limited research being conducted with patients at the early stages and the majority of research designs in the field uses large mixed samples of patients with differing neuropathology and disease severities (Rosen et al.,2005). However, it is apparent that as the incidence of AD+P is reported to be manifest in only 40 to 60 percent of all AD patients (Paulsen et al.,2000; Forstl et al., 1994) it cannot be interpreted as an inevitable and nonspecific concomitant of increased disease severity (Sweet et al., 2003). Converging evidence for this conclusion has been demonstrated by studies that have reported that whilst AD+P prevalence increases from mild to moderate stages, its incidence decreases in the late stages (Devanand, Jacobs, Tang et al., 1997).

Study at the endophenotypic level may provide more insight into the aetiology of the emergence of the AD+P phenotype. The fact that some individuals express the AD+P phenotype at an early stage compared with others may reflect variance in the extent to which the endophenotype is expressed within individuals. This would also indicate that the threshold of AD, or other neurodegenerative, pathology required to reveal the phenotype would vary considerably amongst individuals as a function of individual differences in endophenotypic expression.

There is also consistent evidence that AD+P denotes increased vulnerability for more severe cognitive impairment (Sweet et al., 2003; Stern et al., 1987; Paulsen et al., 2000) and that psychosis, especially of the delusional type may be related to impairments in a specific set of cognitive abilities (Shanks & Venneri, 2004; Venneri, Shanks, Staff et al., 2000; Shanks & Venneri, 2002). Whilst causality

has yet to be conclusively established, the increased liability for severe cognitive impairment in AD+P has previously been interpreted as evidence that the real phenotype of AD+P is accelerated cognitive decline (Sweet et al., 2003).

However, the way in which psychosis is inextricably associated with cognitive impairments in disorders such as schizophrenia (Sweet et al., 2003; Sweet & Pollock, 1999) and depression (Vinkers et al., 2004) suggests psychosis and cognitive dysfunction are likely to be subserved by a shared mechanism, rather than implying a causal pathway whereby exaggerated cognitive impairments instigate psychosis. The implication that there may be a combined liability of psychosis and excessive cognitive dysfunction in neurodegenerative disorders may be helpful to note when selecting a viable endophenotype. Consequently, the endophenotype should be theoretically associated or at least compatible with models of the cognitive and physiological contributions to the development of psychosis (Shanks & Venneri, 2004; Ellis & Lewis, 2001; Frith, 1999).

The relationship between increased cognitive impairment and variance in onset of AD+P relative to disease stage appears to suggest that AD+P, rather than being an artefact of the more severe stage of illness is supported by a distinct pathology subserving the generation of psychotic symptoms and the associated excess cognitive impairments (White & Cummings 1996). Findings that are congruent with this concept have been emerging from studies of cognition and psychosis in subjects with schizophrenia (Garety et al., 2003).

In relation to AD+P, Sweet et al., (2003) propose three distinct causal pathways through which AD+P onset can be explained (See Figure 1.2 below).



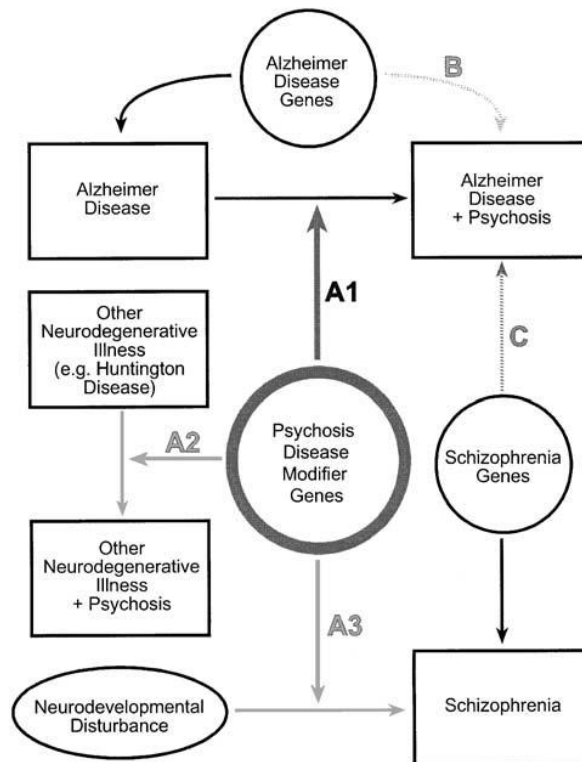


Figure 1.2. Pathways to AD and AD+P (Sweet et al., 2003, p.387).

Firstly, Sweet et al., suggest certain genetic modifier alleles confer risk of psychosis after AD onset or subsequent to the onset of other neurodegenerative or neurodevelopmental illnesses. Secondly, they suggest that genes that constitute risk for idiopathic psychoses like schizophrenia could also contribute to psychosis liability given certain neurological conditions. A third pathway proposes that specific AD pathology alone could lead to AD+P. Expanding on this idea Error et al. (2005) suggest the effects of genetic variation could be exerted through a neurodegenerative process such as AD and this may accelerate the neurodegenerative process in a manner which generates AD+P. Alternatively, and more in line with our hypothesis, Error et al. posit that through the course of neurodevelopment, genetic factors could create a risk factor phenotype which would manifest AD+P through the addition of AD pathology.

#### ***1.4 ALZHEIMER'S DISEASE AND SCHIZOPHRENIA***

With reference to the above model, it is interesting to speculate whether there may be even more concomitant features between the genes which confer risk for schizophrenia and those which predispose individuals to psychosis due to AD or other neurodegenerative pathology. Whilst delusions are a prevalent feature of neurodegenerative disorders such as AD, within the clinical literature they are characterised as hallmark symptoms of schizophrenia. Although psychosis is by no means unique to schizophrenia 'it has long served as the prototype psychosis' (White & Cummings, p.188). There is considerable resemblance between the positive symptoms in dementia disorders and those manifest in schizophrenia although in dementia disorders such as AD, delusions are usually unsystematised and loosely held (Goodman, 1953) and visual hallucinations are more frequent, whilst auditory hallucinations are more prominent in schizophrenia (white & Cummings 1996). Evidence suggests there may be shared genetic factors underlying both disorders (Sweet et al., 2003) an examination of the similarities and differences between these disorders may therefore help to clarify why these shared genetic factors can lead to schizophrenia, relative health or to psychosis due to a neurodegenerative disease such as AD.

In both diseases, neuroimaging studies have consistently revealed ventricular enlargement and larger cortical sulci (Johnstone, Crow, Frith et al., 1976) and atrophy of medial temporal structures (White & Cummings, 1996).

Neuropathology, neuroimaging and neuropsychological studies have also reliably implicated frontal lobe dysfunction as being a central feature of the pathogenesis of schizophrenia (Weinberger et al., 2001) and AD (Cummings et al., 2003).

Convergent metabolic abnormalities include reduced frontal and medial temporal

metabolism and pathological changes in the limbic system are also observed in both disorders although they are more severe in AD than schizophrenia.

In terms of neurochemistry, the dopamine hypothesis is the most accepted neurochemical explanation for the positive symptoms of schizophrenia (Sue et al., 2004). This hypothesis suggests psychotic symptoms are due to overactivity of the dopaminergic system. Supporting evidence for this hypothesis has been derived from the finding that dopaminetic drugs can produce positive schizophrenia like symptoms (Honey et al., 2008; Corlett et al., 2007) and that these symptoms can be ameliorated through pharmacological devices designed to reduce dopaminergic activity.

In AD, alterations in the cholinergic system, with reduced concentrations of acetyltransferase and acetylcholine are the most evident neurochemical changes (Cummings, 2003). It has been argued that as a dynamic balance of dopamine and acetylcholine is essential to the regulation of striatal processes, any alteration in either neurotransmitter which distorts this balance could result in psychosis (White & Cummings, 1996). Although the dopaminergic excess evidenced in schizophrenia is not apparent in AD, reduced cholinergic levels and maintained dopamine levels would nevertheless create a dopamine dominance that could lead to psychotic symptoms (Cummings, Gorman & Shapira, 1993). This could also explain the reasons why AD+P is more successfully treated with anti dementia medications such as cholinergic agents (Bullock, 2005) rather than the dopamine receptor blocking agents that have considerably more success in treating the positive symptoms of schizophrenia (Sue et al., 2003).

Apart from convergence in terms of positive systems between the two disorders, there are parallels to be found between negative symptoms in schizophrenia (deficit state; White & Cummings, 1996) and AD including avolition, apathy, diminished emotional responsivity and reduced initiation of goal directed behaviours (White & Cummings, 1996; Andreason & Olson, 1982; Andreason, 1982; Ruben, Morris & Berg, 1987) further similarities between the two disorders become apparent later in the course of AD as affect becomes flattened, poverty of speech becomes marked and initiation of spontaneous movement is decreased (Reisberg, 1983).

Such similarities between the two disorders may imply that they could be subserved by shared mechanisms (White & Cummings, 1996; Carnacella & Oberling, 2004). However, whilst the convergence is noteworthy and may suggest latent variables that could contribute to psychotic states in both cases, caution is necessary when trying to generalise findings from schizophrenia research.

Schizophrenia research has dominated the study of psychotic symptoms. As a result schizophrenia has frequently been used as a model for understanding the aetiology of psychosis in disorders such as AD. Unfortunately this approach has had limited success in terms of generalisability, which is most likely due to the problematic nature of patient studies with individuals with schizophrenia. Studies involving schizophrenic patients invoke confounds to experimental study including medication status, hospitalisation, stigmatisation and the fact that cognitive abnormalities in domains such as intelligence, memory and executive function typify the disorder (Claridge, 1994; Heinrichs, 2004; Woodward, Buchy,

Moritz & Liotti, 2007). Furthermore, due to the well described prodromal period that continues from late adolescence to early adulthood, the relatively circumvented age risk of onset (Hyde et al., 2008) and the consistently noted neurodevelopmental abnormalities that characterise the disorder, the schizophrenic brain may be a misleading model through which to try to interpret and generalise research findings to explain psychosis in individuals who appear to have been developmentally normal, until later life, when the onset of neurodegeneration has revealed positive symptoms.

Furthermore, apart from the similarities between the two disorders, the differences in neuropathology in addition with the fact that AD is actually rare in individuals with schizophrenia (Kotrla, Chacko, Harper & Doody, 1995; Arnold et al., 1998), the typically early onset and obvious neurodevelopmental abnormalities of schizophrenia all imply that the mechanisms which lead to psychosis in the two disorders may not be entirely shared (Sweet, Nimgaonkar, Devlin & Jeste, 2003). However, whilst schizophrenia itself may not be the best model from which to derive an aetiological theory of psychosis in neurodegenerative disorders perhaps a model where genes confer an increased but unexpressed risk for psychosis would be more appropriate. Assessment of such putatively ‘at risk’, but nevertheless healthy, individuals would respect both the evidence for the similarities and differences between schizophrenia and AD. Such a model would have to ask questions about the factors that contribute to these individuals’ increased susceptibility to psychosis, how variance in such a vulnerability may be expressed in a population and what features have moderated this risk so it manifests as health rather than schizophrenic decompensation.

Consequently, this model would predict that individuals who are genetically at risk for psychosis, but at a level that is protective against decompensation, are liable to manifest psychotic symptoms through a neurodegenerative process such as AD (Eror et al., 2005) or through any other significant neuropathological or neuropharmacological developments. Eror et al., also predict that individuals who manifest psychosis due to neurological disorders (AD in their particular model) would have elevated subsyndromal levels of psychosis prior to disease onset. Whilst psychopathology (Delawalla et al., 2006) and neurocognition (Egan et al., 2001) have been cited as reliable endophenotypes for genetic vulnerability for schizophrenia (Smith et al., 2009) our endophenotype must reflect the substantive health of these individuals. Therefore we predict that subsyndromal psychosis will be evident at trait level in personality. Based on our prior conclusions (Brien et al., 2008) we also anticipate that psychosis prone personality traits will be reflected genetically as individual differences in brain structure and to be associated with personality and neuroanatomically related neurocognitive processes.

### ***1.5 INDIVIDUAL DIFFERENCES RESEARCH***

Recently the individual differences approach has been gaining attention from cognitive neuroscientists as being an especially elucidating method for understanding the mechanisms of brain function (Kosslyn et al., 2002). Kosslyn et al., (2002) advocate that group based work should be combined with individual differences research to reveal the connections between biology and psychology.

The study of individual differences has recently proven essential to revealing processes that have previously been obfuscated through group level research.

Whilst biological systems have always been considered to be exceptionally prone to variation, until recently this variation has been treated like nuisance variables which should at least be limited and ideally removed entirely (Plomin & Kosslyn, 2001; Kosslyn et al., 2002). However Kosslyn et al., (2002) see this variation, which is unavoidable in studies investigating the biological underpinnings of mental processes, as salient data in its own right.

The notion that individual differences afford a unique way to formulate and test various psychological theories is not especially new (Underwood, 1975; Lamiell, 1981). Underwood (1975) believed individual differences can reveal considerably more consistent results than conventional group-based methods and that this variability is more capable of demonstrating the true structure of psychological functions. Kosslyn et al. (2002) have since modified and extended Underwood's account of the importance of the individual differences approach to emphasise the way in which individual differences can further understanding of the relationship between psychology and biology. If each participant is regarded at the individual level, whilst individual differences are interpreted in the context of variance in the population, there should be less disparity between psychology and biology. In order to adhere to this model, one must relate naturally occurring variation in a specific ability or characteristic to variance in the function of an underlying mechanism that is present in the species. Examples where this approach has been successfully applied to account for inconsistencies in neurocognitive and neurobiological results will be discussed in more detail in section 1.7.

## ***1.6 PERSONALITY***

Personality is perhaps the most fundamental naturally varying expression of individual differences. Whilst individual differences in personality have been the subject of immense debate in personality psychology, it is only recently that individual differences in personality traits are being considered important factors in relation to inter-subject variability in neurocognition, neurobiology and neuropathology. Recent immunological studies have demonstrated that certain personality types and traits may be associated with specific biological and psychological illnesses (Capitano, Abel, Mendoza et al., 2008).

There are specific fundamental assumptions that must be noted when trying to understand the differences between individuals that may contribute to their liability for a certain type of disorder (Kuntsiet al., 2005). It is essential therefore that the candidate endophenotype mirrors such variability or individual differences and that these differences are expressed between and within individuals reliably throughout the lifespan (Kuntsiet al., 2005). As personality has been described as being heritable (Loehlin, 1992), stable in time and dependent on genetic and neurobiological factors (Gardini et al., 2009), personality traits can meet both these assumptions, they are inherently associated with great variability between individuals, they appear to be expressions of underlying neural mechanisms and, as personality traits are ostensibly temporally stable, test-retest reliability can be easily established (De Geus & Boomsma, 2001).

Many endeavours have been made to describe and define personality, understand its aetiology and make predictions based on these assumptions. Typically theories



of personality aim to describe individual differences in emotions, cognitions and behaviour that are relatively stable across the adult lifespan. Personality describes the characteristics that contribute to an individuals' innate sense of consistency or continuity. Similarly, Allport's (1961) definition of personality, which still appears relevant today, suggests that personality is dynamically organised, constructed of active processes, psychological and also intimately related to physiology, that personality causally determines an individuals' relationship with the world, is involved in patterns, recurrences and consistencies and is evident through behaviours, thoughts and emotions (Carver & Shier, 2004).

There are many different perspectives of personality and these perspectives are reflected in a variety of theories. Within a certain perspective, theories can differ substantially, and in the discipline of personality psychology, diverse theoretical and methodological approaches, themes and controversies persist (John, Robbins & Pervin 2008). However, the majority of theories appear to share the ontological principles outlined in the definition above. The most predominant perspectives on personality include: dispositional, biological, psychoanalytic, neoanalytic, learning, phenomenological and cognitive self-regulation (Carver & Sheier, 2004). However, it is the dispositional and biological perspectives which are most relevant to the aims of the current thesis.

The dispositional perspective relates to the theory that individuals have relatively stable dispositions that are manifest across various situational contexts. They are demonstrated in overt behaviour in a number of ways, but they are deeply ingrained within an individual (Carver & Shier, 2004). The biological perspective,

which is not mutually exclusive from dispositional theories, suggests that as personality is genetically determined, dispositions are inherited.

### ***1.6.1 THE DISPOSITIONAL PERSPECTIVE***

As briefly outlined above. The dispositional perspective assumes that individuals are consistent in their thoughts, emotions and actions and that one's dispositional nature is contextually and temporally enduring (Carver & Shier, 2004). Another major theme of this perspective is individual differences and exploration of the way in which patterns of dispositional characteristics differ between individuals.

The desire to categorise individuals into different types has been well documented since approximately 400 B.C. (Carver & Shier, 2004). Typologies have persisted from the 'humours' to 'introversion and extraversion' (Jung, 1933; Eysenck, 1967). Originally in typologies traits were viewed as distinct categories that were not continuous, in this view an individual could either be one or the other (Carver & Shier, 2004). However contemporarily, it is preferred to conceive of individuals as being comprised of continuous trait dimensions. In this account, individuals differ in the extent to which they possess certain traits and the degree of presence versus degree of absence of a given trait is said to be distributed across and within individuals (Carver & Shier, 2003).

The term trait denotes consistent patterns of behaviour. Trait research in personality psychology has generally concentrated on number, nature and organisation of fundamental traits. Methodologically, trait research has relied on factor analysis to identify those trait dimensions that are applicable to people in

general. There has been much debate concerning the issue as to whether traits are most appropriately regarded as nomothetic or ideographic. The ideographic approach rejects the search for basic traits in favour of concentrating on traits that are unique to a given individual. This position suggests that as every person is unique, so is every trait (Allport, 1961) and it is therefore artificial to try to directly compare individuals because we all reside on different scales. Even within the same traits, its connotations (Dunning & McElwee, 1995) or importance (Britt & Shepperd, 1999) could differ so enormously between individuals that they could still not reliably be compared. Fortunately, the dominant position in personality psychology is occupied by the more empirically amenable nomothetic view, in which a trait or dimension holds the same meaning for everyone. In this account, an individual's uniqueness is reflected in their combinations and extents of multiple dimensions (Eysenck, 1952).

### ***1.6.1.1 EYSENCK'S THEORY OF PERSONALITY***

Eysenck's theory of personality represents one of the major trait theories in personality psychology and it has been cited as the most influential *theoretically based* approach to traits (Carver & Shier, 2004). Rather than empirically selecting the traits that comprise personality (Cattell, 1965), Eysenck constructed his theory of personality through an *a priori* method which extracted well developed ideas from the typologies devised by Hippocrates and crystallised by Galen of the four humours. These humours refer to distinct dimensions of character that were originally identified as phlegmatic, melancholic, sanguine and choleric traits. Eysenck suggested that these four facets could be better represented by two supertraits. Eysenck's original theoretical account of personality is thus focused

on two domains of personality; introversion-extraversion and emotionality-stability (or neuroticism; Eysenck, 1967; Eysenck 1990; Eysenck & Eysenck, 1985). Extraversion refers to tendencies to be outgoing, sociable, talkative, responsive, affable, lively and carefree. It is also highly related to arousal, excitement seeking, activity and emotional states (Canli et al., 2010). Introversion resides at the opposite end of this spectrum and is characterised by inhibition, harm avoidance and social withdrawal. The emotional stability or neuroticism dimension reflects an individual's threshold for resisting or coping with psychological upset and distress.

Despite its original composition of just two supertraits, this theory creates much potential for diverse representation of individual differences in personality. As both dimensions are entirely continuous, individual differences in personality can be reflected by combinations of high and low loadings on each dimension which can lead to very different personality types. The extent to which one dimension is important to the construction of an individual's personality is therefore highly dependent on where a person resides on the other dimension (please refer to Table 1.2) . For example, an introverted but emotionally stable individual would be even-tempered, reliable, calm, careful, peaceful and passive, whereas an introverted individual, who was emotionally unstable, or highly neurotic, would be unsociable, pessimistic, moody and anxious. Emotionally stable extroverts are easygoing, sociable and responsive however a highly neurotic extravert is likely to be impulsive, changeable, restless and aggressive.

Table 1.2. Frequent traits across Eysenck's supertraits (adapted from Carver & Shier, 2004)

	Emotionally Stable	Emotionally Unstable
Introvert	Passive Careful Thoughtful Peaceful Controlled Reliable Even-Tempered Calm	Quiet Pessimistic Unsociable Sober Rigid Moody Anxious Reserved
Extravert	Sociable Outgoing Talkative Responsive Easygoing Lively Carefree Leader Like	Active Optimistic Impulsive Changeable Excitable Aggressive Restless Touchy

Eysenck developed the Eysenck Personality Questionnaire (EPQ; Eysenck & Eysenck, 1975) to assess these dimensions. Eysenck's theory is also hierarchical, extraversion and neuroticism are supertraits which exist at the type level, these supertraits are made of component traits which are distinct qualities from which the supertrait is comprised, and in turn these component traits are informed from the habitual response level that is formed by specific behavioural stimulus responses (Eysenck, 1967).

Eysenck later proposed psychoticism as a third dimension, although he did not attempt to fully reconcile this later dimension with his original model.

Psychoticism is manifest in personality as hostility, manipulation, disregard of social restraint, and pursuit of intense sensations. Whilst impulsivity was

originally a component trait of extraversion, the construct was subsequently found to be more related to psychoticism (Eysenck, 1967). Another fundamental tenet of Eysenck's theory, that extraversion, neuroticism and psychoticism are associated with nervous system structure and functioning will be discussed later in this chapter with reference to the biological basis of personality. Extraversion and neuroticism have been regarded as two of the most fundamental traits and have been influential to several personality theories (Pervin & John, 1999)

### ***1.6.1.2 FIVE FACTOR MODEL***

There are obvious comparisons between the five-factor model of personality (FFM) and Eysenck's supertraits. The FFM is based on the way in which many different personality theories began to converge on ideas about fundamental traits. The FFM suggests the structure of personality may be comprised of five superordinate factors. One of the first accounts of a five factor model emerged through a failure to reproduce Catell's (1947) 16-factor structure (Fiske, 1949). Consistent subsequent replications of these five factors led to a large body of mostly confirmatory evidence for the persistence and representativeness of these five factors. Evidence for a FFM of personality has since emerged from many cultures (Church, 2001; McCrae & Costa, 1997) and even from animal studies (Gosling, 2001). However, despite the large body of confirmatory evidence, not all subsequent studies have successfully replicated the factor structure (Benet & Waller, 1995).

Another issue involved with the FFM involves the degree of consensus concerning what the five factors actually are (Carver & Shier, 2004). However

setting aside the issues of nomenclature, in principle this theory describes personality in terms of the extent to which an individual possess the following traits; *neuroticism* (emotional regulation and constancy), *extraversion* (interpersonal preferences), *openness to experience* (curiosity, receptiveness and emotionally responsiveness), *agreeableness* (friendliness, affability and responsiveness) and *conscientiousness* (organisation, persistence and self direction) (Sue et al., 2003). Individuals have been found to vary considerably in the extent to which they manifest these factors.

These traits have been found to influence behaviour, thoughts and emotions in a variety of ways (Zillig et al., 2002). Neuroticism is mostly concerned with affect, conscientiousness appears most related to behaviour and cognition, openness has been found to have affective and behavioural implications but to be most involved with cognition, extraversion has less involvement with cognition and is more concerned with behaviour and affect and agreeableness appears to be represented, behaviourally, cognitively and emotionally (Carver & Shier, 2004).

Furthermore, the FFM has been found to be amongst one of the most popular models of personality through which to interpret personality disorders (O'Connor & Dyce, 1998). Such conclusions have led to speculation that personality disorders can be characterised as extreme maladaptive variants of these five factors (Widiger, Trull, Clarkin, Sanderson & Costa, 1994). As a result, the FFM has been used extensively by clinicians to assess and compare different personality disorders. For example, individuals with obsessive compulsive disorder (OCD) have been found to score highly in the conscientiousness factor,

whereas individuals with antisocial personality disorder have been found to score especially low on this factor (Sue et al., 2003). The FFM has also been useful in the conceptualisation that understanding the aetiology of personality disorders is inextricable from investigating the determinants of personality in normal individuals. This approach assumes that personality disorders are extreme expressions of the same fundamental traits that underlie all personality.

## ***1.6.2 BIOLOGICAL THEORIES OF PERSONALITY***

According to John et al (2008), for centuries the relationship between personality and biology has encouraged much speculation. Allport, (1937) a pioneer in personality psychology believed that psychophysical systems subserved personality, Murray (1938) viewed traits as physic chemical forces in the brain and Freud also related much of his theory to psychobiological systems.

### ***1.6.2.1 CLONINGER'S THREE DIMENSIONAL MODEL OF TEMPERAMENT AND CHARACTER***

Cloninger (1986) proposed a model whereby three main dimensions of personality were central to understanding individual differences; novelty seeking, reward dependence and harm avoidance. Novelty seeking refers to a proclivity for action directed behaviours and it is expressed as a compelling inclination towards explorative activity as a response to novel situations and stimuli, impulsive decision making, overzealous reaction to reward cues and a lack of emotional inhibition. On the contrary, harm avoidance describes a propensity to inhibit behaviours, it is characterised by caution, pessimism and apprehension and is manifest behaviourally as a pessimistic outlook, negative anticipation of future



problems, a fear of uncertainty, aversion to strangers, accelerated fatigability, passivity and avoidance of novelty. Reward dependence describes the innate tendency to maintain behaviours that have previously been associated with reward and reinforcement, reward dependent individuals are likely to depend heavily on social attachments and the approval of others and be sentimental and persistent. More recently, empirical evidence suggested that persistence, one of the subscales from reward dependence, actually represents a fourth dimension of personality that was independent from the original three (Gusnard, Ollinger, Shulman et al., 2003). Persistence in this context refers to an innate capacity to internally generate and maintain arousal and motivation in the absence of external reward. Persistent individuals are generally found to be highly industrious, meticulous, conscientious, ambitious, high achieving, hard working and perfectionist (Gardini et al., 2009). Accordingly, the Tri-dimensional personality questionnaire (Cloninger, 1986; inclusive of the newly independent factor persistence) was devised to measure and assess these four fundamental dimensions of personality. Three character related dimensions; self directedness, cooperativeness and self transcendence were later included which are assessed alongside the original dimensions in the Temperament and Character Inventory (Cloninger et al., 1993).

The uniqueness of Cloninger's theory resides in its ontological background in the neurobiology of brain function and systems as the majority of personality theories have been extensively informed by factor analysis which does not consider essential information about the evolution, structure and function of the brain (Cloninger, 1987; Cloninger 1986; Gardini, Cloninger & Venneri, 2009). In this respect, the devices used to measure these dimensions, the Tri-dimensional

Personality Questionnaire (TPQ) and later the Temperament and Character Inventory (TCI), were constructed from evidence derived from within-individual differences in learning as opposed to the between-subject differences in behaviour that are seminal to most personality theories and assessment tools.

The existence of three independent dimensions of personality has been supported by studies using various constructs (Eysenck, 1967; Sjobring, 1973; Cloninger, 1986) and as a consequence, different techniques have been used to try to define a representative trivariate system of personality variation. However, according to Cloninger, biopsychosocial models, which have been developed through an understanding of biogenetic variation are more amenable to neurobiological and genetic studies than existing scales which have evolved through factor analysis (FFM) or theory (Eysenck, 1967). Robinson (1985) also suggests as personality structure is biologically determined, factor analysis is not an appropriate method to answer such questions and proposes that realising the neurophysiological underpinnings of personality is a more sufficient basis for resolving such issues.

Although Eysenck's dimensions originated from theory, they were characterised through factor analysis. In light of criticisms concerning the dimensions that have been derived from factor analysis, Gray (1983) suggested that rather than revealing extraversion and neuroticism, the axes in Eysenck's model should be rotated to its diagonals to reveal the more biologically salient anxiety and impulsivity dimensions. For Gray, the anxiety dimension refers to passive and avoidant behaviour and reflects variance in a central behavioural inhibition system whereas impulsivity indicates variance in a central behavioural activation system. However Cloninger (1986) thought that harm avoidance and novelty seeking were

more appropriate descriptors of Gray's anxiety and impulsivity dimensions respectively.

Similarities have also been drawn between Pavlovian concepts of the relationship between individual differences and the nervous system and the neurophysiological underpinnings of Eysenck's extraversion and neuroticism dimensions (Robinson, 1982) which are also consistent with Gray and Cloninger's conceptualisations of anxiety or harm avoidance and impulsivity and novelty seeking. According to Robinson, these traits represent distinct 'arousability' dimensions which Pavlov associated with excitatory and inhibitory processes of the diffuse thalamocortical system (Robinson, 1982).

### ***1.6.2.2 GENETIC ASSOCIATIONS WITH PERSONALITY***

The role of heredity in the development of personality has been extensively studied in relation to the heritability of certain personality characteristics. In an early study specifically designed to establish whether traits are biologically or environmentally determined Scarr, Webber, Weinberg and Wittig (1981) investigated the heritability of personality traits in biologically related and adoptive families. If despite separation, biologically related individuals display similar personality characteristics then heredity is essential to personality development. If on the contrary, more similarity is demonstrated between the characteristics of adoptees and adoptive families then learning and environment can be assumed to be more important. However, the findings suggest that both genetic and environmental factors are important and that neither is sufficient to entirely explain variance in personality. Furthermore, it has been suggested that as

genetic characteristics may influence an individuals' personality characteristics this may, in turn, determine the environment they experience to a considerable extent (Sue et al., 2003). This core gene-environment paradox makes attempts to distinguish the genetic and environmental contributions to personality even more problematic.

A good example of the complexity of gene environment interaction is the way in which schizophrenia patients and their relatives appear to have a unique temperament and character (Cloninger et al., 1993) profile compared with the general population (Smith et al., 2008; Bora & Veznedaroglu, 2007; Glatt et al., 2006; Kurs et al., 2005). Genetic heritability has been demonstrated through the way in which sibling temperament has been found to be intermediate between their schizophrenic relatives and controls. However, other research suggests that non psychotic siblings possess more self-directedness and cooperativeness than their schizophrenic siblings and controls (Bora & Veznedaroglu, 2007; Smith et al., 2008). This is consistent with an environmental hypothesis, whereby non-psychotic siblings attain certain gains from having to cope with their schizophrenic relatives (Smith & Greenberg, 2008) and from caregiver roles (Smith et al., 2008). However Gillespie et al., (2003) argue that personality traits such as self-directedness are also genetically heritable and it is possession of such traits that protect these siblings (who have a higher genetic risk for schizophrenia) from developing psychosis. Smith et al., (2008) propose that the protective facets of self-directedness and cooperation could be supported by evidence that they are highly correlated with crystallised IQ and working memory and were uncorrelated with psychopathology. Both genetic and environmental explanations are highly plausible, are supported by substantial evidence and serve as an excellent example

of how genetic and environmental contributions to personality are inextricably and often intractably involved.

However, despite uncertainty regarding the contribution of genes and environment to personality, there is a large body of evidence supporting the primacy of the role of genetics in personality. Studies assessing the genetic contribution to extraversion and neuroticism (Benjamin et al., 1996; Ebstein et al., 1996; Lesch et al., 1996) have demonstrated that robust genetic associations subserved these dimensions. Similarly, individual variations of Cloninger's dimensions of personality have been found to be largely genetically determined (Cloninger, 1987; Cloninger, 1986; Comings et al., 2000).

In Cloninger's model, variation in each dimension has subsequently been associated with activity in a specific monoaminergic pathway; whereby low basal dopaminergic activity has been correlated with novelty seeking, high serotonergic activity has been associated with harm avoidance and low basal noradrenergic activity with reward dependence (Cloninger, 1986). It is assumed that due to polygenetic inheritance, variance in each dimension of personality should approximate normal distribution (Cloninger, 1986). This ought to result in the majority of individuals phenotypically expressing intermediate rather than extreme traits.

Twin studies have estimated heritability for dimensions of the FFM (Lochlin, 1992; Jang, Livesley & Vernon, 1996; Riemann, Angleitner & Strelau, 1997) and Cloninger's Tri-dimensional model of temperament and character (Cloninger,

Pryzbeck & Svrakic et al., 1994) to be between 40 and 60 percent. In addition, traits that exist along the continuum with impulsivity, aggression and novelty-seeking have had significant estimated heritabilities reported from 40 to 80 percent (Coccaro, Bergeman, & McClearn, 1993; O'Connor, Foch, Sherry et al., 1980). More specific genetic associations with personality traits include findings that anxiety related personality traits have been associated with a short allele of a functional insertion-deletion variant of the SERT gene (Lesch et al., 1996) and aggression associated traits have been correlated with variants of the monoamine oxidase and catechol-O-methyl-transferase genes (Caspi et al., 2002; Kotler et al., 1999).

### ***1.6.2.3 EVIDENCE FOR PERSONALITY FROM ANIMAL***

#### ***MODELS***

Personality traits have also been found to be reliably measurable in animal studies (Gosling, 2001; Gosling & Vazire, 2002, Vazire & Gosling, 2003). A psychobiological model to explain sensation seeking behaviour has been derived from animal studies of neurotransmitters, hormones and enzymes (Zuckerman, 1996). Associations between dopamine receptors and novelty seeking have been found in mice studies (Paulus & Geyer, 1999) and associations between personality, physiology and behavioural neuroendocrine and immunological responses have been observed in rhesus macaque monkeys (Capitanio et al., 1999). Capitanio et al (1999) found that individual differences in trait sociability were predictive of both behavioural and immunological responses which, in turn, predicted increased survival length in monkeys (Capitanio et al., 1999).

### ***1.7 PERSONALITY AND BRAIN FUNCTION***

Personality traits appear to be reflected in neurobiological features (Turner et al., 2003; O’Gorman et al., 2006). Differences in the systems such as the amygdala, neuroendocrine and limbic system, which are consistently found to be involved in emotional processing, appear to be inextricably associated with personality and psychopathological states (Haas & Canli, 2009). The function of these systems has been shown to vary as a function of personality traits.

Functional neuroimaging studies have positively associated regional cerebral blood flow (rCBF) in the anterior cingulate and anterior and posterior insula with novelty seeking, found inverse correlations between harm avoidance and rCBF in parahippocampal, precentral, postcentral, superior frontal, fusiform and inferior temporal and between reward dependence and rCBF in parahippocampal, anterior cingulate, insula, precentral, superior and middle frontal, superior temporal gyrus and precuneus (Sugiura et al., 2000). In addition high persistence has been associated with increased activation in orbitomedial prefrontal cortex and ventral striatum (Gusnard et al., 2003). Several functional imaging studies have examined extraversion and neuroticism using specific activation tasks and have shown consistent association between these traits and prefrontal and amygdala activations (Canli et al., 2001; Gusnard et al., 2004).

Recent reviews have suggested that compared with psychobiological traits such as those defined by Cloninger, functional imaging studies have been less successful in establishing clear associations between brain activity and extraversion and neuroticism and FFM traits (Schmidtke et al., 2004; Eysenck, 1990). Schmidtke et al. (2004) attribute the lack of clarity in neural activity and these traits to

overemphasis on global measures of cortical activity and suggest theories of affect, neurophysiology and personality should be integrated into a single model in order to predict individual differences in regional variation. The need to unify theoretical and factor analysis established dimensions of personality with affective and neurofunctional hypotheses reflects the superiority of a biologically derived model such as Cloninger's which appears to have produced more salient neuroanatomical trait associations.

Canli et al., (2001) suggest that dimensional similarities between personality and emotion reflect their mediation by a common neural substrate. Consequently, personality traits are assumed to mediate the way in which emotional stimuli are processed via this common substrate (Canli, et al., 2001). In a study designed to assess how stable personality traits moderate brain activation to emotional stimuli Canli et al. (2001) found individual differences in processing emotional stimuli were correlated with extraversion and neuroticism. Extraversion was associated with reactivity to positive images whereas neuroticism was correlated with reactivity to negative stimuli. This converges with findings that extraversion and neuroticism have been associated with positive and negative mood states respectively (Costa & McCrae, 1980; Canli, Amin, Haas & Omura, 2004).

Personality has also been observed to be correlated with between subject variance in attention to emotionally laden stimuli (Amin et al., 2004; Haas et al., 2006), specific attentional biases have been demonstrated for extraversion (Derryberry & Reed, 1994; Canli et al., 2001), neuroticism (Reed & Derryberry, 1995; Canli et al., 2001) and harm avoidance (Most et al., 2006). Individual differences in personality structure have also been found to correspond with variation in



emotional memory, for instance it is well documented that memories that are emotionally arousing are better remembered than those that are less arousing (Bradley et al., 1992; Libkuman et al., 2004), however this process varies considerably between individuals (Rusting, 1999). Through the adoption of an individual differences approach this variance has been explained. It appears that variance in trait psychopathology reliably predicts these differences in emotional memory facilitation (Haas & Canli 2008).

Such findings have led to speculation that some inconsistencies in prior studies assessing brain function in emotional processing may be due to differences in personality traits. For instance, Canli et al (2001) suggest that null results in amygdala activation to negative stimuli could be a result of over representation of highly extraverted individuals in the sample. Similarly, the individual differences approach could explain why the caudate has been found to be differentially involved in the processing of emotional stimuli (Lane, Reiman, Bradley et al., 1997). Inconsistencies in caudate activity may be explained by Canli et al's results which suggest the caudate responds more or less strongly to positive or negative stimuli in different individuals as a function of extraversion. Such an account highlights the importance of considering the effects of personality on behavioural and neurological responses. In addition, Canli et al (2001) propose that the individual differences approach could explain why certain neuropharmacological drugs can have such markedly different effects on people. This model would explain the differential effects of procaine, a drug which has been found to produce both intense fear and euphoria (Ketter et al., 1996; Canli et al., 2001). Canli et al., have found that these quite polarised reactions may be explained by variance in personality traits whereby highly extraverted individuals

appear likely to react to the drug with euphoria and highly neurotic individuals seem more predisposed to have an intense fear reaction (Canli et al., 2001). The way in which individual differences in personality could potentially moderate pharmacological effects and the implications of this for the endophenotype will be discussed in Chapter 7.

In total, such evidence contributes to the idea that through taking individual differences in personality into account, inconsistent findings from behavioural data, brain activation patterns and reactions to certain drugs can be reconciled (Canli et al., 2001; Canli et al., 2002; Canli et al., 2004).

Individuals with personality disorders have been found to score at extreme ends of the normal distribution of a given trait (Widiger et al., 1994). Like the neuroimaging studies described above, that assessed the relationships between specific traits and brain function, recent imaging research has also indicated that individual differences in personality disorders are highly related to functional activation (Gray et al., 2002; Gusnard et al., 2003; Gordon et al., 2004).

Associations between variance in brain systems and personality traits have been found in evidence from many neuropsychiatric disorders including depression, suicidal behaviour, bipolar disorder, schizophrenia, drug addiction, pathological and social gambling and social anxiety disorder (Gardini et al., 2009) psychopathy and borderline personality disorder.

For example, in obsessive compulsive disorder (OCD), brain abnormalities have frequently been noted in the orbitofrontal cortex, the parietal cortex and the

striatum. In functional imaging studies, psychopathy has been frequently associated with dysfunction of the orbital, ventromedial prefrontal, anterior cingulate cortex (Damasio et al., 1994; Raine et al., 1994) and temporal cortex (Amen et al., 1996). Amygdala dysfunction and impaired hippocampal functioning also appears to contribute to psychopathy (Blair, 1997). Trait psychopathy in non-clinical individuals has been associated with functional differences in the cortical areas required to perform an emotional recognition task (Gordon et al., 2004). Individuals high in trait psychopathy primarily were found to use the right dorsolateral prefrontal cortex when performing an emotional recognition task compared with low scorers who activated a distributed emotional network. This converges with findings that clinically diagnosed psychopaths demonstrate a converging pattern of increased frontal activation when responding to emotional tasks (Keihl et al., 1999). Borderline personality disorder has been associated with noradrenergic and opiate dysfunction (Van der Killok, 1987), serotonin (Hollander et al., 1994) and dopamine (Lucas et al., 1987) and hypometabolism in premotor and prefrontal cortex, anterior cingulate and thalamic, caudate and lenticular nuclei (Fuente et al., 1997).

### ***1.7.1 RESTING STATE***

The majority of neuroimaging studies of personality have concentrated on pathological populations and have used task based approaches where cognitive tasks, which have been chosen to be personality specific or relevant, are employed to dissociate areas that are activated as a function of these individual differences. As discussed above, these approaches have produced interesting results, especially when the tasks are emotionally salient. However, these approaches have limitations as they require effective cognitive behavioural or emotional

probes that specifically target psychological constructs. Structural imaging and resting state studies avoid this issue and allow quantification of more intrinsic baseline activity.

Resting state studies have demonstrated that compared with introverts, extraverts show higher left frontal blood flow (Stenberg et al., 1990) whilst depressed patients, who research suggests are likely to have very high neuroticism traits (Canli et al., 2001; Clark, Watson & Mineka, 1994) have been found to have reduced perfusion in the left frontal lobe (Baxter et al., 1989). Extraversion has also been associated with increased regional blood flow in the left (Johnson et al., 1999) and right amygdala (Canli et al., 2001).

In another resting state study, positron emission tomography (PET) was used to assess associations between measures of regional cerebral blood flow whilst healthy participants were at rest and traits measured by the TPQ. Higher harm avoidance was found to be reflected in increased regional cerebral blood flow (rCBF) in the left inferior parahippocampal gyrus and left pulvinar. Harm avoidance was negatively correlated with rCBF in the left superior temporal gyrus and left parahippocampal gyrus. Higher novelty seeking scores were associated with increased rCBF in the medial frontal and right superior temporal gyrus. Negative correlations were found between novelty seeking and rCBF in the left cuneus and right middle frontal gyrus (Salloum et al., 2010).

In addition, resting state functional connectivity (RSFC) analyses have related individual differences in RSFC with trait dimensions of social competence (Di Martino et al., 2009) and aggression (Hoptman et al., 2009). In a recent study

investigating the relationship between RSFC and the FFM, neuroticism was associated with the dorsomedial prefrontal cortex, extraversion with paralimbic structures, openness with dorsolateral prefrontal cortex, agreeableness with posteromedial extrastriate and primary motor areas and conscientiousness with the medial temporal lobes (Adelstein et al., 2010).

### ***1.7.2 BRAIN STRUCTURE***

There has been much speculation concerning whether differences in brain structure contribute to the formation of different individual personality types. Such speculation has largely arisen from evidence that certain personality traits and emotional behaviours are characteristic of brain injuries to specific neural structures and circuits. In addition, observations of such traits and emotional behaviours in individuals with no known brain injuries has contributed to theories which posit environmentally or genetically mediated differences in neural anatomy may explain individual differences in personality. For example, according to Kolb and Whishaw (2003), based on theoretical accounts of the function of the temporal lobes that have emerged from patient and normal studies, one could hypothesise that a hypercritical individual may have comparatively smaller or less active temporal lobes than less hypercritical individuals.

The case of Phineas Gage, initially reported by Harlow (1868), still represents the most publicised evidence for the relationship between personality and brain structure (Kolb & Whishaw, 2003). Although Gage survived an explosion that drove an iron tamping bar (of approximately one meter by three centimetres) through the front of his head, his personality was completely altered.

Subsequently there have been many case studies documenting the effects of brain injury on personality. Although the predominant focus is on clinical descriptions of personality change after frontal lesions, there are unfortunately fewer systematic studies (Kolb & Whishaw, 2003). According to Blumer and Benson (1975), pseudodepression and pseudopsychopathy represent the two major types of personality change that are frequently observable in patients with frontal lobe lesions. Pseudodepression manifests as apathy, inertia, indifference, lack of interest in social relationships, loss of goal directed behaviours, emotional flattening and reduced verbal output. Pseudopsychopathy refers to the manifestation of immature behaviour, disinhibition, coarse language, promiscuity and increased motor activity. The complete syndromes are associated with bilateral frontal lobe lesions however features of pseudodepression appear to be most associated with left frontal lobe lesions whereas elements of pseudopsychopathy appear to be more associated with right frontal damage (Kolb & Whishaw, 2003). Whilst personality changes due to brain injury have been well documented, Kolb and Whishaw argue that they have not been adequately specified as these behavioural changes are frequently described in a general subjective manner.

In addition, converging evidence for the role of the frontal lobes in personality has been provided from monkey studies (Butter & Snyder 1972) which have demonstrated that frontal lesions in alpha males result in deposition to the bottom of their hierarchy. This appears to be due to the effects of the lesion on the monkey's ability to engage appropriately in the complex social interactions that are necessary for success in their society (Kolb & Whishaw, 2003). The most robustly documented changes in personality after frontal lesions in monkeys

include: reduced social interaction, loss of social dominance, inappropriate social interactions, altered social preferences, reduced affect and reduced vocalisation (Kolb & Whishaw, 2003).

There is however a relationship between premorbid and post injury personality that must be considered. Whilst there is consistency between lesion site and content of personality change it must be noted that this is evident at group level, at the individual level there is considerably more inter-subject variability in personality changes and emotional alterations of brain injured individuals than is evident in tests of cognitive function. Similarly, in another animal study of post lesion personality change, whilst most monkeys' personalities manifested the typically expected changes that were previously discussed, there were exceptions where previous premorbid personality traits persisted and contributed to post lesion social behaviour (Peters and Ploog, 1976).

Other structures that appear to subservise personality include the temporal lobes. Temporal lobe personality is another example of the relationship between brain structure and personality. Disorders of the temporal lobes are innately connected to disturbances of affect. Temporal lobe epilepsy is associated with a specific personality profile which manifests as increased attention to trivia, overemphasis on minutiae of life, pedantic speech, egocentricity, perseveration in relation to discussion of self, paranoia, religiosity, aggression and agitation. Right temporal lobe patients have been identified as more obsessional whilst left temporal lobe patients have been described as more preoccupied with grandiose philosophical questions especially referring to personal destiny (Bear & Fedio, 1977).

There is also evidence that structural variance in the morphology of brain structures is associated with variance in distinct personality traits (Gardini et al., 2009). For instance, in structural studies of extraversion and neuroticism (Omura et al., 2005; Wright et al., 2006) the prefrontal cortex has been found to be thicker in the right compared to the left in extraverts (Omura et al., 2005; Wright et al., 2006) and inverse associations between high neuroticism and lower grey matter in orbitofrontal cortex have also been reported (Rauch et al., 2005; Wright et al., 2006). Structural neuroimaging studies have also suggested that individuals with psychopathic traits have reduced grey matter in the prefrontal and temporal cortex and have reduced posterior parahippocampal volumes and larger callosal volumes (Basoglu et al., 2008). Further evidence that individual differences in personality traits might be biologically determined and be associated with volumetric variability in specific regions of the brain have been advanced by a recent neuroimaging study of Cloninger's personality dimensions. In this study, novelty seeking was positively correlated with higher grey matter volume in frontal and posterior cingulate region, harm avoidance was negatively associated with less grey matter volume in the orbito-frontal, occipital and parietal lobes, reward dependence was negatively correlated with grey matter in the caudate and rectal gyrus and finally, persistence was positively associated with the precuneus, paracentral lobule and parahippocampal gyrus (Gardini et al., 2009). Such findings contribute to the evidence that individual differences in personality traits appear to be reflected in structural variance of discrete brain regions and that it is this neuroanatomical variance which determines individual differences in the expression of personality traits (Gardini et al., 2009).



### ***1.8 PRE-MORBID PERSONALITY***

Pre-morbid personality may serve as an endophenotype for the emergence of psychosis in neurological disorders as individual differences in certain traits have been found to be associated with certain symptom profiles in various neurological diseases. In addition, different pre-morbid personality profiles have been found to indicate vulnerabilities to psychosis in neurodegenerative disorders. For instance, Low et al., (2002) assessed the contribution of caregiver rated pre-morbid personality on the five factor inventory to psychosis in dementia and found higher pre-morbid neuroticism was predictive of delusions and higher agreeableness of hallucinations. There are obvious problems with retrospective research, however retrospective associations between symptoms and pre-morbid personality may suggest prospective research themes. Eventually, such research may clarify knowledge of the aetiology of the emergence of psychosis in degenerative diseases. This will help elucidate this association for diagnostic purposes and will hopefully elaborate the processes that underlie psychotic behaviour. It may also have further explanatory power such as why different pharmacological treatments are more or less appropriate for certain people, and why under the same typical disease process some individuals develop early psychosis whereas others do not.

### ***1.9 INTERACTIONISM***

Interactionism may provide a framework for understanding the complex interactions that may or may not lead to our endophenotypes' phenotypic expression.

One of the main criticisms of trait psychology stemmed from the finding that trait measures and behaviour were often not as highly correlated as expected (Mischel, 1968; Vernon, 1964). This led to debate, that occupied much of trait psychology from 1970 to 1990 (Carver & Shier, 2004), concerning whether traits are useful if they do not entirely predict peoples actions. Two theoretical viewpoints were proposed to answer this issue; situationism and interactionism. Situationism occupied the most extreme position of the two, suggesting behaviour was entirely determined by situational variables, this theory was mostly rebuked in favour of interactionism.

Interactionism, which describes a more balanced attempt to address issues surrounding inconsistency between traits and actions (Ekehammer, 1974; Endler & Magnusson 1976; Pervin, 1985) may be a useful model to inform our theoretical viewpoint of how certain personality traits may endophenotypically lead to psychosis in neurological disorders. Interactionism proposes that behaviour is influenced through interaction between traits and situations. According to Carver and Shier (2004) when a given situation and trait are examined, there are three systemic sources of behaviour influence. Firstly, variations in the situation could affect all individuals, for example Carver and Shier suggest certain stressful situations could cause depression in any individual. Secondly, individual differences in a trait could affect all situations, again using depression as an example they suggest certain individuals who are more susceptible to depression will be more depressed than those who are less prone to depression. Thirdly that situation and trait can interact, based on individual differences in traits, situational variability will affect people in different ways. This interaction can take many forms however the model below (Figure 1.3) is

based on the predictions proposed by the current thesis for the way in which neurological pathology (situation) can cause psychosis in individuals who have a predisposing personality type, but not in others.

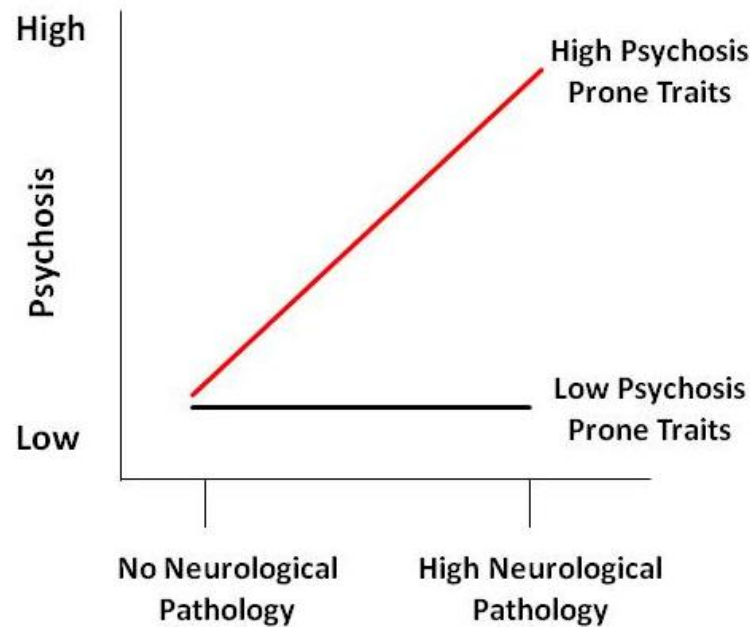


Figure 1.3. Interaction between psychosis prone traits and neurological pathology, however, variations in this pathology only affect individuals with trait susceptibility (Adapted from Carver & Shier's (2004) interactional model of depression and environment).

### ***1.9.1 DIATHESIS STRESS MODEL***

The model proposed in the current thesis is not suggesting that psychosis prone individuals will be more likely to develop neurodegenerative disorders but that psychosis prone personality traits may be latent vulnerability or susceptibility markers that would be expressed endophenotypically should significant neurological stress occur. This idea is also compatible with a biopsychosocial diathesis-stress model. The diathesis-stress theory was first described by Meehl (1962) and was later developed by Rosenthal (1970) deleted, in this theory predispositions to develop a certain illness (diathesis) interact with certain

environmental situations (stressors). These stressors activate the vulnerability and cause the disorder to manifest. However, in the absence of such stressors, the predisposition may never materialise.

## CHAPTER 2

# SCHIZOTYPY

### ***2.1 SCHIZOTYPY AS AN ENDOPHENOTYPE FOR PSYCHOSIS***

In the previous chapter, a model was outlined whereby premorbid personality was identified as a putative endophenotype for explaining the aetiology of psychosis in neurological disorders. Several broad personality theories and dimensions were discussed in terms of the dimensional and biological perspectives of personality psychology. In the current chapter, the focus will narrow as schizotypy is proposed as the most salient expression of individual differences in personality that has the potential to indicate an endophenotypic vulnerability to psychosis.

### ***2.2 DEFINITION AND CHARACTERISTICS OF SCHIZOTYPY***

According to a large literature base, above all other expressions of personality, schizotypy, especially positive schizotypal dimensions, may provide the most salient model through which to identify and explore latent psychosis susceptibility as it has been described as a vulnerability marker of psychosis proneness (Claridge, 1994; 1997). Schizotypy has been conceptualised as a personality dimension that is specifically characterised by unusual beliefs, bizarre perceptual experiences, anhedonia and social withdrawal (Weinstein, McKay & Ngan, 2008). Positive schizotypy is especially related to strange perceptual experiences, idiosyncratic thought, paranoid ideation, magical thinking and ideas of reference. Schizotypy appears to be a multidimensional construct that reflects multiple cognitive, emotional and biological mechanisms (Vollema, Sitskoorn et al., 2002;

Yaralian et al., 2000), which appear to operate throughout the lifespan (Badcock & Dragovic, 2005). Whilst the mechanisms which subserve the expression of schizotypy are not fully understood, an accumulation or interaction of genetic, neurodevelopmental, neuropsychological and psychosocial factors are believed to underlie this personality type (Kwapil, Barrantes-Vidal & Silva, 2007).

Schizotypy reflects qualitatively similar, but quantitatively much less severe, features that are analogous with the symptoms expressed in Schizotypal Personality Disorder (SPD) and schizophrenia (van Os et al., 2000; Verdoux & van Os, 2002; Buchy, Woodward & Liotti, 2006). Schizotypy has been characterised and operationalised through several different perspectives. However, in the current thesis, the conceptualisation that schizotypy is a personality trait with clinical analogies which was largely derived from Schizotypal Personality Disorder (Raine, 1991) informs the theoretical and experimental work.

### ***2.2.1 SCHIZOTYPAL PERSONALITY DISORDER***

The term personality disorder describes distinct clinical syndromes characterised by persistent symptoms which influence an individual's interactions with the world (Sue et al., 2003). In the *DSM-IV-TR*, personality disorders are defined as reflecting a persistent pattern of internal experience and behaviour that is present in cognition, emotions, interpersonal relationships and impulse control which significantly deviate from cultural norms (American Psychiatric Association (APA), 2000). Personality disorders are distinguished from normal expressions of individual differences in personality dimensions when inflexible, persistent and

maladaptive traits cause an individual functional problems and/or significant distress to the self or others (Sue et al., 2003).

Schizotypal personality disorder (SPD) refers to a personality disorder that is characterised by social withdrawal, unusual or bizarre behaviour, cognitions, perceptions and beliefs. Whilst there are little qualitative differences between the symptoms of SPD and the characteristics of schizotypy, there are considerable quantitative differences between the severities of the features expressed through the two constructs.

SPD describes a persistent pattern of social and interpersonal impairments, the disorder is usually apparent from childhood or early adolescence and its expression is manifest in various contexts (APA, 2000). Many individuals with this disorder believe that they are in the possession of special and/or magical powers, they may also be subject to persistent illusions, aberrant perceptual experiences, ideas of reference (which refer to misinterpretations of causal incidents and beliefs that external events convey special meanings solely for that individual) and paranoid ideation. In addition, superstition beyond the acceptable norms defined by one's subculture, strange speech including digression and vagueness in conversation and the idiosyncratic use of words and phrases is often associated with SPD (Sue et al., 2003). Interpersonal relationships are frequently problematic for individuals with SPD, whilst their behaviour may indicate that these individuals do not desire close relationships, unlike individuals with Schizoid Personality Disorder (which is characterised by social isolation, emotional bluntedness, indifference to others, lack of capacity and desire to form relationships with others; APA, 2000), people with SPD often convey sorrow

about their lack of close relationships (Sue et al., 2003). According to the APA (2000), the prevalence of SPD has been reported to be approximately 3 percent and appears to be slightly more common in males than females. It has also been proposed that the idiosyncrasies observed in SPD stem from distorted or impaired cognitive abilities (Sue et al., 2003).

Diagnostically, it is important that schizotypal experiences are interpreted in the context of an individual's cultural background. Therefore, before reaching a diagnosis of SPD, one must be aware that certain culturally endorsed concepts, especially those that pertain to certain religious ideologies, may be easily mistaken for schizotypal ideation (APA, 2000; Sue et al., 2003). One must also account for the way in which superstition, delusions and even hallucinations may be more acceptable and even encouraged in some cultures (APA, 2000). It is also inherently important to be sensitive to such cultural issues in studies of schizotypy, as scores can be greatly influenced by context and culture, they should always be compared with appropriate normative data (Raine, 1991).

Individuals with SPD express many characteristics that are analogous with the symptoms that are manifest in schizophrenia, however in SPD these are expressed in a less serious form. Accordingly, a higher risk of SPD has been found in first-degree relatives of individuals diagnosed with schizophrenia when compared with the relatives of healthy controls (APA, 2000). In addition, there appears to be a considerable elevation in schizophrenia and other psychotic disorders in the relatives of probands with SPD (APA, 2000).



Individuals with SPD are more likely to seek help for related symptoms such as depression and anxiety rather than for the personality disorder per se (APA, 2000). SPD also appears to be a diathesis for psychotic episodes in response to stress although the disorder itself is not characterised by persistent psychotic symptoms (APA, 2000). Furthermore, such psychotic stress episodes are usually not sufficient to meet diagnoses such as Brief Psychotic Disorder or Schizophreniform Disorder. In terms of course, SPD appears to remain quite stable with only a small proportion of SPD individuals decompensating to schizophrenia or to other disorders that are typified by persistent psychosis such as Delusional Disorder.

According to the *Diagnostic and Statistical Manual DSM-IV-TR*, diagnostic criteria for Schizotypal Personality Disorder include the following definition and characteristics:

- A. Pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships as well as by cognitive or perceptual distortions and eccentricities of behaviour, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:
- (1) ideas of reference (excluding delusions of reference)
  - (2) odd beliefs or magical thinking that influences behaviour and is inconsistent with subcultural norms (e.g., superstitiousness, belief in clairvoyance, telepathy, or “sixth sense”; in children and adolescents, bizarre fantasies or preoccupations)
  - (3) unusual perceptual experiences, including bodily illusions
  - (4) odd thinking and speech (e.g., vague, circumstantial, metaphorical, over-elaborate, or stereotyped)

- (5) suspiciousness or paranoid ideation
  - (6) inappropriate or constricted affect
  - (7) behaviour or appearance that is odd, eccentric, or peculiar
  - (8) lack of close friends or confidants other than first degree relatives
  - (9) excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears rather than negative judgements about self
- B. Does not occur exclusively during the course of schizophrenia, a Mood Disorder with Psychotic Features, another Psychotic Disorder or a Pervasive Developmental Disorder.

Note: If criteria are met prior to the onset of Schizophrenia add “Premorbid,” e.g., “schizotypal Personality Disorder (Premorbid).” (*Diagnostic and Statistical Manual Of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR, 2000) p.701).

Whilst the *DSM*'s characterisation of SPD describes the way in which the personality disorder is qualitatively similar but quantitatively distinct from schizophrenia, it is still underpinned by categorical conceptions of the separation between sanity and psychosis, illness and normality. However, the similarities and differences between the two syndromes are important for understanding how disorders with a common genetic diathesis can lead to different degrees of phenotypic expressions of symptoms that are ostensibly the same. This concept has important implications for understanding schizotypy as a dimensional model of psychosis proneness.

### ***2.2.2 RELATIONSHIP BETWEEN SCHIZOTYPY, SPD AND SCHIZOPHRENIA***

Kraepelin (1919) was the first individual to describe the way in which the relatives of schizophrenic patients also frequently demonstrate abnormal personalities.

These subsyndromal features were later described as latent, borderline or uncertain schizophrenia and were found in the biological rather than adoptive relatives of adoptees with schizophrenia (Kety et al., 1968). This led to the initial conceptualisation of Schizotypal Personality Disorder and several other schizophrenia spectrum disorders which were found to be elevated in the biological relatives of schizophrenic individuals compared to the relatives of controls (Kendler et al., 1981; Siever et al., 1990). In turn, such observations also led to the construct of schizotypy, as a non-clinical counterpart of disorders such as SPD and schizophrenia that is relatively normally expressed throughout the general population (Weinsterin, McKay & Ngan, 2008).

Evidence suggests that a shared genetic diathesis subserves schizotypy, SPD and schizophrenia (Kety et al., 1967; Fanous, Gardener, Walsh et al., 2001; Silverman et al., 1993), both SPD and schizophrenic probands have been found to have nearly the same probability of having a schizophrenic relative (Kendler et al., 1993) and schizotypy has been found to be elevated in the non psychotic relatives of individuals with schizophrenia (Fanos et al., 2001), and SPD (Raine, 1991). In light of this genetic framework, the expression of schizotypy has been theorised to range from the normal population, to subclinical schizophrenia-spectrum personality disorders such as SPD, to schizophrenia itself (Kwapil, et al., 2008).

In addition, more recent studies suggest that rather than signifying a specific phenotypic liability just for schizophrenia (Battaglia et al., 1997), schizotypal traits also represent a broader phenotypic expression of a psychosis phenotype (Kety et al., 1994). Mata et al. (2003) suggest that the specificity of schizotypy to schizophrenia is an illusion borne from the way in which most studies have narrowly concentrated on the relationship between schizotypy and schizophrenia instead of assessing the relationship between schizotypy and a wider range of psychotic states. Moreover, when other psychotic illnesses were considered, Mata et al. (2003) found that schizotypal traits were elevated in the relatives of probands with several different psychotic illnesses and they found no differences in the distribution of schizotypal features amongst relatives of patients with schizophrenia and the relatives of patients with various other psychotic diagnoses. This further advances the dimensional breadth of the schizotypy construct from the schizophrenia spectrum to a broader psychosis prone continuum.

### ***2.2.3 DIMENSIONAL PERSPECTIVES***

Traditionally, the psychosis phenotype was conceptualised as representing dichotomous symptoms that were not concomitant with normality (Krabbendam et al., 2004). However more recently, the notion that psychotic tendencies reside on a continuum has gained more support (Claridge & Broks, 1984; Eysenck & Eysenck, 1975; Claridge, 1997).

A fundamental theoretical theme in the schizotypy literature pertains to the extent to which the concept of schizotypy can be regarded as representing a dimensional construct (McCreery & Claridge, 2002). Whilst most evidence converges on the

theme that rather than being a unitary concept, schizotypy is best conceived of as a multidimensional construct that reflects various cognitive and biological mechanisms (Badcock & Dragovic 2006), from this point explanations differ in the extent to which they ascribe dimensionality to schizotypy. Claridge, (1994; 1997) notes the dimensionality of schizotypal traits can be construed from three viewpoints; the quasidimensional, the dimensional and the fully dimensional.

The quasidimensional perspective (Rado, 1953; Meehl, 1962) is oriented around the concept that psychosis represents a pathologically abnormal state. From this perspective, continuity in schizotypy relates to the variance in the expression of clinical symptoms. Therefore, in this model, schizotypal symptoms reflect less overtly expressed features of schizophrenic disease mechanisms. This explains why this approach is called *quasi*-dimensional, because it only refers to one dimension which is comprised of a gradient that reflects how explicitly the symptoms of schizophrenia are expressed. For Rado, a schizotypal individual will always have an enduring vulnerability to schizophrenia (Rado, 1953).

In contrast, the dimensional approach, largely influenced by Eysenck's personality centred model for psychoticism, proposes that as all individuals reside on the same continua, there is also a natural continuum between individuals with few and many schizotypal traits. Consequently, those who display psychosis are merely at the most extreme upper end of a universal common dimension. In this account, schizotypy is a true personality trait which, whilst nonstandard, is comparable to other expressions of individual differences like extraversion or neuroticism (Lawrence and Peters, 2004). This model would also regard specific symptoms of schizophrenia as reflections of exaggerated physiological and

psychological mechanisms of schizotypal personality (Badcock & Dragovic, 2006). Lawrence and Peters (2004) argue that whilst schizotypal traits may be deviant, in the dimensional model, these traits are regarded as a form of healthy diversity in individual differences rather than reflecting the diluted but clinically relevant psychotic symptoms proposed by the quasidimensional model.

The fully dimensional perspective (Claridge 1997; 1999) is compatible with the dimensional trait theory of psychosis proneness and also encompasses the quasidimensional disease model. The quasidimensional perspective is negotiated into the fully dimensional account through the suggestion that it acts as a parallel continuum that is also graded and is reflected in the spectrum of SPD to schizophrenia, this is separate from but related to schizotypy as a personality trait (McCreery & Claidge, 2002). This continuum reflects the idea that schizophrenia is a breakdown process and it is the factors that lead to this breakdown which distinguish the clinical schizotypy continuum from the trait range. This suggests that more is involved in psychotic decompensation to schizophrenia than high schizotypy alone, although there is evidence that individuals who express extreme schizotypal traits are still at an increased risk of developing other psychotic illnesses (Weinstein, McKay & Ngan, 2008; Kwapil, Miller & Zinser, 1997; Gooding, Tallent & Matts, 2005).

#### ***2.2.4 SCHIZOTYPY AND HEALTH***

In line with the dimensional model, schizotypy has been found to be normally (Weinstein, McKay & Ngan, 2008) and half-normally (Van Os, Linscott, Myin-Germeys et al., 2009) distributed in the general population. In the half normal

distribution, the majority of the sample were found to have very low values however, a significant fraction of participants also had much higher scores (Van Os et al., 2009; Modinos et al., 2009). Even the most idiosyncratic of schizotypal traits have been identified in healthy individuals, with no evidence of clinical pathology within the general population. For instance, positive schizotypal elements such as paranoid thinking have been found to be dimensionally expressed across the normal population (Freeman, Pugh, Antley et al., 2008). The same dimensionality has also been demonstrated for even more non-standard traits such as paranormal beliefs (Brugger & Mohr, 2008), false perceptual experiences (Tsakanikos & Reed, 2005), delusional ideation and hallucinatory experiences (Altman, Collins & Mundy, 1997). Within a non-psychotic population of adolescents, 33 percent reported that they had experienced hallucinations and 24 percent reported delusional ideation, these non clinical experiences were found to be associated with schizotypal thought processes (Altman, Collins & Mundy, 1997). Other studies have reported a 17.5 percent prevalence of positive psychotic symptoms in the 'healthy' general population (van Os et al., 2000).

Such findings converge with the dimensional trait theory of schizotypy and the fully dimensional model, and have led to concepts such as 'healthy' (McCreery & Claridge, 2002) and 'benign' (Jackson, 1997) schizotypy. This has facilitated the separation of schizotypy from a disease context. These conceptualisations have been furthered by evidence that most individuals who exhibit high levels of schizotypal personality traits rarely decompensate into full blown psychosis (Kwapil, Barrantes-Vidal & Silva, 2007).

Despite the relationship between schizotypal traits and the symptoms of clinical disease entities such as schizophrenia, it does not inevitably follow that individuals with high schizotypal traits are less healthy than those with lower traits. In some respects, certain schizotypal features have been found to be advantageous. For instance, individuals who score highly on positive schizotypy measures, those which are most associated with psychosis proneness, have been found to attain high academic achievements (Nettle, 2006), to be especially happy (McCreery & Claridge, 1995), to have better problem-solving abilities (Jackson, 1997) and to be more creative (Claridge, 1993; Claridge 1998) than individuals with lower positive traits. Amongst these findings, the association between creativity and positive schizotypy has especially provoked a substantial amount of interest and research.

Although levels of creativity have consistently been found to be elevated in the relatives of individuals with schizophrenia (Andreason, 1987; Kinney et al., 2000), there is little evidence for enhanced creativity in individuals with schizophrenia (Andreasen & Powers, 1975; Keefe & Magara, 1980). Such findings suggest that it may actually be the expression of non-clinical schizotypy in healthy individuals that facilitates creativity (Claridge, 1993; Claridge 1998). Positive associations between schizotypy and creativity have been demonstrated by several studies assessing healthy adults (Folley & Park, 2005; Schuldberg, 2000; Tsanikos & Claridge, 2005; Weinstein & Graves, 2002), specific creative professionals (Burch et al., 2006; Nettle & Clegg, 2006) and healthy relatives of schizophrenic probands (Andreason, 1987; Kinney et al., 2000).



Such evidence has led evolutionary psychologists to propose that the robust relationship between schizotypy and creativity may represent one of the reasons why schizophrenia risk alleles have not been deselected. The creativity benefit model offers an explanation as to why, despite considerable reproductive costs, risk alleles for schizophrenia spectrum disorders persist in the population. The model posits that these alleles are still present because of the putative creativity benefits of schizotypy (Andreasen, 1987; Crow, 2000; Eysenck, 1995; Miller & Tal, 2007; Nettle & Clegg, 2006).

Such evidence supporting the possible health benefits of positive schizotypy is important to our concept of positive schizotypy as an endophenotype for a psychosis phenotype of neurological disorders. In our model we suggest that individuals with psychosis prone personality traits such as schizotypy may be susceptible to develop psychosis through neurodegenerative processes despite having led relatively normal lives with no prior overt psychoses. Health benefits may explain how individuals with a psychosis prone diathesis remain healthy throughout the life span. This places our theory in accordance with a fully dimensional model. Schizotypy is distinguished from schizophrenia and SPD through its non-clinical characterisation and the way in which it appears to be a reflection of variance in individual differences. This also supports the idea that whilst schizotypy represents a diathesis for psychosis, high positive schizotypy alone is not sufficient for a clinical expression of full blown psychosis but that the involvement of other factors, in our case neurodegenerative processes or neuropharmacological factors, are necessary to cause a clinical psychotic state that is quantitatively and pathologically different from schizotypy as a personality dimension. Thus schizotypy is the diathesis and neurodegenerative or

neuropharmacological factors represent the *stress* in our diathesis-stress model of psychosis. Furthermore, the way in which these trait analogies transcend schizophrenia and incorporate a broader spectrum of psychosis proneness makes schizotypy an even more appropriate endophenotype for a neurological stress model of psychosis as it suggests that a distinct aetiology from that which mediates schizophrenic psychoses, subserves neurological psychosis.

### ***2.2.5 SCHIZOTYPY AS AN EXPERIMENTAL MODEL***

As discussed in Chapter 1, an endophenotype should prove to be an especially useful experimental model because it demonstrates the pathophysiological markers of disease in non clinical healthy individuals thereby avoiding confounds such as treatment, chronicity and institutionalisation that are introduced in patient studies. For these reasons, schizotypy has frequently been investigated as an endophenotype for psychosis.

Due to the fact that individuals with high schizotypal traits are ostensibly normal, a large body of research has investigated the extent to which individual differences in schizotypal personality traits can reveal information about psychosis especially with reference to schizophrenia (Badcock & Dragovic, 2006). The use of a non-clinical ‘normal’ population that appears to share a genetic diathesis with the disorder of interest and that expresses traits that are analogous with clinical psychotic symptoms, enables associations and dissociations to be made that are otherwise impossible to assess discretely in clinical populations (Badcock & Dragovic, 2006).

According to Badcock & Dragovic (2006) the extent to which individual differences in schizotypal personality can improve discernment of the mechanisms involved in schizophrenia resides on the degree of similarity that can be established between the clinical state of schizophrenia and schizotypal personality in non-clinical healthy individuals. Using schizotypal personality as a less complex model with fewer confounds for understanding schizophrenia assumes that the characteristics of schizotypal personality are capable of expressing the vast heterogeneity of schizophrenia (Badcock & Dragovic, 2006). Similarities between the positive, negative and disorganised symptoms of schizophrenia and a three factor structure of schizotypy demonstrates sufficient biological and cognitive continuity between the personality traits and schizophrenia to suggest schizotypy is an appropriate model to clarify the mechanisms which subserve schizophrenia (Badcock & Dragovic, 2006).

More generally, the expression of individual differences in schizotypy and its sub factors have been found to be especially relevant for understanding the mechanisms that subserve the formation and maintenance of psychosis and the ways in which schizotypal processes may be protective against, and potentiating for psychosis (Mohr & Leonards, 2005).

### ***2.3 ASSESSMENT AND MEASUREMENT***

There is a large body of research dedicated to the assessment of individual differences in schizotypy. Self-report measures that have been specifically devised to assess schizotypy appear to be divided into those which measure psychosis proneness in terms of the positive and negative features of schizotypy, those

which are based on the DSM criteria for SPD and suggest a three factor structure of schizotypy and those which are based on large factor analysis studies and propose a four factor structure. Quite considerable variation in factor structure has been reported, these differences appear to be a result of different statistical methods and from the use of diverse assessment methods (Badcock & Dragovic, 2005; Yaralian et al., 2000).

### ***2.3.1 POSITIVE AND NEGATIVE FACTORS OF PSYCHOSIS PRONENESS***

Originally, two factors (positive and negative) were presumed to subserved individual differences in schizotypy, (Siever & Gunderson, 1983; Widiger et al., 1986). Largely based on the positive and negative features of schizophrenia, the positive factor is comprised of schizotypal features such as ideas of reference, magical thinking, perceptual aberrations, paranoia and strange speech, whereas the negative factor reflects social anxiety, lack of close friends and constricted affect (Raine, 1991). Subsequently, many self report scales have been developed to measure various positive and negative aspects of schizotypy or psychosis proneness. Measures such as the Psychoticism scale (Eysenck & Eysenck, 1975), Schizophrenism (Venebles et al., 1990) and the STA (Claridge & Broks, 1984) have been widely used to assess schizotypy. Instruments such as the Magical Ideation (Chapman, Chapman & Raulin, 1979) and the Perceptual Aberration Scales (Eckblad & Chapman, 1983) have been especially developed to measure positive aspects of schizotypy and the Physical and Social Anhedonia scales (Chapman et al., 1976) have been developed for measuring negative schizotypal processes.

In terms of research, psychosis proneness assessment tools appear to be salient measures of psychosis proneness (Chapman et al., 1995; Raine et al., 1995). However, these scales appear less appropriate for genetic studies of positive schizotypy (Clementz et al., 1991; Katsanis et al., 1990; Claridge et al., 1983; Claridge & Beech, 1996) as they have been criticised for having limited scope (Mason & Claridge, 2006) and they appear to sensitise individuals with a family history of schizophrenia to their own risk for psychosis (Yaralian et al., 2000; Mohr & Leonards, 2005). This sensitisation has been found to lead to defensive responding which results in artificially lower scores on items that are obviously related to familial risk of psychosis.

### ***2.3.2 THREE FACTOR STRUCTURE***

More recently, rather than a two syndrome model (Kelley & Coursey, 1992); Raine & Allbutt, 1989), a three factor model which reflects positive, negative and disorganised dimensions (Brekke et al., 1994; Buchanan & Carpenter, 1994) has been found to offer a better explanation of individual differences in schizotypal traits (Raine, Reynolds, Lencz et al., 1994). These three factors have also been found to reflect the heterogeneity and multiple genetic aetiologies in schizophrenia (Loughland & Williams, 1997).

The three factor model represents all nine characteristics of SPD as defined by the *DSM* (APA, 1987; 2000) through three factors; Cognitive Perceptual, Interpersonal and Disorganised. The Cognitive Perceptual factor is similar to the positive factor outlined above, although in this model strange speech was found to load onto a separate factor. The Cognitive Perceptual factor is comprised of ideas

of reference, magical thinking, unusual perceptual experiences, suspiciousness or paranoid ideation. These features are in line with the Reality Distortion Syndrome of positive schizophrenia (Liddle, 1987; Williams, 1996) for instance, magical thinking could be interpreted as a benign version of delusional ideation and aberrant perceptual experiences, a non clinical concomitant of hallucinations (Loughland & Williams, 1997).

The Interpersonal factor closely parallels the negative factor of the earlier two factor model and refers to social anxiety, lack of close friends, paranoid ideation and constricted affect. The Disorganised sub-factor reflects odd speech and odd behaviour, odd speech is proposed to be a schizotypal dimension of schizophrenic thought disorder, and odd behaviour mirrors the bizarre behaviour evidenced in schizophrenia. The Schizotypal Personality Questionnaire (SPQ; Raine, 1991) was devised to measure these three factors whilst still representing the original nine subscales for schizotypal traits proposed by the *DSM*.

A three factor structure, as measured by the SPQ, has been consistently replicated in both schizophrenia and schizotypal personality and this has been found to be constant across age, sex, culture, religious association, family background and psychopathology (Badcock & Dragovic, 2006; Fossati et al., 2003; Reynolds et al., 2000; Rossi & Daneluzzo, 2002). The SPQ also appears to be less vulnerable to defensive responding than positive psychosis proneness scales, whilst the items in the positive factors may be similar between the two types of scales, reporting positive items on the SPQ endorses substantially more normal experiences than responses to similar items on psychosis proneness scales suggest (Yaralian et al., 2000).

### ***2.3.3 FOUR FACTOR STRUCTURE***

There has been a vast amount of research dedicated to the factor analysis of schizotypy scales (McCreery & Claridge, 2002) which has led to the partial consensus that the schizotypy construct is comprised of at least three but no more than four sub-factors. The four factor model was first proposed by Bentall, Claridge and Slade (1989) and is comprised of Aberrant Perceptions and Beliefs, Introvertive Anhedonia, Cognitive Disorganisation and Asocial behaviour. The first three of these factors correspond quite closely with Raine's (1994) Cognitive Perceptual, Interpersonal and Disorganised sub factors respectively, although social anxiety is associated with the interpersonal factor in Raine's model and with Cognitive Disorganisation in Claridge et al's., (1996). It is the last factor, asocial schizotypy, which represents the main difference between the two questionnaires (McCreery & Claridge, 2002). This factor reflects social nonconformity, impulsivity and disinhibition of mood and was derived from the inclusion of Eysenck's P-Scale (Eysenck & Eysenck) the hypomania scale (Eckblad and Chapman, 1986) and the Borderline Personality scale (Claridge & Broks, 1984) in the original factor analysis.

In the Oxford, Liverpool Inventory of Feelings and Experiences (O-LIFE, Mason et al., 1995), the most widely used measure for the assessment of a four factor structure of schizotypy (Mason & Claridge, 2005), this fourth factor has also been referred to as Impulsive Nonconformity (Mason et al., 1995; Vollema & van den Bosch, 1995). However, as this factor does not appear to indicate cognitions or behaviour it has been criticised for not reflecting an authentic schizotypy dimension (Pickering, 2004). Furthermore, according to the APA, individuals with SPD rarely demonstrate impulsive behaviours and converging evidence

suggests Impulsive Nonconformity scores are not elevated in relatives of individuals with schizophrenia (Claridge et al., 1983), higher scores on this factor do not predict psychosis (Chapman et al., 1994), nor do they discriminate between schizophrenic patients and healthy controls (Cochrane et al., 2010) and this factor has been found to actually reflect the absence of schizotypal traits (Loughland & Williams, 1997). Such findings appear to suggest that a three factor model offers the most appropriate account of individual differences in schizotypy.

## ***2.4 COGNITIVE CORRELATES***

Many studies have investigated the cognitive correlates of schizotypy, examined the extent to which cognitive performance varies as a function of a quasi dimensional schizotypal continuum and assessed the way in which individual differences in dimensional schizotypy are related to variations in cognitive performance.

Apart from genetic similarities, neuropsychological similarities have been found to be shared between individuals with schizophrenia, SPD and schizotypy (Dickey et al., 1999). Several studies have found associations between individual differences in the expression of schizotypy and differences in cognitive functions that are qualitatively similar to, but quantitatively less pronounced, than those evidenced in schizophrenia (Peters et al., 1994; Park et al., 1995; Gray et al., 2002; Tsakanikos & Reed, 2005). For instance, selective attention deficits which have been implied to be central to schizophrenia have been found in individuals with SPD, healthy relatives of schizophrenics and individuals with higher scores on measures of schizotypal personality (Hoffer et al., 1999; Trestman et al., 1995). Impairments in eye tracking (Siever et al., 1994; Clementz et al., 1995) and



verbal learning (Voglmaier et al., 1997) have also been demonstrated in individuals with high, compared with low schizotypal traits. Poor spatial working memory (Park & McTigue, 1997), impaired performance on the Wisconsin card Sorting task (Daneluzzo et al., 1998), and reduced latent inhibition (Baruch et al., 1988) have also been associated with higher total schizotypy scores (Raine, 1995).

Other studies have investigated the way in which individual differences in scores within schizotypal sub factors may be reflected in variance in cognitive performance in specific tasks. For instance, non clinical individuals with lower scores on the unusual experiences sub factor of the positive factor of the O-LIFE were found to have decreased verbal fluency, whereas participants who scored higher on this positive measure demonstrated increased verbal fluency (Tsakanikos & Claridge, 2004). When assessing the contribution of individual differences in separate schizotypal sub factors, the odd speech sub factor of the disorganisation factor and the magical ideation sub factor of the cognitive perceptual factor were associated with the elevated normative associations (Lenzenweger, Miller, Maher & Manschreck, 2007) that have been frequently observed in schizophrenic patients (Maher, Mansschreck, Linnert & Candela, 2005). Positive schizotypal symptoms have also been found to predict false perceptual experiences in non clinical individuals (Tsakanikos & Reed, 2005). High positive schizotypy (Moritz et al., 1998) and high total schizotypy (Skosnik et al., 2001) have also been associated with reduced negative priming and defective mentalising has been found to be related to positive and negative, but not disorganised factors (Langdon & Coltheart, 1999).

Combined and individual features of schizotypy have been especially useful in studies investigating the factors which contribute to delusion formation. In fact in the *DSM-IV*, isolated delusions are hypothesised to be intrinsically part of schizotypal processes (APA, 1995). Evidence from previous research has substantiated the relationship between subclinical ideas of reference and delusional ideation in individuals with manifest schizotypal thought processes (Altman, Collins & Mundy, 1997). In addition, there is remarkable convergence between the reasoning biases found in studies of delusions in schizophrenia and psychosis and the reasoning processes of schizotypal individuals (Lawrence & Peters, 2004; Colbert & Peters, 2002; Garety et al., 1991). Many of the cognitive biases and impairments which have been implied in delusion formation and maintenance have also been found in individuals with non-clinical schizotypy (Buchy et al., 2007) including, jumping to conclusions (Garety, Hemsley & Wessely, 1991; Sellen, Oaksford & Gray, 2005) liberal acceptance (Moritz & Woodward, 2004), attributional bias (Bentall, Kinderman & Kaney, 1994), knowledge corruption (Moritz & Woodward, 2006), poor theory-of-mind (Frith, 1994) and a bias against disconfirmatory evidence (BADE; Buchy et al., 2007)

### ***2.5 BRAIN FUNCTION AND STRUCTURE***

Several personality traits have been found to be associated with neurobiological factors and variance in brain structure development. Whilst the research base for schizotypy and brain function and structure is less extensive than that for the personality traits outlined in the previous chapter, several studies have investigated the relationship between schizotypy and the brain in terms of: hemispheric asymmetry (Gruzelier & Doig, 1996; Leonhard & Brugger, 1998; Nunn & Peters, 2001; Weinstein & Graves, 2002), electrophysiology (Kidd &

Powell, 1993; Kimble, Lyons, O'Donnell, et al., 2000), and neurotransmitter activity (Siever et al., 1993).

Individually, positive schizotypal features have been associated with developmental variance in synaptic density (Gruzelier & Kaiser, 1996), neurochemical dopaminergic dysfunction as suggested by higher levels of homovanillic acid CSF (Siever et al., 1993) and electrophysiological deficits (Perry et al., 1997; Salisbury et al., 1996). Neurological soft signs (objective neurological abnormalities that are minor and non-localisable, Barkus, Stirling, Hopkins & Lewis, 2006) which have been detected in schizophrenic individuals and their relatives (Dazzan & Murray, 2002; Wolff & O'Driscoll, 1999) have also been found to be associated with psychosis proneness in non clinical populations as measured by the positive factor of the O-LIFE (Barkus et al., 2006).

Unfortunately, fewer studies have investigated the relationship between schizotypy and brain structure. To date, most of the studies concerned with schizotypy and brain structure have investigated the neural correlates of SPD rather than trait schizotypy (Dickey, McCarley, Voglmaier et al., 1999). In line with findings from individuals with schizophrenia, studies investigating grey matter differences in individuals with SPD have evidenced sulcal enlargement (Cannon et al., 1994) and reduced grey matter volume in the left superior temporal gyrus (Dickey et al., 1999). Like persons with schizophrenia, individuals with SPD have also been found to have larger ventricular brain ratios (Siever et al., 1995) and in line with a continuum perspective, ventricular volume in individuals with SPD appears to be intermediate between normal controls and individuals with schizophrenia (Buschsbaum et al., 1997).

Further studies are required to extend our knowledge of the association between brain structure and function and the expression of schizotypy across quasi-dimensional and dimensional spectrums. Investigating brain function and structure in schizotypy may advance knowledge of the mechanisms which subserve schizotypal processes along a spectrum from schizotypy to schizophrenia and those which subserve more normally distributed dimensional trait schizotypy. To date, only a few studies have assessed the relationship between brain structure and schizotypy. Reduction of prefrontal volume has been associated with higher levels of trait schizotypy (Raine et al., 1992) and participants with high positive schizotypy have been found to have larger global volumes and larger regional volume in the medial posterior cingulate and the precuneus when compared with participants with lower scores (Modinos et al., 2009) these findings will be discussed in further detail in Chapter 6.

### ***2.6 MODELING THE ENDOPHENOTYPE***

In order to be a valid endophenotype for explaining the aetiology of psychosis in neurological stress, schizotypy must fulfil several important criteria. In line with Gottesman & Gould's (2003) specifications for an endophenotype, schizotypy is associated with illness in the population (Weinstein, McKay & Ngan, 2008; Kwapil, Miller & Zinser, 1997; Gooding, Tallent & Matts, 2005), it is heritable (Raine & Baker, 1992), state independent (manifests in an individual whether or not illness is active) (McCreery & Claridge, 2002; Jackson, 1997), within families, schizotypy and illness cosegregate (Kendler et al., 1981; Siever et al., 1990) and schizotypy is found in the unaffected relatives of probands at a higher rate than in the general population (Mata et al., 2003). In addition, schizotypy also meets Waldman's (2005) criteria that an endophenotype must have good

psychometric properties (Raine, 1991, Raine et al., 1994) and it represents a more fundamental trait than the phenotype (psychosis as a manifestation of neurological disorders) but it is still highly associated with psychosis. The way in which schizotypy also reflects sufficient variance in individual differences to explain its differential contribution to a liability for psychosis (Kuntsi et al., 2005) and the fact that these differences are heritable and expressed between and within individuals reliably throughout the lifespan (Kuntsi et al., 2005) furthers the validity of regarding schizotypy as an endophenotype.

The most compelling source of supporting evidence for investigating the extent to which schizotypy could serve as an endophenotype for the emergence of psychosis in neurological stress comes from findings that prior to dementia onset Alzheimer's disease patients with psychosis have been found to have increased schizotypal symptoms (Elise et al., 2005) and that a higher degree of subsyndromal psychoses and premorbid schizotypal symptoms have been found to be more severe in AD patients who also have psychosis (Erer et al., 2005). The association between premorbid schizotypal traits and the emergence of psychosis in AD confirms that schizotypy could be an ideal endophenotype for investigating the aetiology of the emergence of psychosis due to neurological stress such as neurodegeneration. Therefore, schizotypy may represent a diathesis for non-clinical psychosis proneness to become expressed psychiatrically through a neurodegenerative process such as AD. This is in line with Elise et al's (2005) hypothesis which suggests that perhaps a gene that confers a small risk for psychosis interacts with neurological illness to produce psychotic symptoms.

## CHAPTER 3

# AIMS AND OBJECTIVES

As is evident from the research presented in the previous chapters, personality dimensions, especially schizotypal traits appear to suggest a promising endophenotype and diathesis for the manifestation of psychosis due to neurological stressors such as neurodegeneration. Whilst there is an immense body of research that has investigated schizotypy as an endophenotype for schizophrenia, no prospective study has examined the relationship between schizotypy and psychosis in relation to neurological disorders. However, justification that the relationship between premorbid schizotypal traits and neurological psychosis may be worthy of further investigation has been suggested by two prior retrospective studies (Elise et al., 2005; Eror et al., 2005).

In this thesis, the plausibility of schizotypy as an endophenotype for the aetiology of positive symptoms in neurological disorders will be explored through behavioural and neuroimaging methodologies with both normal and pathological populations.

The behavioural studies will investigate the extent to which individual differences in non clinical dimensional schizotypy in a normal population can be associated with the cognitive and affective processes that have been found to be behaviourally and neurologically related to psychosis, especially those which may be relevant for delusional manifestations of psychosis. These studies will employ

both group differences and correlational approaches to investigate the differences between individuals with high, low and intermediate positive schizotypy scores in order to assess how these processes may be mediated as a function of schizotypy. The relationship between schizotypy and psychosis will also be assessed in pathological populations.

The rationale behind the neuroimaging studies is based on the hypothesis surmised from the results of the voxel based regression of delusions in AD (Brien et al., 2008), that the specific regional associations found may be due to individual differences in structural genetic vulnerability. Thus the neuroimaging studies in the current thesis will assess whether individual differences in schizotypal traits in normal individuals, are associated with variance in the brain regions which have been related to psychosis in previous studies. Neuroimaging will also be employed in a patient study which was devised to validate schizotypy as an endophenotype for neurological psychosis. In the following paragraphs, details of the experimental work that was undertaken for this thesis will be outlined.

In Chapter 4, the expression of individual differences in schizotypal traits will be investigated using the Schizotypal Personality Questionnaire – Brief (SPQ-B; Raine, & Benishay 1995) in a large screening study of a normal population of 700 individuals. This study will generate internally valid normative data for determining high and low cut off scores to facilitate the identification of individuals for further study. In order to advance an understanding of this population, a sub-group of representative individuals with various high, low and intermediate scores on the positive Cognitive Perceptual factor of the SPQ-B will undergo more detailed neuropsychological and personality assessments. The

neuropsychological assessments that will be employed include word span tasks - as measures of working memory, letter fluency - as an evaluation of executive function, the national adult reading test (NART; Nelson, 1982) – as a gauge of verbal intelligence and Ravens Progressive Matrices (Raven et al., 2003) - as a measure of non-verbal intelligence. Apart from providing a description of the neuropsychological profile of these individuals, the inclusion of these tests will identify whether it is necessary to control or co-vary for potential differences in specific cognitive domains between these individuals in future studies. More detailed personality profiling will be comprised of the full Schizotypal Personality Questionnaire (SPQ, Raine, 1991), a scale of Magical Ideation (Eckblad & Chapman, 1983), and the Tri-dimensional Personality Questionnaire (Cloninger et al., 1991).

An abnormal spreading activation in semantic networks has been frequently observed in schizophrenia and this semantic spreading has been associated with delusional ideation. In Chapter 5, the extent to which this extends to nonclinical individuals with high positive schizotypy scores will be investigated. The first experiment that will be reported in this chapter assessed the relationship between schizotypy and a semantic reasoning using the WAIS similarities task (Wechsler, 1981). Wason selection tasks (Cheng & Holyoak, 1985) were employed as additional reasoning measures to investigate the extent to which high and low schizotypies depend on reasoning ability or semantic spreading processes to negotiate the similarities task. In the second study that was devised to assess semantic spreading in schizotypy, participants were asked to produce words for several semantic and phonological fluency tasks. In a related study, the words that were produced in both the semantic and phonemic fluency tasks were



independently rated according to their familiarity, imageability, typicality and frequency, these ratings were then applied to the original fluency data to assess whether individuals with high positive schizotypy evince similar idiosyncratic semantic memory organisation to that which has been well documented and associated with psychosis in schizophrenia and to discern the extent to which idiosyncrasies in semantic memory may be advantageous (Mohr et al., 2001) and adaptive (Folley & Park, 2005) for these non-clinical individuals.

In Chapter 6, three experiments assessing affective interference, personal memory and the neuroanatomy of positive schizotypal personality traits will be presented. Emotional processing may represent a behavioural domain that is mediated significantly by personality (Canli et al., 2005). Due to evidence that memory and attentional biases may be associated with psychosis, a novel emotional Stroop task was devised to assess the way in which these processes vary as a function of schizotypy. The emotional Stroop was comprised of words that are associated with the Cognitive Perceptual factor of positive schizotypy and it was used to assess whether variability in the ability to inhibit the semantic content of words chosen to be emotionally relevant to positive schizotypal personality is reflected in individual differences in schizotypy. The use of a personality relevant task should reveal the influence of personality on emotional responsivity. This task was also used as the basis of a memory bias study to see if positive schizotypal participants demonstrate biases to remember psychosis congruent rather than neutral words in recall and recognition memory. Confabulation, which has been frequently associated with delusions in neurodegenerative disorders such as AD is notoriously difficult to provoke in healthy individuals, however the current methodology may be subtle enough to elicit confabulation through false alarm

responses to new items on the recognition paradigm. The second experiment that will be described in this chapter investigated semantic and episodic autobiographical memory (ABM) as a function of schizotypy using the Autobiographical Memory Questionnaire (Ivanoiu et al., 2006). This data will allow assessments to be made concerning the way in which differences between high and low schizotypies may interact with differences in episodic and semantic autobiographical memory. Whilst many studies have investigated the organisation of semantic memory in schizotypy, to date no study has investigated whether semantic spreading or idiosyncratic memory organisation extends to personal semantic memories. The study of ABM will also facilitate investigation of the interplay between schizotypy and episodic memory. Episodic memory may be important for understanding the mechanisms that underlie the formation of delusions as deficits in personal episodic memory have frequently been associated with delusions in schizophrenia (Aleman et al., 1999; Danion et al., 2007; Lepage et al., 2007) and AD (Lee et al., 2007). Evidence from behavioural studies suggests that impairments of personal episodic memory retrieval for late adulthood and recent life periods are strongly associated with confabulations and delusional memories (Cooper et al., 2006; Lee et al., 2007). In addition, the brain areas that have been found to be associated with delusions in AD involve structures that are also believed to be relevant for personal episodic memory retrieval (Bruen et al., 2008). Consequently, in the final experiment in this chapter the findings of a study devised to identify the neural substrates which subserved schizotypal personality dimensions will be presented. Recent neuroimaging advances have expanded explanations of individual differences in certain personality dimensions through characterising the relationship between structural variance in specified brain structures and distinct personality traits (Gardini et al.,

2009). Individual differences in the expression of schizotypal traits have been found to be heritable, to depend on genetic and neurobiological factors and to be associated with cognitive, behavioural and emotional functions. However, the mechanisms which mediate the variation and expression of schizotypal traits are not well defined. Voxel wise regression analyses will be used to investigate the neural correlates involved in total and sub factor schizotypy scores. This will enable comparisons to be made between the regions that are associated with positive schizotypy and those identified in the prior study investigating the neural correlates of delusions in Alzheimer's disease.

In Chapter 7, studies that were designed with the objective of validating the endophenotype in clinical populations will be presented. In order to see how the endophenotype interacts with different neurological aetiologies, a case series will describe the relationship between schizotypy and psychosis in patients with varied presentations. Examples of the interaction between schizotypy and neurodegenerative, neuropharmacological and environmental stressors will be described. An additional experimental study will investigate whether individual differences in schizotypy can explain psychotic reactions to Parkinson's disease (PD) medications such as Levodopa. Behavioural results will demonstrate the relationship between schizotypy and the manifestation of delusional psychosis in Levodopa treated PD patients and voxel based correlational analysis will be used to demonstrate how much variance in neuropsychiatric manifestations of Levodopa medicated PD patients can be explained by positive schizotypy scores. As a control condition, behavioural and anatomical data will be presented for another neuropsychiatric behaviour that is not hypothesised to be related to positive schizotypy.

Ethics approval for all the experimental work that will be presented in this thesis was granted by the joint University and NHS Trust Regional Ethics Committee.

## CHAPTER 4

# EXPRESSION OF SCHIZOTYPAL TRAITS IN A NORMAL POPULATION

### *4.1 INTRODUCTION*

The objective of this thesis is to identify if schizotypal traits in the normal population may indicate a vulnerability or diathesis to the presentation of psychosis, especially delusions, in abnormal ageing. Prior to dementia onset, AD patients with psychosis have been found to have increased schizotypal symptoms (Elise et al., 2005; Eror et al., 2005) and a higher degree of subsyndromal psychoses (Eror et al., 2005). Such findings have led to tentative hypotheses which suggest that perhaps a gene that confers a small risk for psychosis interacts with neurological illness to produce psychotic symptoms (Elise et al., 2005) and have also informed our specific hypothesis that schizotypy may represent a diathesis for non-clinical psychosis proneness to become expressed psychiatrically through neurodegenerative processes. However, in order to assess the extent to which individual differences in the expression of schizotypy have the potential to indicate an endophenotypic vulnerability to psychosis it is important to understand how psychosis proneness is expressed in a normal, non-clinical, healthy population.

Before assessment of schizotypal traits in the normal population can be undertaken, it is necessary to clarify the model of factor structure and the

perspective of dimensionality that will be used to operationalise and assess schizotypy throughout this thesis. Based on the review of two, three and four factor representations discussed in Chapter 2, it appears that individual differences in schizotypy are most accurately reflected through a three factor structure (Brekke et al., 1994; Buchanan & Carpenter, 1994; Raine, Reynolds, Lencz et al., 1994; Loughland & Williams, 1997). Whilst this thesis is ostensibly concerned with the positive factors that are most associated with psychosis proneness (Claridge, 1994; 1997), it is important not to limit the scope of the research by only investigating this factor. Using a measure which assesses the full range of the construct will allow a better understanding of the relationships between positive, negative and disorganised factors within the sample and will facilitate identification of whether variance in negative or disorganised factors also contributes to variation in the dependent variables that are hypothesised to be related to high positive schizotypy.

In terms of dimensionality, it is anticipated that the data acquired in this initial screening study will support the concept of healthy schizotypy in the context of a fully dimensional model. The fully dimensional account of schizotypy (McCreery & Claridge, 2002) suggests that breakdown processes separate the quasi dimensional schizotypy spectrum from the dimensional continuum. Such a distinction may explain how the majority of individuals with high dimensional schizotypy remain healthy (Kwapil, Barrantes-Vidal & Silva, 2007) because this dimension is quite separate from a disease context. In addition, McCreery and Claridge (2002) argue that on the dimensional spectrum, high schizotypy alone is not sufficient for schizophrenic decompensation whereas on the quasi dimensional spectrum, individuals are at a higher risk of full blown psychosis due to their

genetic vulnerability to schizophrenic breakdown mechanisms. Understanding the way in which these breakdown processes interact to contribute to psychosis in individuals on the quasi dimensional schizotypy spectrum would be useful in studies interested in the aetiology of schizophrenic psychoses along the schizoid taxon, however as the focus of the current study is concerned with understanding why psychosis emerges in neurodegenerative disorders, it is more appropriate to assess individuals on the healthy dimensional schizotypy spectrum.

In the model which informs this thesis, high schizotypy is also believed to be unlikely to lead to full blown schizophrenic psychosis as dimensional schizotypy is characterised as representing individual differences in a slightly eccentric (Lawrence and Peters, 2004), but normal (Weinstein, McKay & Ngan, 2008) dimension of personality. However, in this model, schizotypy still represents a psychosis diathesis as it reflects a latent variable that could become expressed endophenotypically as psychosis through neurodegenerative processes.

Schizotypy has been found to be normally (Weinstein, McKay & Ngan, 2008) and half-normally (Van Os et al., 2009) distributed in the general population and schizotypal traits have been regarded as a form of healthy diversity in individual differences (Lawrence and Peters, 2004; Claridge 1997; 1999). In the current study, the extent to which the expression of schizotypal traits in the normal population traits is compatible with a fully dimensional account of schizotypy will be assessed. In accordance with the three factor model, the expression of individual differences in schizotypal traits will be investigated using the Schizotypal Personality Questionnaire – Brief (SPQ-B; Raine, & Benishay 1995) in a large screening study of a normal population of 700 individuals. According to

Badcock and Dragovic (2005), the SPQ is widely used to assess individual differences in the vulnerability to psychosis in the normal population and it reflects an assessment tool that is compatible with the endophenotypic conceptualisation of these traits. Factor analytic studies have yielded much evidence to support a three factor model of schizotypy (Raine et al., 1994).

Apart from divining the extent of normality in the distribution of schizotypal traits in the sample, it is the objective of the current study to understand how these are expressed between individuals in terms of age and sex. The majority of SPQ standardisation studies have focused on young individuals under the age of 25 (Badcock & Dragovic, 2005). Although Fossati et al. (2003) argue that the latent factor structure does not change with age, this finding has limited implications for explaining the relationship between factor structure and age as it was deduced through the comparison of adolescents with a mean age of 16.4 and university students with a mean age 21.93. More recently, the three factor model has also been demonstrated to accurately characterise the structure of schizotypy in mature individuals with a mean age of 39.9 (Badcock & Dragovic, 2005).

However, it is the aim of the current study to assess whether there are differences in schizotypy and sub factor scores between individuals who are between 18 and 54 and those whose ages range from 55 and 100 years of age. Previous research suggests that compared with younger persons, older individuals are often found to have lower schizotypy scores (Fossati et al., 2003; Chen et al., 1997). However, this difference has not been found to compromise the integrity of the three factor structure within older individuals (Badcock & Dragovic, 2005). Consequently in the current study, it is predicted that older individuals will endorse fewer



schizotypal experiences than the younger group but they will also demonstrate similar relationships between schizotypal factors to those found in the younger group.

Apart from age related differences, the expression of schizotypal traits has also been found to differ between the sexes (Raine 1992). These sex differences have been found to mirror the distribution of symptoms found between the sexes in schizophrenia (Badcock & Dragovic, 2005) where females have been found to score higher on positive sub-scales and males to score higher on negative and disorganised ones (Raine et al., 1992). In the current study, it is predicted that sex differences in our sample will be in line with these prior findings.

Due to the fact that mean and cut-off scores have been found to vary from one sample to another and from country to country (Raine & Benishay, 1995), this study will also be employed to generate internally valid normative data for determining high and low cut off scores to facilitate the identification of individuals for further study. As discussed in Chapter 2, some culturally endorsed concepts may be easily confused for schizotypal ideation (APA, 2000; Sue et al., 2003) and schizotypy scores can be influenced significantly by the research context (Yaralian et al., 2000; Mohr & Leonards, 2005). In recognition of such issues, Raine (Manual For the SPQ, accessed December, 2007) suggests that rather than relying on existing published norms, researchers should develop their own cut-offs based on normative data that has been derived from within their sample. In the original paper, extreme groups were defined as those who score within 10% high-low cut offs (Raine, 1991), however in the current study a more constrained 5% cut off criteria will be used to identify high and low scorers.

The positive schizotypal factor has especially been demarcated as an indicator for psychosis prone individuals (Chapman, Chapman & Raulin, 1976) therefore, the Cognitive Perceptual factor which corresponds to positive schizotypy in the SPQ-B ought to be more likely to identify high and low psychosis-prone individuals than the full SPQ-B or any of its other factors. Consequently, scores on the Cognitive Perceptual factor will be used to identify and recruit individuals for further studies. Selection of participants based on positive scores, should circumvent problems that have been reported in previous studies (Woodward et al., 2007) where total SPQ scores have been used to identify participants. Unlike our specific psychosis-related scale, broader selection criteria of the total SPQ score makes it impossible to assess directly whether it is psychosis proneness or a combination of positive, negative and disorganised features that is associated with dependent variables. The identification of high and low scorers on the Cognitive Perceptual factor may enable clearer dissociations to emerge between the mechanisms that support normal cognition and behaviour and those which may contribute to psychosis vulnerability and the cognitive features that have been associated with this susceptibility.

## ***4.2 EXPERIMENT 1 – POPULATION STUDY***

### ***4.2.1 METHOD***

Opportunity samples were collected from staff and students from the University of Hull and from the Hull community, all participants from the older group were living independently. Many of the individuals in the younger group were first or second year psychology students, as these individuals are required to achieve a quota of research participation credits, it was anticipated that they may be more

amenable to participate in the more prolonged protocols that were planned to be undertaken with individuals with various SPQ-B Cognitive Perceptual scores.

#### ***4.2.2 PARTICIPANTS***

After excluding 12 participants based on the criteria outlined in section 4.2.3 in total data from 700 individuals were included in the analyses for this study. The group was comprised of 442 females and 258 males, with a mean age of 30.6 ( $SD = 16.90$ , range 18-96), and with mean years of education of 14.37 ( $SD = 2.35$ , range 25-9). In terms of age, 87% of individuals were under 55 years of age.

These individuals will be referred to as the young group which was comprised of 607 participants, 223 males and 384 females, their ages ranged from 18-54 with a mean age of 24.64 years ( $SD = 9.56$ ), and their years of education ranged from 9-25 years with a mean of 14.65 ( $SD = 2.08$ ). The remaining 13% of individuals whose ages were over 55 will be referred to as the older group. This group was comprised of 93 participants, 35 males and 58 females, ages ranged from 55-96 with a mean age of 65.45 years ( $SD = 10.45$ ), years of education ranged from 9-22 years with a mean of 12.54 ( $SD = 3.11$ ).

#### ***4.2.3 GENERAL HEALTH QUESTIONNAIRE***

Prior to participation, and after giving their informed consent, all participants were asked to complete a brief questionnaire detailing their demographic and background information. The questionnaire also included questions about medication status, substance abuse history, mental health issues, previous head injuries/ seizures, stroke and dementia status. Exclusion criteria included serious head injury, stroke, dementia, substance abuse, psychiatric disorder and current use of anti-psychotic or psychoactive medication.

#### ***4.2.4 SCHIZOTYPAL PERSONALITY QUESTIONNAIRE – BRIEF***

The Schizotypal personality questionnaire – brief version (SPQ-B; Raine & Benishay, 1995) was used to assess schizotypal traits in the current study. The SPQ-B is a quick, 22 item instrument which is based on the full schizotypal personality questionnaire (SPQ; Raine, 1991), for each item, participants were asked to indicate a “Yes” or “No” response. Each "Yes" response on the SPQ-B scores one point, total scores therefore range from 0 to 22. The SPQ-B is ideal for the purposes of the current study as it may be used to screen large numbers to assess schizotypal predispositions prior to further confirmatory tests.

Unlike the SPQ, it is not possible to derive the nine subscale scores using the SPQ-B however, this instrument still produces a total score and scores for the three sub factors; Cognitive Perceptual, Interpersonal and Disorganised. Like the SPQ, the SPQ-B can be used with both adults and adolescents, and with normal and pathological populations. The SPQ-B is comprised of the most reliable items from the full SPQ, intercorrelations between SPQ-B factors and SPQ factors range from .89 to .94 internal reliabilities of the subscales range from .72 to .80 and test-retest reliability ranges from .86 to .95 (Raine & Benishay, 1995). Criterion validity for the SPQ-B is high for total score (.66), Cognitive Perceptual (.73) and Interpersonal (.63) factors, but it is lower for the Disorganised factor (.36) (Raine & Benishay, 1995).

#### ***4.2.5 RESULTS***

The means, standard deviations and ranges for age, education and SPQ-B total and sub factor scores for both age groups and for males and females within these groups can be found in Tables 4.1, 4.2 and 4.3.

Table 4.1. Means (standard deviations; ranges) for demographic and SPQ-B variables for the younger group.

	<b>Young group (N = 607)</b>		<b>Males (N = 233)</b>		<b>Females (N = 384)</b>	
	<b>M</b>	<b>(SD; Min-Max)</b>	<b>M</b>	<b>(SD; Min-Max)</b>	<b>M</b>	<b>(SD; Min-Max)</b>
<b>Age</b>	<b>24.67</b>	<b>(9.56; 18-54)</b>	<b>26.02</b>	<b>(10.24; 18-54)</b>	<b>23.83</b>	<b>(9.05; 18-54)*</b>
<b>Education</b>	<b>14.65</b>	<b>(2.08; 9-25)</b>	<b>15.00</b>	<b>(2.51; 10-25)</b>	<b>14.48</b>	<b>(1.77; 10-25)*</b>
<b>SPQ-B (0-22)</b>	<b>7.56</b>	<b>(4.48; 0-22)</b>	<b>8.00</b>	<b>(4.71; 0-22)</b>	<b>7.29</b>	<b>(4.32; 0-22)</b>
<b>CogPer (0-8)</b>	<b>3.07</b>	<b>(2.00; 0-8)</b>	<b>2.84</b>	<b>(2.84; 0-8)</b>	<b>3.19</b>	<b>(1.98; 0-8)*</b>
<b>Interpersonal (0-8)</b>	<b>2.59</b>	<b>(2.23; 0-8)</b>	<b>2.91</b>	<b>(2.40; 0-8)</b>	<b>2.40</b>	<b>(2.10; 0-8)*</b>
<b>Disorganised (0-6)</b>	<b>1.90</b>	<b>(1.80; 0-6)</b>	<b>2.27</b>	<b>(1.85; 0-6)</b>	<b>1.69</b>	<b>(1.73; 0-6)**</b>

**\*\*Difference is significant between Males and Females at the .01 level (2-tailed)**

**\* Difference is significant between Males and Females at the .05 level (2-tailed)**

Table 4.2. Means (standard deviations; ranges) for demographic and SPQ-B variables for the older group.

	<b>Older group (N = 93)</b>		<b>Males (N = 35)</b>		<b>Females (N = 58)</b>	
	<b>M</b>	<b>(SD; Min-Max)</b>	<b>M</b>	<b>(SD; Min-Max)</b>	<b>M</b>	<b>(SD; Min-Max)</b>
<b>Age</b>	<b>65.45</b>	<b>(10.45; 55-96)</b>	<b>64.17</b>	<b>(7.27; 55-86)</b>	<b>66.22</b>	<b>(11.97; 55-96)</b>
<b>Education</b>	<b>12.54</b>	<b>(3.11; 9-22)</b>	<b>12.85</b>	<b>(2.82; 9-22)</b>	<b>12.36</b>	<b>(3.27; 9-22)</b>
<b>SPQ-B (0-22)</b>	<b>6.78</b>	<b>(4.18; 0-16)</b>	<b>5.82</b>	<b>(4.29; 0-16)</b>	<b>7.36</b>	<b>(4.04; 0-16)</b>
<b>CogPer (0-8)</b>	<b>2.88</b>	<b>(2.20; 0-8)</b>	<b>2.34</b>	<b>(2.20; 0-7)</b>	<b>3.21</b>	<b>(2.15; 0-8)</b>
<b>Interpersonal (0-8)</b>	<b>2.96</b>	<b>(2.08; 0-8)</b>	<b>2.51</b>	<b>(2.05; 0-7)</b>	<b>3.22</b>	<b>(2.07; 0-8)</b>
<b>Disorganised (0-6)</b>	<b>1.03</b>	<b>(1.33; 0-6)</b>	<b>1.09</b>	<b>(1.38; 0-5)</b>	<b>1.00</b>	<b>(1.32; 0-6)</b>

Table 4.3. Comparison of means (standard deviations; ranges) for demographic and SPQ-B variables for the older and younger groups.

	Young group (N = 607)		Older group (N = 93)	
	M	(SD; Min-Max)	M	(SD; Min-Max)
<b>Age</b>	<b>24.67</b>	<b>(9.56; 18-54)</b>	<b>65.45</b>	<b>(10.45; 55-96)</b>
<b>Education</b>	<b>14.65</b>	<b>(2.08; 9-25)</b>	<b>12.54</b>	<b>(3.11; 9-22)**</b>
<b>SPQ-B</b> (0-22)	<b>7.56</b>	<b>(4.48; 0-22)</b>	<b>6.78</b>	<b>(4.18; 0-16)</b>
<b>CogPer</b> (0-8)	<b>3.07</b>	<b>(2.00; 0-8)</b>	<b>2.88</b>	<b>(2.20; 0-8)</b>
<b>Interpersonal</b> (0-8)	<b>2.59</b>	<b>(2.23; 0-8)</b>	<b>2.96</b>	<b>(2.08; 0-8)</b>
<b>Disorganised</b> (0-6)	<b>1.90</b>	<b>(1.80; 0-6)</b>	<b>1.03</b>	<b>(1.33; 0-6)**</b>

\*\*Difference is significant between the Young and Older group at the .01 level (2-tailed)

\* Difference is significant between the Young and Older group at the .05 level (2-tailed)

In a multivariate analysis of variance in the general linear model, SPQ total and factor scores were entered into a model as dependent variables and sex and age group were modelled as factors. Multivariate between group effects were significant for sex ( $F[4,693] = 3.95$ ;  $p = 0.004$ ;  $\eta^2 = 0.02$ ) and age ( $F[4,693] = 8.73$ ;  $p = 0.001$ ;  $\eta^2 = 0.05$ ) but there was no significant interaction between sex and age.

Subsequently, independent t-tests were computed to assess the main effect of age group, significant differences between the younger and older group were found for the Disorganised factor  $t(147.97) = 5.55$ ,  $p < 0.001$ . In terms of demographic variables, number of years of education  $t(105.06) = 6.32$ ,  $p < 0.001$  were also significantly different between the two groups. No other differences were found to be significant between the younger and older groups.

Further independent t- tests (all 2 tailed) revealed that the main effect of sex in the model was likely to be due to differences between the means for the males and females in the younger group between the Cognitive Perceptual  $t(605) = 2.06$ ,  $p < 0.05$ , Interpersonal  $t(415.95) = 2.62$ ,  $p < 0.01$  and Disorganised factors  $t(605) = 3.92$ ,  $p < 0.001$ . In terms of demographic variables differences between males and females in this group were significant for age  $t(491.03) = 2.65$ ,  $p < 0.01$ , and education  $t(352.36) = 2.51$ ,  $p < 0.01$ . No other differences between males and females were statistically significant in the younger group. The lack of an age x sex interaction can be interpreted in light of the fact that for the older group, none of the differences between the means for the males and females reached statistical significance.

Correlations between SPQ-B total, sub factor scores and demographic variables within the younger group can be found in Table 4.4. Age was significantly positively correlated with education  $r = 0.1$ ,  $p < 0.05$  and significantly inversely correlated with sex  $r = - 0.11$ ,  $p < 0.01$ , with the SPQ-B  $r = - 0.13$ ,  $p < 0.01$  and with the Cognitive Perceptual  $r = - 0.19$ ,  $p < 0.01$  and Disorganised factors  $r = - 0.19$ ,  $p < 0.01$ . Sex was inversely correlated with education  $r = - 0.11$ ,  $p < 0.01$  and with the Interpersonal  $r = - 0.11$ ,  $p < 0.01$  and Disorganised  $r = - 0.16$ ,  $p < 0.01$  sub factors and positively correlated with the Cognitive Perceptual sub factor  $r = 0.08$ ,  $p < 0.01$ . Finally, as expected, the SPQ-B was strongly positively correlated with the Cognitive Perceptual  $r = 0.7$ ,  $p < 0.01$ , Interpersonal  $r = 0.78$ ,  $p < 0.001$  and Disorganised factors  $r = 0.76$ ,  $p < 0.001$ . The three factors were also positively intercorrelated, Cognitive Perceptual with Interpersonal  $r = 0.26$ ,  $p < 0.01$ , and Disorganised  $r = 0.33$ ,  $p < 0.01$ , and Interpersonal with Disorganised  $r = 0.44$ ,  $p < 0.01$ .

Table 4.4. Correlations between SPQ-B, sub factors and demographic variables for the younger group.

	Age	Sex	Education	SPQ-B	Cognitive Perceptual	Interpersonal	Disorganised
Age		-.11**	.10*	-.13**	-.19**	.06	-.19**
Sex	-.11**		-.11**	-.08	.08*	-.11**	-.16**
Education	.10*	-.11**		.03	-.50	.07	.05
SPQ-B	-.13**	-.08	.03		.70**	.78**	.76**
Cognitive Perceptual	-.19**	.08*	-.05	.70**		.26**	.33**
Interpersonal	.06	-.11**	.07	.78**	.26**		.44**
Disorganised	-.19**	-.16**	.05	.76**	.33**	.44**	

\*\*Correlation is significant at the .01 level (2-tailed)

\* Correlation is significant at the .05 level (2-tailed)

Age and education were then partialled out to see if correlations between sex and the SPQ-B and its factors were still significant. Except for the association between Cognitive Perceptual and sex, all the correlations reported above remained significant, in the same direction and Pearson's  $r$  did not rise or fall by more than 0.02. However when age and education were controlled for, the association between Cognitive perceptual and sex became non significant  $r = 0.06$ .

Correlations between SPQ-B and its factors with demographic variables for the older group can be found in Table 4.5. Age was inversely correlated with education  $r = -0.4$ ,  $p < 0.01$ . Again as expected, the SPQ-B was strongly positively correlated with the Cognitive Perceptual  $r = 0.80$ ,  $p < 0.001$ , Interpersonal  $r = 0.76$ ,  $p < 0.001$  and Disorganised factors  $r = 0.67$ ,  $p < 0.001$ . The three factors were also positively intercorrelated, Cognitive Perceptual with Interpersonal  $r = 0.34$ ,  $p < 0.01$ , and Disorganised  $r = 0.39$ ,  $p < 0.01$ , and Interpersonal with Disorganised  $r = 0.32$ ,  $p < 0.01$ .



Table 4.5. Correlations between SPQ-B, sub factors and demographic variables for the older group.

	Age	Sex	Education	SPQ-B	Cognitive Perceptual	Interpersonal	Disorganised
Age		.10	-.40**	-.04	-.01	-.05	.02
Sex	.10		-.08	.18	.19	.17	-.03
Education	-.40**	-.08		.08	.11	.03	.06
SPQ-B	.04	.18	.08		.80**	.76**	.67**
Cognitive Perceptual	-.01	.19	-.11	.80**		.36**	.39**
Interpersonal	.05	-.16	.03	.76**	.34**		.32**
Disorganised	.02	-.03	.06	.67**	.39**	.32**	

\*\* Correlation is significant at the .01 level (2-tailed)

\* Correlation is significant at the .05 level (2-tailed)

The distributions of scores on the Cognitive Perceptual factor of the SPQ-B for the younger and older groups can be found in Figures 4.1 and 4.2.

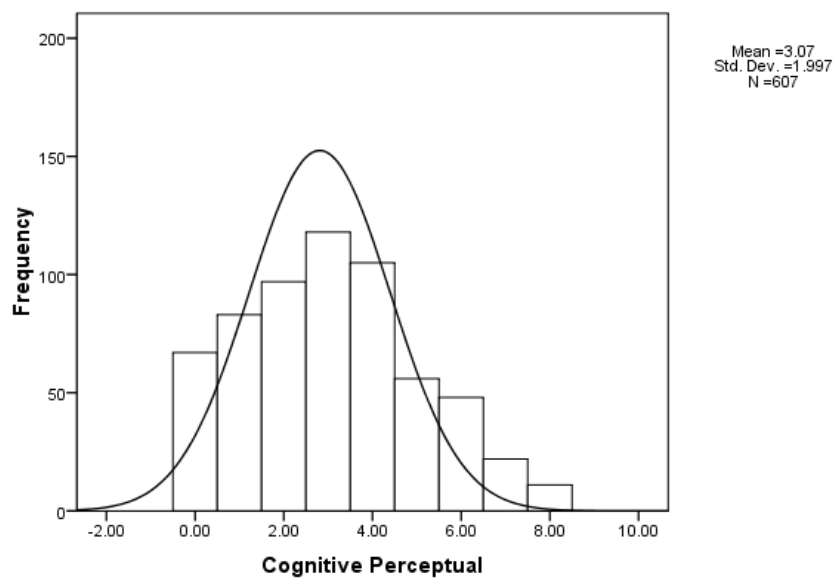


Figure 4.1. Distribution of scores for the Young group on the SPQ-B Cognitive Perceptual factor.

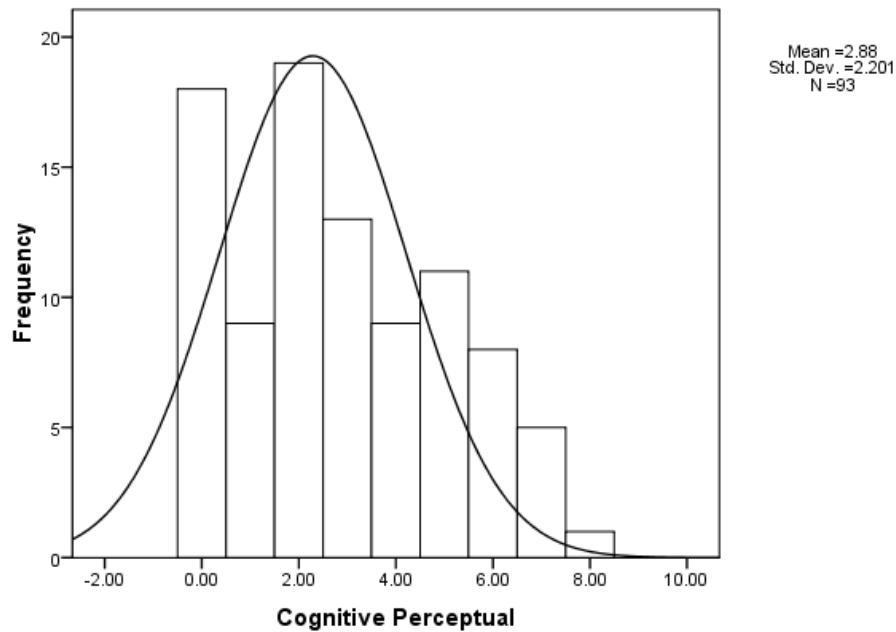


Figure 4.2. Distribution of scores for the Older group on the SPQ-B Cognitive Perceptual factor.

For both the older and younger groups the 5% high low cut-off scores on the Cognitive Perceptual sub factor were 7-8 and 0 respectively.

#### **4.2.6 CONCLUSION**

When age and sex were modelled as factors and the SPQ-B and sub factors as dependent variables, multivariate analysis of variance revealed main effects between the young and older age groups for sex and age. Further analyses revealed that the main effect of age group could be attributed to differences in scores on the Disorganised sub factor of the SPQ- B where the younger group scored higher on this factor (M 1.9, SD 1.8) than the older group (M 1.03, SD 1.33). The significant difference between the young and older means for the Disorganised factor is consistent with the literature that schizotypal traits are often higher in younger individuals (Raine, 1991).

As no differences were found to be significant between males and females in the older group, the main effect of sex appears to be due to differences between male and female SPQ-B and sub factor scores in the young group. As predicted, in the younger group females ( $M 3.19 SD 1.98$ ) scored significantly higher than males ( $M 2.84 SD 2.84$ ) on the Cognitive Perceptual Factor and males ( $M 2.91 SD 2.4$ ) scored significantly higher than females ( $M 2.4 SD 2.1$ ) on the Interpersonal and Disorganised factors (males  $M 2.27 SD 1.85$ ; females  $M 1.69 SD 1.73$ ). These findings are consistent with the correlational analyses whereby higher sex (i.e. female) was associated with higher cognitive perceptual scores and lower sex (i.e. male) was associated with higher Interpersonal and Disorganised scores. This is consistent with previous studies where males have been found to score higher on negative symptom sub-scales (disorganisation, no close friends, constricted affect, eccentric-odd behaviour; Miller & Burns, 1995; Roth and Baribeau; 1997; Langdon and Coltheart, 1999), whilst females have been found to score higher on the positive sub-scales such as ideas of reference, odd beliefs/magical thinking, and social anxiety subscales (Raine, 1992; Langdon and Coltheart, 1999). Raine (1995) argues such sex differences are analogous to the sex differences reported in schizophrenic symptomatology. However, whilst our results are similar to previous findings of sex differences on schizotypal scales, when age and education were partialled out of the correlation analysis, the association between sex and the Cognitive Perceptual sub factor was no longer significant. Therefore, age and education may be accountable for the variance which contributes to the significant difference observed between males and females on this factor that was demonstrated by the t-test. Similarly, other studies have failed to replicate the finding that females score higher than males on the Cognitive perceptual factor (Miller & Burns, 1995). In fact, some studies have even found that males score

higher than females on this factor (Kremen et al., 1998). Raine (accessed 2007) suggests such discrepancies are likely to be due to the way in which (like the correlations reported here) the effect sizes for sex differences are quite small, and that sex differences in schizotypal symptomatology may merely be an exaggeration of small sex differences found in normal individuals.

In terms of demographic variables in the young and older group, there was a significant difference between years of education whereby the younger group had significantly more years of education ( $M$  14.65  $SD$  12.54) than the older group ( $M$  12.54,  $SD$  3.11). Differences in years of education are most probably a cohort artefact and are consistently reported in studies examining young and older participants. These differences can also be accounted for by the education bias incurred by the fact that the young group was largely comprised of people at university whereas the majority of the older group were sampled from local individuals who may not have necessarily had a university education. A significant difference in years of education was also found between males and females in the younger group where males had significantly higher years of education ( $M$  15.00,  $SD$  2.51) than the females ( $M$  14.83,  $SD$  1.77). This difference is most likely to be due to the significant difference in the ages of males and females in this group as the males were older ( $M$  26.02,  $SD$  10.24) and therefore more likely to have spent a longer time in education than the females ( $M$  23.83,  $SD$  9.05), this interpretation is also supported by the significant positive correlation between age and education, and the inverse correlation between age and sex, as males were coded as a 1 and females as a 2, this demonstrates that higher ages are associated with lower gender scores (ie. males) in the young group.

In line with Raine and Benishay's (1995) study, in both young and older groups the SPQ-B was highly significantly correlated with its Cognitive Perceptual, Interpersonal and Disorganised factors. .70, .78, .76 respectively for the younger group; .80, .76, .67 for the older group. Correlations between each factor for both groups also closely replicates previous findings and is consistent with our prediction that the older group would demonstrate similar relationships between schizotypal factors to those found in the younger group. This is also in line with prior evidence that, despite possible differences in specific total and factor scores, the three factor structure of schizotypy is invariant with age and is a suitable structure through which to characterise schizotypy in older adults (Badcock & Dragovic, 2006).

For the younger group, age was significantly inversely correlated with the SPQ-B and the cognitive-perceptual and disorganised factors. This reflects the way in which scores on these factors have been found to decrease with age in other studies (Raine, 1991; Chen et al., 1997; Fossati et al., 2003). However, in the older group, these associations failed to reach significance and, as discussed, the only SPQ-B factor that differed significantly between the young and older groups was the Disorganised factor. This may be due to moderating effects of developmental processes or it may reflect age related inhibitions which impacts on the reporting rather than the experience of disorganised experiences (Chen et al., 1997). The Disorganised factor includes items such as 'some people think I am a very bizarre person' and 'I am an odd, unusual person' that may be associated with a positive 'unique' self image in younger individuals but may invoke more negative connotations in older individuals which may lead to defensive responding (Yaralian et al., 2005).

In terms of distribution, the expression of Cognitive Perceptual traits closely resembles normality in the younger group, especially if the two highest scores were grouped, but it is half normally distributed in the older group. The skewed distribution in the older group may simply be a reflection of the smaller sample size, although it does resemble the half normal distribution reported by Van Os et al., (2009). However, for both age groups the high and low 5 % cut off scores were over 7 for the high scorers and 0 for the low scorers. The variance in individual differences in schizotypy demonstrated in this large healthy sample of individuals with mixed gender, age and background appears to be consistent with the dimensional spectrum of the fully dimensional account of schizotypy.

### ***4.3 EXPERIMENT 2 – NEUROPSYCHOLOGICAL PROFILE***

Several neuropsychological similarities have been demonstrated by individuals with schizophrenia, SPD and schizotypy (Dickey et al., 1999). Associations have also been found between individual differences in schizotypal traits and differences in cognitive functions that are qualitatively similar to, but quantitatively less pronounced, than those evidenced in schizophrenia (Peters et al., 1994; Park et al., 1995; Gray et al., 2002; Tsakanikos & Reed, 2005; Hoffer et al., 1999; Trestman et al., 1995; Voglmaier et al., 1997; Park & McTigue, 1997; Daneluzzo et al., 1998; Baruch et al., 1988).

From the implication that cognitive impairments and behavioural symptoms are inextricably connected in schizophrenia, research has demonstrated that the problems manifest in language, working memory and reasoning in schizophrenia may mediate the symptoms of thought disorder and delusions (Frith 1992, Goldman-Rakic 1994, Bell et al 2006). The rationale that cognitive deficits may

be associated with specific schizophrenic symptoms has been extended to individuals with high levels of schizotypy, where similar but less severe impairments have been related to behavioural expressions of schizotypal traits (Raine, 1991; Matheson & Langdon, 2008; Tsakinkos, 2004). However, there is conflicting evidence for a cognitive deficit hypothesis of schizotypy. Whilst some research corroborates the cognitive deficits hypothesis through findings such as higher educational attainment (Tobacyk, 1984; Messer & Griggs 1989) and more years of education (Musch & Ehrenberg 2002) predict fewer positive schizotypal traits, other research has failed to find supporting evidence for the hypothesis. Evidence to the contrary has varied from studies reporting no differences between high and low schizotypal individuals in reasoning tasks (Irwin, 1993) to those that actually report that higher intelligence (Jones, Russell & Nickel, 1977) academic achievements (Nettle, 2006), problem-solving abilities (Jackson, 1997) and levels of creativity (Claridge, 1993; Claridge 1998) are associated with high schizotypy and high positive schizotypy.

Such inconsistencies between findings have prompted debate concerning the tenability of a cognitive deficits hypothesis which predicts individuals with high schizotypal traits have lower cognitive capacity. In the current study, individuals whose scores on the Cognitive Perceptual sub factor of the SPQ-B fell in the high and low 5% cut offs and individuals whose scores fell within three intermediate groups from the large population that was collected for the previous experiment were recruited for further study. The focus of Experiment 2 is centred on description and assessment of cognitive profile as a function of positive schizotypy in relation to short term memory, verbal intelligence, executive function and non-verbal reasoning ability. The tests were chosen to characterise

key areas of cognitive functioning, they were not chosen to be especially relevant for schizotypy as tests that are hypothesised to reveal differences between individuals with high and low levels of positive schizotypy will be explored in the subsequent experimental chapters. As the experiments in this thesis progress, it is essential to know whether any possible differences that may emerge between individuals are related to the Cognitive Perceptual independent variable or to possible differences in a specific cognitive ability. The inclusion of these tests will therefore enable the identification of whether or not it is necessary to control or co-vary for potential differences in certain cognitive domains between these individuals in future studies.

#### ***4.3.1 METHOD***

#### ***4.3.2 PARTICIPANTS***

In total 75 individuals were selected for this study, they were recruited from the individuals who had participated in the previous study and whose scores fell in the high and low 5% cut offs of 7-8 and 0 and three groups of individuals with intermediate scores (1-2, 3-4, 5-6) on the Cognitive Perceptual factor of the SPQ-B. Of the 75 individuals who participated in this study 49 were female and 26 male, 69 were right and 6 were left handed, their ages ranged from 18 – 46 with a mean of 20.76 (*SD* 4.99) and their years of education ranged from 11 – 23 (one student had completed previous higher education courses) with a mean of 14.26 (*SD* 1.62).

Due to the fact that it was important to keep in contact with these individuals over a prolonged period of assessment, only first and second year psychology students were considered for inclusion. Each semester these students are required to



participate in a set quota of departmental psychology studies, this participation forms part of the credit allocated for one of their courses. Due to this requirement it was assumed that these students would be more agreeable to participate in a long research protocol than those who would receive no form of reward and that they would also be more easily contactable and readily available for further studies. It is also beneficial to use this student group as it is comprised of university students of similar ages and educational backgrounds which should help to keep the sample as homogenous as possible in all respects apart from SPQ-B Cognitive Perceptual scores. The gender ratio in the current study reflects the gender distribution of the psychology department as more females are registered for this degree than males. Furthermore, whilst the gender ratio was not exactly balanced for the whole group, it was well balanced between the groups.

### ***4.3.3 GENERAL HEALTH QUESTIONNAIRE***

Prior to participation, and after giving their informed consent, all participants were asked to complete the same questionnaire described in section 4.2.3. The exclusion criteria were consistent with that which was outlined in the previous experiment.

### ***4.3.4 THE SCHIZOTYPAL PERSONALITY QUESTIONNAIRE***

The Schizotypal personality questionnaire (SPQ; Raine, 1991) is an extensive 74 item instrument which is based on the DSM criteria for schizotypal personality disorder. The SPQ can be used with both adults and adolescents, and with normal and pathological populations.

The SPQ yields a total score, together with scores for each of the three main sub-factors; Cognitive Perceptual, Interpersonal, and Disorganized (the internal reliabilities of the total scale ranges from .90 to .91 and sub-scales range from .71 to .78, and test-retest reliability of .82 has been reported; Raine, 1991). Each "Yes" response on the SPQ scores one point. Total scores therefore range from 0 to 74.

#### ***4.3.5 NEUROPSYCHOLOGICAL TESTS***

Based on evidence of the core cognitive areas that could influence performance in further experiments, the following neuropsychological tests were used to ascertain whether any differences found between high positive schizotypy (HPS) and low positive schizotypy (LPS) participants were attributable to differences in intelligence, executive function or reasoning ability. Word span, short and long were included to measure short term memory, phonemic fluency was the covariate measure of executive function, the National Adult Reading Test (NART; Nelson, 1982) provided a measure of verbal IQ and Ravens progressive matrices (Raven et al., 2003) was included as a means of assessing non-verbal reasoning ability.

The administration of each of these tests is relatively simple. For the short and long word span tasks, the examiner read strings of words to the participant (starting with 3 and increasing by one word per trial until the participant fails two consecutive trials) participants were asked to repeat the words in the same order, the score is the total number of words repeated correctly. For the phonemic fluency task, participants were asked to verbally generate as many words as possible beginning with 3 separate letters; p, f and l. Participants were given one

minute for each letter. In the NART participants were presented with a list of irregular and infrequent words and asked to read them aloud, due to their irregular spelling there are no clues for pronunciation, therefore participants will only be able to read the word correctly if they have had prior experience of the word. Finally to assess non verbal reasoning, the Ravens Progressive Matrices was administered, in this task participants are asked to identify which item completes a specific pattern.

### 4.3.6 RESULTS

The demographic information (age, sex and education) for each group and the total group can be found in table 4.6.

Table 4.6. Demographic variables (mean and standard deviation) for each group of SPQ-B Cognitive Perceptual scorers.

Cog Per Score	Low Group						High Group					
	0		1-2		3-4		5-6		7-8		Total	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
Age	20.33	4.73	23.20	6.45	21.40	7.42	18.87	0.83	19.67	1.88	20.76	4.99
Education	14.20	1.32	14.27	1.75	15.20	2.37	13.80	0.78	13.87	1.19	14.26	1.62
Sex	M	F	M	F	M	F	M	F	M	F	M	F
n	5	10	7	7	4	11	5	10	4	11	26	49
%	66	44	50	50	73	27	66	44	73	27	65	35

Abbreviations: Cog Per = Cognitive Perceptual sub factor of the SPQ-B, M = Mean, SD = Standard Deviation. Total number =75, number in each group = 15.

One way analyses of variance (ANOVA) revealed that there were no significant differences between the 5 different Cognitive Perceptual score groups in terms of age or education.

The neuropsychological scores for each group and the total group can be found in table 4.7.

Table 4.7. Neuropsychological test scores for each group of SPQ-B Cognitive Perceptual scorers.

Cog Per Score	Low Group						High Group				Total	
	0		1-2		3-4		5-6		7-8		Total	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
Word Short	4.33	1.04	4.60	0.63	4.60	0.74	4.80	0.68	4.93	0.96	4.65	0.83
Word Long	3.40	0.74	3.53	0.64	3.53	0.64	3.47	0.83	3.40	0.70	3.47	0.70
NART	25.67	5.65	28.73	7.27	28.00	5.13	25.53	3.83	26.67	5.50	26.92	5.49
Ravens PM	36.60	5.88	38.80	5.82	38.00	5.25	40.67	2.66	39.67	3.60	38.75	4.89
Phonemic Fluency	42.00	8.34	42.73	14.15	36.46	10.63	42.07	9.46	40.13	12.36	40.68	11.12

Abbreviations: Cog Per = Cognitive Perceptual sub factor of the SPQ-B, NART = National Adult Reading Test, Ravens PM = Ravens Progressive Matrices, M = Mean, SD = Standard Deviation. Total number =75, number in each group = 15.

One way ANOVA revealed that there were no differences between the groups for Word Short ( $F[4,70] = 1.14, p .35$ ) or for Word long ( $F[4,70] = 0.13, p .97$ ), for the NART ( $F[4,70] = 0.99, p .42$ ) for Ravens PM ( $F[4,70] = 1.57, p .19$ ) or for phonemic fluency ( $F[4,70] = .778, p .543$ ).

The Pearson correlations between SPQ-B Cognitive Perceptual, the full SPQ and its factors, demographic variables and neuropsychological tests can be found in Table 4.8. Age was significantly positively correlated with education  $r = 0.56, p < 0.01$ , sex was significantly positively correlated with the NART  $r = 0.24, p < 0.05$ ,

and education was significantly inversely correlated with the Disorganised factor of the full SPQ  $r = -0.24$ ,  $p < 0.05$  and, surprisingly with Phonemic Fluency  $r = -0.25$ ,  $p < 0.05$ .

Scores on the SPQ-B Cognitive Perceptual measure were highly significantly positively correlated with the full SPQ  $r = 0.79$ ,  $p < 0.01$  and the full Cognitive Perceptual factor  $r = 0.85$ ,  $p < 0.01$ , and were also significantly positively associated with the Interpersonal  $r = 0.62$ ,  $p < 0.01$  and Disorganised  $r = 0.60$ ,  $p < 0.01$  factors and with Word Short  $r = 0.26$ ,  $p < 0.05$ . The full SPQ Cognitive Perceptual factor demonstrated the same (but slightly higher) associations as the SPQ-B cog per with the full SPQ, Interpersonal and Disorganised factors and Word Short and was additionally positively associated with performance in the Ravens PM. The full SPQ score was also significantly positively associated with Word Short  $r = 0.25$ ,  $p < 0.05$ .

Significant positive relationships between the SPQ and the Interpersonal  $r = 0.89$ ,  $p < 0.01$ , and Disorganised factors  $r = 0.81$ ,  $p < 0.01$  and between these two factors  $r = 0.59$ ,  $p < 0.01$  were also found. Interpersonal and Disorganised scores were not associated with any of the neuropsychological tests.

Within the neuropsychological tests, Word Short was positively significantly associated with Word Long  $r = 0.23$ ,  $p < 0.01$ , the NART  $r = 0.27$ ,  $p < 0.01$  and with Ravens PM  $r = 0.24$ ,  $p < 0.05$ , the NART was also significantly positively correlated with phonemic fluency  $r = 0.24$ ,  $p < 0.01$ .

Table 4.8. Correlations for all SPQ, demographic and neuropsychological test variables.

	Age	Sex	Education	SPQ-B CogPer	SPQ	Cognitive Perceptual	Interpersonal	Disorganised	Word Short	Word Long	Phonemic Fluency	NART	Ravens
Age				-.20	-.13	-.18	-.05	-.10	.00	.03	.03	.20	-.07
Sex	-.44		.10	.12	.05	.16	.03	-.10	-.03	-.08	.08	.24*	.15
Education	.56**	.10		-.12	-.15	-.10	-.10	-.24*	-.10	-.16	-.25*	.14	-.13
SPQ-B CogPer	-.20	.12	-.12		.79**	.85**	.62**	.60**	.26*	-.03	-.05	-.06	.23
SPQ	-.13	.05	-.15	.79**		.91**	.89**	.81**	.25*	.08	-.09	-.01	.20
Cognitive Perceptual	-.18	.16	-.10	.85**	.91**		.72**	.64**	.27*	.03	-.04	-.01	.27*
Interpersonal	-.05	.03	-.10	.62**	.89**	.72**		.59**	.14	.01	-.20	-.05	.06
Disorganised	-.10	-.10	-.24*	.60**	.81**	.64**	.59**		.21	.12	.01	-.03	.17
Word Short	.00	-.03	-.10	.26*	.25*	.27*	.14	.21		.23*	.22	.27*	.24*
Word Long	.03	-.08	-.16	-.03	.08	.03	.01	.12	.23*		.15	.23	.19
Phonemic Fluency	.03	.08	-.25*	-.05	-.09	-.04	-.20	.01	.22	.15		.24*	.12
NART	.20	.24*	.14	-.06	-.01	-.01	-.05	-.03	.27*	.22	.24*		.22
Ravens	-.07	.15	-.13	.23	.20	.27*	.06	.17	.24*	.19	.12	.22	

\*\* Correlation is significant at the .01 level (2-tailed)

\* Correlation is significant at the .05 level (2-tailed)

### 4.3.7 CONCLUSIONS

The current findings are consistent with the position that high positive schizotypy is not necessarily associated with reduced cognitive performance. Separate One way ANOVA's computed to compare the performance for each group of scorers on the SPQ-B Cognitive Perceptual factor with each neuropsychological test revealed that there were no significant differences between the test performances of any of the groups. These findings may also be related to the homogeneity of the participants, as illustrated by the fact that there were no significant differences between any of the SPQ-B Cognitive Perceptual scorers in terms of age or education.

In the current study, the only variable that was correlated with sex was the NART, the positive direction suggests that females scored higher than males on this task.

It was once widely accepted that females outperformed males on measures of

verbal IQ (Matarazzo et al., 1986), however other studies have suggested these differences are either extinct or very small (Matarazzo et al., 1986; Hyde 1988). The relatively small correlation of  $r = 0.24$  reported here may therefore reflect the slight gender bias and over representation of females in the current sample. Unlike the analysis in the previous study, in the current sample education was inversely correlated with the Disorganised factor of the full SPQ, this could be due to greater sensitivity due to the larger sampling variance of the items in the full version of this factor. In addition, as many of the items in this factor are concerned with verbal ability in expression, it follows that it would be negatively associated with education. The most surprising association was the inverse relationship found between education and phonemic fluency, whilst several studies have reported positive associations between phonemic fluency and education (Tombaugh, Kozak & Rees, 1999; Ratcliff, Ganguli, Chandra et al., 1998), in another study education was found to contribute very little to the prediction of phonemic fluency (Kave, 2005) however, as no evidence has been found that would support an inverse relationship between these variables and because no post hoc intuitions can illuminate this finding any further it must, for now, be considered spurious.

The SPQ-B Cognitive Perceptual factor was highly positively associated with the full SPQ and the full SPQ Cognitive Perceptual factor, this is in line with the intercorrelations between the SPQ and SPQ-B reported by Raine & Benishay (1995). Most importantly, these associations confirm that the Cognitive Perceptual factor of the SPQ-B was a suitable measure through which to identify and group individuals with various positive schizotypy scores for further study. In addition, both the SPQ-B and SPQ Cognitive Perceptual factors demonstrated

very similar correlations with the Interpersonal and Disorganised factors of the SPQ, they were also both positively correlated with Word Short, which is the simpler version of the short term memory task and the full SPQ Cognitive Perceptual factor was independently positively associated with performance in Ravens PM. These associations are consistent with the fully dimensional account of schizotypy (McCreery & Claridge, 2005) and they provide evidence to support the contention that individuals with high positive schizotypy are not necessarily impaired. In fact, whilst there were no significant differences between the groups, the correlation demonstrates simple short term memory and non verbal reasoning increase as a function of higher positive schizotypy scores. The association between the Cognitive Perceptual factor and Ravens PM is in line with findings that reasoning (Jackson, 1997) and non verbal reasoning (Volgalimer, Seidman, Niznikiewicz et al., 2000) may sometimes be elevated in high positive schizotypal individuals. However, it is inconsistent with a large body of literature that has associated positive schizotypy with reasoning impairments. This may be due to the way in which the reasoning tasks employed in these studies have been chosen to be related to specific schizotypal delusion mechanisms (Lawrence & Peters, 2004; Colbert & Peters, 2002; Garety et al., 1991) whereas in the current study, Ravens was chosen as neutral, non-schizotypy-specific reasoning measure. The fact that the SPQ-B Cognitive Perceptual factor was not related to Ravens PM whilst the full SPQ Cognitive Perceptual factor was may again be an artefact of the improved sensitivity which stems from the enhanced sampling of relevant items in the longer version of the full SPQ factor.

The relationships demonstrated between the Interpersonal and Disorganised factors converge with the inter-correlations reported in the previous study and



with the associations reported in the standardisation literature (Raine, 1991). Neither of these factors was associated with any of the neuropsychological tests, which again attests to the health status of these individuals. Several positive associations were found to be significant between the neuropsychological tests, the association between Phonemic fluency and the NART makes sense in light of the verbal nature of both tests, obviously the simpler and more difficult versions of the short term memory tasks were positively associated with one another and the simpler short term memory task was also correlated with performance on the NART and Ravens. Whilst these tests tap different cognitive domains, short term memory has been found to predict performance in other areas of cognition (Awh, Vogel & Barton, 2007).

The analyses discussed here suggest that as there are no significant differences between groups with various scores on the positive schizotypy measure of interest any subsequent associations between high positive schizotypy and dependent variables in future studies with this group of participants are not due to differences in verbal IQ, non verbal reasoning ability, short term memory or executive function neither are they consequent of disparities in years of education or age.

#### ***4.4 EXPERIMENT 3 – PERSONALITY PROFILE***

As briefly discussed in Chapter 2, considerable variance has been found in genetic studies between results obtained with positive psychosis proneness measures such as the Chapman Scales and the positive factor of the SPQ. Contrary to predictions that non psychotic relatives of individuals with schizophrenia would demonstrated higher levels of psychometric schizotypy, when the psychosis proneness scales were administered to the healthy relatives of individuals with schizophrenia, these

non-psychotic relatives scored much lower on measures of positive schizotypy than control participants (Clementz et al., 1991; Katsanis et al., 1990; Claridge et al., 1983; Claridge & Beech, 1996). However, in similar studies which have used the SPQ, first degree relatives of schizophrenic individuals have been found to demonstrate higher positive schizotypal traits than those with no family history of schizophrenia (Kremen et al., 1998). Yarlilian et al. (2000) suggest the failure to find higher scores of positive schizotypal symptoms amongst biological relatives of schizophrenics in studies using psychosis proneness scales may be a function of instrumentation. They suggest the SPQ is more suited to the detection of positive schizotypal features than other psychosis proneness measures and that it appears to be a more sensitive instrument for detecting variation in genetic analyses. They argue this superiority could stem from enhanced sampling ability as the SPQ measures four features of the cognitive perceptual or positive sub factor. For instance whilst the perceptual aberration scale (PAS; Chapman et al., 1978) measures positive schizotypy, it does not assess suspiciousness or referential ideation.

Another reason for discrepant findings between psychosis proneness and SPQ measures could be due to psychological defensiveness. Psychological defensiveness describes the way in which individuals with a family history of schizophrenia could become sensitised to their own risk for psychosis and may defensively respond to psychosis prone measures in scales such as the PAS thus artificially lowering related scores. The SPQ appears less vulnerable to defensive responding, although the content of the items in the cognitive perceptual scale of the SPQ resembles items in psychosis proneness measures, the way in which the SPQ uses more simplistic wording to assess psychosis prone traits decreases the

need to be defensive (Yaralian et al., 2000). Reporting positive items on the SPQ may also endorse substantially more normal experiences than responses to similar items on psychosis proneness scales suggest (Yaralian et al., 2000). Another study found that defensive responses to schizotypy items depend on the research context. However, this is only evident for positive not negative items, participants in this study were asked to complete the SPQ in a psychiatric or creativity context, positive scores were found to be substantially lower in the psychiatry compared with the creativity group (Mohr & Leonards, 2005).

In the current study, no intimation that the experiment was centred on psychosis prone individuals was made as participants were told that the study was investigating personality and cognition. Consequently, there should be no context effects which could lead to defensive responding. Although there is no known family history that could sensitise these individuals, they were aware that they had been recruited based on their SPQ-B scores, however whilst they were not told that they were specifically recruited based on their positive scores, as positive items appear more pathological than negative or disorganised items (Mohr & Leonards, 2005) it is important to ensure the focus of the research has not created a threatening context that could lead to defensive responding. Due to the fact that individual psychosis prone measures have been found to encourage defensive responding (Yaralian et al., 2000) more so than the SPQ, the inclusion of the Magical Ideation questionnaire in this study will enable assessment of whether any element of the research process could be contextually influencing positive schizotypy scores. If this is the case the associations between positive schizotypy and Magical Ideation will be much lower than expected.

In order to further understand the processes that mediate positive schizotypy the participants in the current study will also be asked to complete the Tri-dimensional Personality Questionnaire (TPQ, Cloninger, 1987). The TPQ measures aetiologically distinct independently inherited facets of personality (Cloninger et al., 1998). Temperament refers to ‘biases in automatic responses to emotional stimuli’ (Cloninger et al., 1998, p.22) and the TPQ distinguishes between four temperaments; Novelty Seeking, Harm Avoidance, Reward Dependence and Persistence`. Emerging from theories of brain structure and function, the TPQ is designed to assess differences in learning within an individual rather than differences in behaviour between individuals (Gardini et al., 2009). Consequently associations between SPQ and TPQ factors could be interpreted through models of learning and neurobiological structure and function. Whilst several studies have explored the relationship between schizotypy and character (Gillespie et al., 2003; Bora & Veznedaroglu, 2007), fewer studies have concentrated on the relationship between schizotypy and temperament. However, based on the findings from these few studies, it is predicted that schizotypy will have a strong relationship with Harm Avoidance (Laidlaw et al., 2005; Kurs et al., 2005; Calvo de Padilla et al., 2006).

### ***4.4.1 METHOD***

The participants in the current experiment are the same as those who participated in the previous one. Please refer to sections 4.3.1, 4.3.2 and 4.3.3 for details of the participants, the general health questionnaire and the SPQ.

### ***4.4.2 MAGICAL IDEATION***

Magical ideation has been defined as representing beliefs in causal relationships that are invalid by conventional standards (Eckblad & Chapman, 1983). In the

current study, the 30 item magical ideation (MI) questionnaire (Eckblad & Chapman, 1983) was used as a more focused measure of positive schizotypy. This questionnaire has a true-false format and its development was based on Meehl's (1964) characterisation of magical ideation as a core symptom of psychosis proneness (Eckblad & Chapman, 1983).

#### ***4.4.3 TRI-DIMENSIONAL PERSONALITY QUESTIONNAIRE***

The Tri-dimensional personality questionnaire (TPQ; Cloninger, 1987) was used as a neurobiological personality measure. It is a 100 item true or false instrument. The TPQ assesses four dimensions of temperament: Novelty Seeking (NS), Reward Dependence (RD), Harm Avoidance (HA) and Persistence (PER) these dimensions were discussed in more detail in Chapter 1. NS and HA are comprised of four subscales, RD incorporates three as PER was once considered to be the fourth subscale of RD but is now analysed as an independent dimension. The total scores for each of these four dimensions of temperament were included in the analyses for this study.

#### ***4.4.4 RESULTS***

The demographic information (age, sex and education) for each group and the total group can be found in table 4.6 in the Results section 4.3.5 of the previous experiment.

The personality scores for each group of SPQ-B Cognitive Perceptual scorers and the total group can be found in table 4.9.

Table 4.9. Personality test scores (means and standard deviations) for each group of SPQ-B Cognitive Perceptual scorers.

Cog Per Score	Low Group						High Group					
	0		1-2		3-4		5-6		7-8		Total	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
<b>Magical Ideation</b>	1.13	2.10	3.20	2.80	5.07	3.65	8.07	5.43	9.80	3.97	5.45	4.85
TPQ NS	16.47	5.74	18.80	4.00	17.47	5.33	16.80	4.93	17.00	4.64	17.31	4.89
TPQ HA	13.53	6.21	12.67	6.41	16.86	8.08	18.20	5.70	21.00	8.00	16.45	7.43
TPQ RD	12.73	3.26	10.46	3.56	12.00	3.85	13.80	3.38	13.66	4.22	12.53	3.77
TPQ Per	7.33	1.80	7.20	14.15	6.53	3.07	7.13	2.39	6.47	3.02	6.93	2.67

The mean Magical Ideation (MI) scores for each positive schizotypy score group can be seen in Figure 4.3. A one-way ANOVA demonstrated significant differences between the means of the five groups of SPQ-B Cognitive Perceptual scorers for MI scores ( $F[4,70] = 13.04, p = 0.001$ ). As Levene's statistic was significant Tamhane post-hoc analyses were used to assess where these differences lie. Individuals in the highest 5 % cut off (scorers of 7-8) for positive schizotypy ( $M = 9.80, 95\% \text{ CI } [7.60, 11.99]$ ) endorse significantly higher MI beliefs than those in the lowest 5% cut off for positive schizotypy scores ( $M = 1.13, 95\% \text{ CI } [-0.08, 2.35]$ ), those in the next lowest PS group (who scored only 1-2) ( $M = 3.2, 95\% \text{ CI } [1.64, 4.76]$ ) and those in the middle group of PS scorers (who scored 3-4) ( $M = 5.07, 95\% \text{ CI } [3.04, 7.09]$ ). The means for the middle group ( $M = 5.07, 95\% \text{ CI } [3.04, 7.09]$ ) also differed significantly from those in the lowest group of PS scorers ( $M = 1.13, 95\% \text{ CI } [-0.08, 2.35]$ ). Differences between the means for the lowest group of PS scorers ( $M = 1.13, 95\% \text{ CI } [-0.08, 2.35]$ ) and

the second highest group of PS scorers (5-6) (M = 8.07, 95% CI [5.06, 11.07])

were also significant.

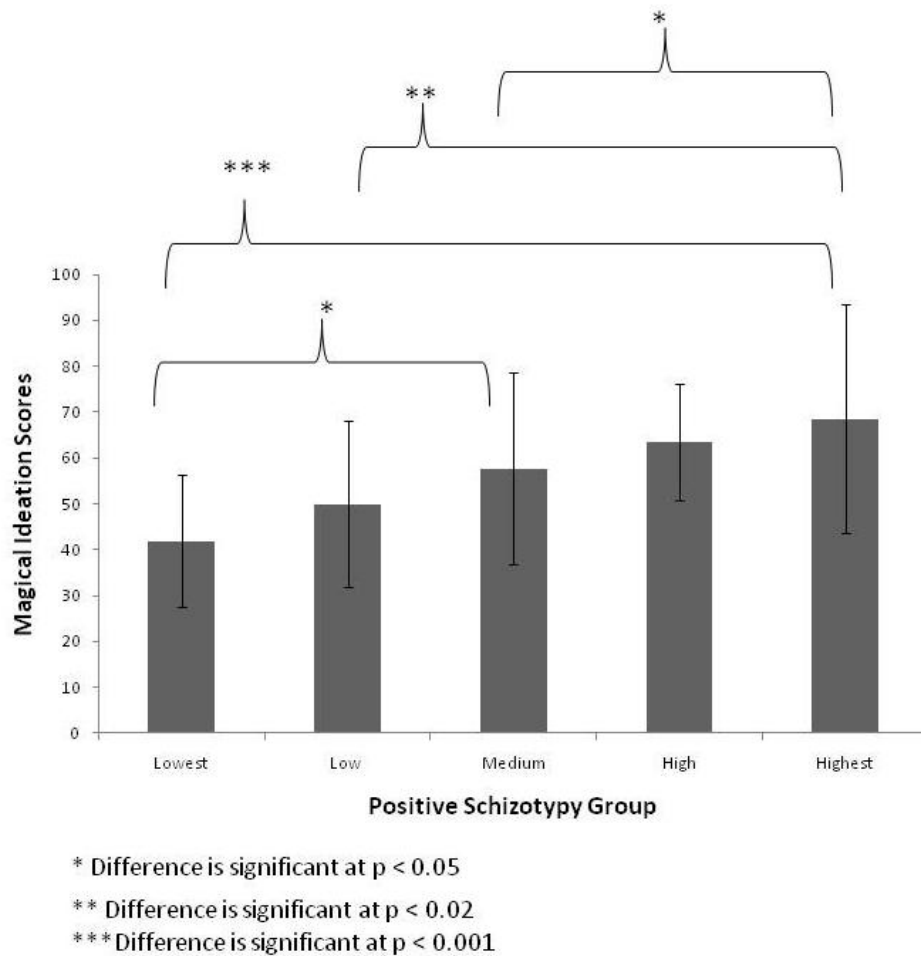


Figure 4.3. Mean Magical Ideation scores for each PS group.

The mean Harm Avoidance (HA) scores for each positive schizotypy score group can be seen in Figure 4.4. A one-way ANOVA demonstrated significant differences between the means of the five groups of SPQ-B Cognitive Perceptual scorers for MI scores ( $F[4,70] = 3.63, p = 0.01$ ). Scheffe post-hoc analysis comparisons of the five groups indicate that the mean Harm Avoidance scores were significantly different between individuals in the highest 5 % cut off (scorers of 7-8) for positive schizotypy (M = 21, 95% CI [16.57, 24.43]) and those in the

second lowest PS group who scored 1-2 on the PS measure (M = 12.67, 95% CI [9.12, 16.22]).

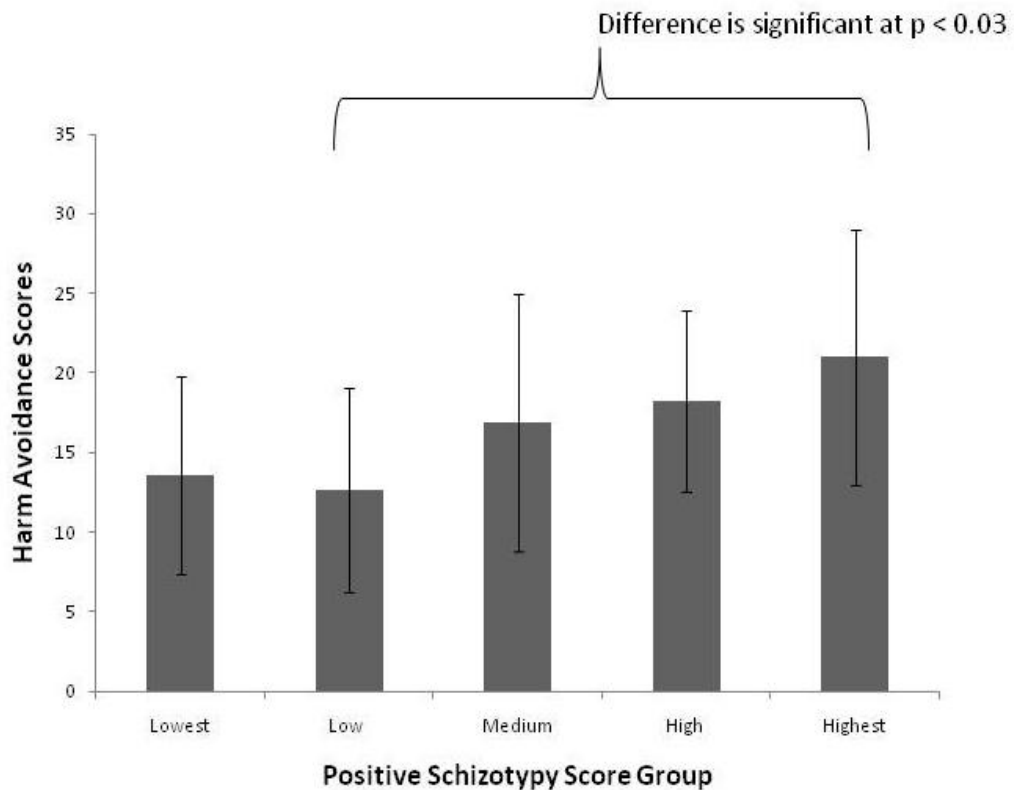


Figure 4.4. Mean Harm Avoidance scores for each PS group.

Further one-way ANOVAs revealed that there were no significant differences between the means of the 5 groups of SPQ-B Cognitive Perceptual scorers for Novelty Seeking, Reward Dependence or Persistence.

Pearson correlations between SPQ-B Cognitive factors, demographic variables and personality tests can be found in Table 4.10. Many of the correlations shown in this table have been described in the previous experiment. Sex was significantly positively correlated with the Harm Avoidance  $r = 0.28$ ,  $p < 0.05$ , Reward Dependence  $r = 0.30$ ,  $p < 0.01$  and Persistence  $r = 0.26$ ,  $p < 0.05$ . Magical



Ideation was significantly positively correlated with all schizotypy measures, at a moderate level for Interpersonal  $r = 0.42$ ,  $p < 0.01$  and Disorganised  $r = 0.54$ ,  $p < 0.01$  and a high level for the SPQ  $r = 0.68$ ,  $p < 0.01$ , SPQ-B Cognitive Perceptual  $r = 0.67$ ,  $p < 0.01$  and most highly for the full Cognitive Perceptual factor  $r = 0.80$ ,  $p < 0.01$ . Magical Ideation was also positively associated with Harm avoidance  $r = 0.35$ ,  $p < 0.01$ . The TPQ measure of Harm Avoidance was also significantly positively correlated with all SPQ factors, with the SPQ-B Cognitive Perceptual factor  $r = 0.38$ ,  $p < 0.01$ , the SPQ  $r = 0.55$ ,  $p < 0.01$ , the Cognitive Perceptual  $r = 0.49$ ,  $p < 0.01$ , the Interpersonal  $r = 0.66$ ,  $p < 0.01$  and Disorganised  $r = 0.23$ ,  $p < 0.05$  factors. Reward dependence was positively associated with the full SPQ Cognitive Perceptual factor  $r = 0.25$ ,  $p < 0.01$ . Persistence was inversely associated with the SPQ  $r = -0.39$ ,  $p < 0.01$ , the Interpersonal  $r = -0.51$ ,  $p < 0.01$  and the Disorganised  $r = -0.41$ ,  $p < 0.01$ . The TPQ measure of Novelty Seeking was inversely associated with Harm Avoidance  $r = -0.44$ ,  $p < 0.01$  and Reward Dependence  $r = -0.35$ ,  $p < 0.01$ . Persistence was positively associated with Reward Dependence  $r = 0.36$ ,  $p < 0.01$ .

Table 4.10. Correlations for all SPQ, demographic and personality test variables.

	Age	Sex	SPQ-B		Cognitive				MI	TPQ_NS	TPQ_HA	TPQ_RD	TPQ_PER
			Education	CogPer	SPQ	Perceptual	Interpersonal	Disorganised					
Age		-.04	.56**	-.20	-.13	-.18	-.05	-.10	-.20	-.15	.04	.11	-.06
Sex	-.04		.10	.12	.05	.16	.03	-.10	.03	-.07	.28*	.30**	.26*
Education	.56**	.10		-.12	-.15	-.10	-.10	-.24*	-.17	-.10	.05	.09	.09
SPQ-B CogPer	-.20	.12	-.12		.79**	.85**	.62**	.60**	.67**	-.04	.38**	.21	-.11
SPQ	-.13	.05	-.15	.79**		.91**	.89**	.81**	.68**	-.12	.55**	.12	-.39**
Cognitive Perceptual	-.18	.16	-.10	.85**	.91**		.72**	.64**	.80**	-.12	.49**	.25*	-.15
Interpersonal	-.05	.03	-.10	.62**	.89**	.72**		.59**	.42**	-.21	.66**	.03	-.51**
Disorganised	-.10	-.10	-.24*	.60**	.81**	.64**	.59**		.54**	.09	.23*	.01	-.41**
MI	-.20	.03	-.17	.67**	.68**	.80**	.42**	.54**		-.13	.35**	.18	.01
TPQ_NS	-.15	-.07	-.10	-.04	-.11	-.12	-.21	.09	-.13		-.44**	-.35**	-.05
TPQ_HA	.04	.28*	.05	.38**	.55**	.49**	.66**	.23*	.35**	-.44**		.20	-.044
TPQ_RD	.11	.30**	.09	.21	.12	.25*	.03	.01	.13	-.35**	.20		.36**
TPQ_PER	-.06	.26*	.09	-.11	-.39**	-.15	-.51**	-.41**	.01	-.05	-.04	.36**	

\*\* Correlation is significant at the .01 level (2-tailed)

\* Correlation is significant at the .05 level (2-tailed)

#### 4.4.5 CONCLUSION

Analysis of the mean magical ideation scores for each group of SPQ-B Cognitive Perceptual scorers suggest that MI scores increase as positive schizotypy increases. This is also supported by the high correlations between MI, both short and long Cognitive Perceptual positive Schizotypy measures and the full SPQ. As MI represents a component of positive schizotypy the high correlation is to be expected. However, based on previous findings that the items in psychosis proneness measures such as MI are more clearly related to pathological ideation than items in the SPQ (Yaralian et al., 2000) one might expect defensive responding in some research contexts. The strong association between MI and positive schizotypy suggests that the individuals in the current study either do not notice or feel threatened by the psychosis proneness research context.

Three of the TPQ dimensions were positively associated with sex, whereby higher scores in Harm Avoidance, Reward Dependence and Persistence were associated

with higher gender scores (i.e. female). TPQ temperaments are known to be gender sensitive (Zohar, Dina, Rosolio et al., 2001; Cloninger, Pryzbeck & Svrakic, 1991) and the positive correlation between female gender HA and RD is consistent with previous studies of the TPQ (Le Bon, Staner, Tecco et al., 1998; Cloninger, Pryzbeck & Svrakic, 1991), the association with female gender and persistence can be interpreted in light of the fact that it was once considered a component of RD, which as stated above has frequently been positively correlated with the female sex. This position is further supported by the way in which RD and PER are significantly positively correlated with one another. The inverse associations between NS and HA and NS and RD, have also been previously described in the standardisation literature (Cloninger, Pryzbeck & Svrakic, 1991).

RD was also found to be significantly positively correlated with the Cognitive Perceptual factor of the full SPQ, and HA was significantly correlated with all schizotypal factors including MI. However contrary to our findings of a positive correlation between high positive schizotypy and higher levels of HA and RD, in a previous study high Harm Avoidance and low Reward Dependence was associated with schizophrenic individuals and their first degree relatives (Laidlaw et al., 2005). The association between higher RD and positive schizotypy in the current study may be interpreted as further evidence for the fully dimensional account of schizotypy where schizotypal traits in the normal population are distinct from the more pathological aspects of schizotypy on the schizophrenia spectrum. It may also suggest that reward dependence could be protective for individuals at risk for schizophrenia from developing psychosis in the same way that other studies have suggested self-directedness appears to be protective against

decompensation (Gillespie et al., 2003; Bora & Veznedaroglu, 2007). Further studies are necessary to explore whether RD is protective against psychosis.

Whilst RD and HA were both correlated with positive schizotypy, HA was correlated with all schizotypal factors including MI. HA was also the only dimension of temperament in which the means across each group of SPQ-B Cognitive Perceptual scorers differed significantly. This difference was found between those in the highest 5% cut off and the second lowest group of scorers, the difference between the highest and lowest 5% cut offs was also approaching significance. Harm avoidance levels in non-psychotic siblings of individuals with schizophrenia have been found to be intermediate between their psychotic siblings and non psychotic controls. Laidlaw et al., (2005) suggest that as these findings are consistent with previous studies of the relationship between persons with schizophrenia and their first-degree relatives (Kurs et al., 2005; Calvo de Padilla et al., 2006) this may provide evidence that HA could be an endophenotype for schizophrenia. This is especially interesting in light of its association with positive schizotypy, the endophenotype we propose is associated with neurological psychosis.

The association between the cognitive perceptual factor and harm avoidance may also be explained by previous studies which have related positive schizotypy to heightened emotional arousal, especially to information that could be perceived as threatening (Fisher et al., 2004). This correlation may also be interpreted through the dominant right hemisphere theory of schizotypy, which suggests a right hemispheric processing bias may subserve schizotypal individuals' creative fluency, paranormal beliefs and delusion proneness, as the right hemisphere is

responsible for the processing of emotional information. Without a dominant left hemisphere to regulate emotional responses interpreted by the right hemisphere, emotional information could be laden with aberrant salience.

Recently harm avoidance has been negatively correlated with grey matter in bilateral orbito frontal areas (Gardini et al., 2009); this area has been consistently reported as central to emotional responses. The bilateral frontal and right parietal negative association found by Gardini et al, also mirrors a network that has frequently been found to be disrupted in individuals with delusions (Brien et al., 2008, Shanks & Venneri, 2002). Apart from causing inhibition and avoidance of perceptually rich stimuli, which may also explain the association between HA and the Interpersonal factor. Gardini et al's. finding that lower grey matter in posterior occipital structures is associated with harm avoidance may represent an area that is especially vulnerable to abnormal brain ageing processes such as neurodegeneration, so this structural vulnerability that is associated with HA, when combined with a high positive schizotypal personality could potentially subserve perceptual aberrations and misidentifications.

## CHAPTER 5

# SCHIZOTYPY AND SEMANTIC SPREADING

### *5.1 INTRODUCTION*

An abnormal spreading activation in semantic networks has been observed in schizophrenia. This facilitation has been related to psychosis and especially delusions. In the current study, whether this extends to nonclinical individuals with high scores on the cognitive perceptual schizotypy sub scale was evaluated with reference to semantic reasoning and fluency. Moreover, whether this extension of semantic spreading through the schizophrenia spectrum may be manifest as a positive feature in nonclinical individuals who possess high schizotypal traits was also assessed.

The term ‘delusion’ refers to a range of erroneous beliefs, incorrect inferences and interpretations about external reality that are firmly sustained despite what constitutes incontrovertible and obvious proof or evidence to the contrary (DSM-IV-TR, 2000). Early accounts of delusions conceptualised this phenomena as irreducible (Jaspers, 1963). However, the emergence of cognitive psychology and psychiatry have provided evidence that dysfunction in fundamental aspects of the cognitive systems which subserve functions such as reasoning and semantic memory could contribute to the development and continuance of delusions.

Recently, several theories have linked the development of delusional thought and the presence of delusional symptoms with cognitive biases. It appears that,

compared to non deluded patients, deluded patients evince a ‘jumping to conclusions bias’ demonstrated by the way in which they require less information than controls to reach a conclusion (Dudley et al., 1997; Garety et al., 1991; Sellen, Oaksford & Gray, 2005). Other cognitive biases and impairments implied in delusion formation and maintenance include, liberal acceptance (Moritz & Woodward, 2004), attributional bias (Bentall, Kinderman & Kaney, 1994), knowledge corruption (Moritz & Woodward, 2006), poor theory-of-mind (Frith, 1994) and a bias against disconfirmatory evidence (BADE; Moritz & Woodward, 2006; Buchy, Woodward & Liotti, 2007; Woodward, Moritz, Cuttler & Whitman, 2006).

Reasoning errors made during the stages of hypothesis formation may also lead an individual to develop improbable hypotheses and overestimate the likelihood that such hypotheses are true. Reasoning biases have been especially associated with delusional individuals when the content includes information that is emotionally salient or threat related. However, rather than reflecting global reasoning deficits these biases tend to be specific, (Lawrence & Peters, 2004), and more evident for emotionally salient (Kemp, Chua, McKenna & David, 1997) and delusion-congruent stimuli (Rossell, Shapleske & David, 1998). Such biases have been suggested to have a causal role in the formation of delusional beliefs (Lawrence & Peters, 2004). Similarly, in tests of logical reasoning, schizophrenic patients with positive symptoms have been found to be impaired in all reasoning conditions and to be unable to mobilise a belief-laden reasoning mechanism compared with controls (Goel, Bartolo, St. Clair & Venneri, 2002).

Other studies have focused on the way in which differences in semantic memory may be associated with delusions. As delusions involve alterations in personal meaning and belief, they have also been interpreted as manifestations of abnormal semantics. This association may account for reasoning biases such as the jumping to conclusions bias as such judgements rely on prior knowledge, beliefs and experience, all of which are stored in semantic memory (Sellen, Oaksford & Gray, 2005). Converging evidence that problems in semantic memory could lead to delusion formation (McKenna, 1991) may explain why deluded schizophrenics are impaired at analogical reasoning tasks, because the perception of analogy also depends on semantic knowledge (Gick & Holyoak, 1980; Simpson & Done, 2003).

Based on findings in the schizophrenia literature it appears that although well defined, the association between schizophrenia and range of semantic impairments is still in need of further clarification. Disorganised language is a primary clinical feature of schizophrenia. The verbal output of individuals with this disorder is characterised by incoherent and unintelligible speech, tangential and idiosyncratic responses and a prevailing loosening of conceptual associations (Chen et al., 1994).

The way in which schizophrenic individuals idiosyncratically form associations between concepts is well documented (Green et al., 2004; Chen et al., 1994) and is thought to be due to semantic memory deficits (McKenna, 1994; Payne, 1973; Spitzer et al., 1993a; Spitzer et al., 1993b). Many studies have reported positive associations between psychotic symptoms and semantic memory although the mechanism that mediates the relationship between impaired semantic memory and



positive symptoms is not clearly understood. However, this association is not always evident when the schizophrenia phenotype is expressed in normal individuals in the form of schizotypy. In fact, evidence suggests that in healthy individuals with high positive schizotypy (HPS) the idiosyncratic way in which semantic memory appears to be organised may be advantageous (Mohr et al., 2001). Whilst in schizophrenia patients, dysfunctional semantic memory and its related effects in other cognitive domains has been associated with both the presence and severity of delusions (Frith 1992; Goldman-Rakic 1994; Rossell et al 1999; Bell et al 2006), when positive schizotypal traits are expressed as individual differences in healthy individuals, semantic memory differences have been found to have adaptive qualities (Folley & Park, 2005).

Research focused on understanding the way in which semantic memory is structurally supported in the brain have used assessments such as sentence and category verification tests, lexical decision tasks, semantic fluency tests and word association paradigms. Such research has informed theoretical models of how concepts are stored, associated and retrieved in semantic memory. Classical models of semantic memory such as the Hierarchical Network Model (Collins & Quillian, 1969) characterise semantic memory as a network comprised of interconnecting concepts. In this model, the number of shared properties between concepts determines their similarity and dictates their proximity in the semantic network.

However, more recent theories argue against the assumption that concepts are hierarchically stored based solely on their perceptual similarities. In response, the Spreading Activation Model (Collins & Loftus, 1975) proposes that thinking

about or perceiving a concept automatically activates associated concepts. The strength of activation is a function of the distance between representations, when concepts are closely stored they strongly activate each other, however activation is weak when concepts are stored at a distance from one another.

The theory of spreading activation has helped to characterise the semantic memory deficits in schizophrenia and the manifestation of delusions has been associated with an abnormal increased spreading activation in semantic networks. For individuals with delusions the semantic network has been found to spread faster and further. Furthermore, concepts that are less related are more readily activated by these individuals than those activated by controls (Spitzer et al 1993a, Spitzer et al 1993b). This theory converges with Bleuler's Loosening of Associations (Bleuler, 1911) and may help explain why, when compared to controls, schizophrenic individuals produce more tangential and idiosyncratic associations.

Semantic memory impairments in schizophrenia may be manifest due to a selectional preference for personally salient rather than relevant associations. Understanding the role of dopamine in normal individuals may help to explain the basis of this selection. Dopamine should be responsible for the way in which the salience of external events and internal representations are interpreted (Kapur, 2003). However as Kapur (2003) suggests, in schizophrenic individuals a dysregulated hyperdopaminergic system may lead to an aberrant assignment of salience whereby concepts or associations are selected on the basis of their experienced salience rather than their relevance. According to this hypothesis, for

schizophrenic individuals, delusions would be interpreted as a consequence of the cognitive effort necessary to make sense of aberrantly salient experiences.

Informed by evidence which suggests there is a shared genetic vulnerability between individuals with schizophrenia, SPD and those with high levels of schizotypal personality traits, recent research has investigated the extent to which semantic impairments manifest along the schizotypy continuum (Niznikiewicz et al., 1999). Disorganized speech in both schizophrenia and schizotypy has been hypothesized to result from abnormalities in how concepts activate one another in semantic memory and schizotypy has been associated with decreased use of context to activate related items and inhibit unrelated items (Kiang & Kutas, 2005). Furthermore, deluded patients have been found to have reduced semantic fluency production, more idiosyncratic lexical organisation and impoverished logical word associations than non-deluded patient controls (Rossell, Rabe-Hesketh, Shapleske & David, 1999). Such evidence may be an artefact of disorganised semantic storage obfuscating efficient access.

Similarly, thought disorder has been interpreted as arising from a failure to use semantic information to constrain thought and language (Honey et al., 2008). This failure manifests clinically as impaired semantic generation, this effect has been measured by semantic association and sentence completion tasks. Ketamine has been found to provoke symptoms that are characteristic of delusions in normal individuals, and when subjects undertake the sentence completion task under a sub-psychotic dose of ketamine, the frontal and temporal response to this task was convergent with the response to this task of schizophrenic patients with thought disorder (Honey et al., 2008). The suggestion that frontotemporal activity in

semantic processing could be a ‘vulnerability marker’ of this symptom may be generalisable beyond schizophrenia and interpreted in line with the relationship between semantic association and delusions in general. However, more evidence is needed to assess the extent to which such vulnerability markers can predict the emergence of psychosis.

Based on the literature presented above, the studies presented in this chapter are concerned with ascertaining how semantic reasoning and language organisation are related to delusion proneness, as measured by positive schizotypy in a sample of healthy individuals, and to characterise the way in which this semantic system activates or spreads as a function of high positive schizotypy.

## ***5.2 EXPERIMENT 1 – ASSOCIATIVE REASONING***

In Chapter 4, the impression that high schizotypies have lower reasoning skills (Wierzbicki, 1985) was not found to extend to non verbal reasoning. However, in this experiment the focus is on the way in which semantic elements of reasoning tasks may be especially relevant for individuals with high positive schizotypy.

On syllogistic reasoning tasks, individuals with high positive schizotypal (PS) traits have been found to make more errors than low PS participants (Wierzbicki, 1985). However, on a conditional inference task, high schizotypies have been found to exhibit a ‘logic-like’ performance (Sellen et al., 2005). Sellen et al., conclude that in this task schizotypies produced a normative logic like performance not because of increased reasoning ability but because they failed to take all possible information into account before reaching a conclusion. This resembles a jumping to conclusions bias (Garety, Hemsley & Wessely, 1991;

Sellen, Oaksford & Gray, 2005) and illustrates one of the ways in which schizotypal cognitive processes can actually be adaptive. In this context, a cognitive bias that has been found to be related to schizotypy enables these individuals to achieve normal scores, although they appear to achieve these scores in a different manner from individuals with lower levels of schizotypy.

This finding prompted the rationale that informs the focus of current investigation, namely that there may be other tasks in which high positive schizotypies may produce a normative response, but the way in which they reach this response may differ from the way in which the task was approached by individuals with lower positive schizotypal traits.

In the current study, the WAIS similarities (Wechsler, 1981), a fundamentally semantic task, which is typically a measure of abstract verbal or analogical reasoning and concept formation will be used to assess whether high positive schizotypies negotiate this as a typical reasoning task or whether these individuals recruit a different mechanism to reach a conclusion. In this task, participants are asked in what way two items are similar, as the task progresses the similarities between the items become less concrete and progressively more abstract. Based on studies within the reasoning literature which have found associations between schizotypy and poorer performance in verbal reasoning tasks (Voglmaier et al., 2000), it could be hypothesised that high PS participants will perform less well than low PS participants. However, based on the semantic association element of this task in combination with evidence from semantic spreading studies in schizotypy (Miller & Chapman, 1983; Ward et al., 1991; Kiang & Kutas, 2006), findings that the semantic network of high PS individuals spreads faster and

further (Spitzer et al 1993) and those which suggest that for healthy individuals with positive schizotypy this could lead to gains in semantic tasks (Mohr et al., 2004), it could be predicted that high positive schizotypal personality traits may lead to improvements in the ability to make semantic associations between concepts that increasingly become more abstractly associated.

In order to infer which processes are mediating the performance of high PS and low PS participants, three Wason selection tasks (Cheng & Holyoak, 1985) were used to assess deductive reasoning. These tasks, which vary in semantic content from abstract, to abstract permission to concrete permission, were employed to assess the extent to which differing levels of semantic facilitation in reasoning performance contribute to the associative abilities of the high and low schizotypy groups as demonstrated by performance on the Similarities task.

### ***5.2.1 METHOD***

#### ***5.2.2 DATA COLLECTION***

Opportunity samples were collected from students from the University of Hull and individuals from the Hull community.

#### ***5.2.3 PARTICIPANTS***

After excluding 7 participants based on the exclusion criteria outlined in the General Health Questionnaire described in Chapter 4 section 4.2.3, in total data from 315 individuals were included in the analyses for this study. The group was comprised of 164 females and 151 males, with a mean age of 29.74 ( $SD = 11.67$ , range 18-54), and with mean years of education of 15.10 ( $SD = 2.69$ , range 9-25).

Ethics approval for the current study was granted by the joint University and NHS Trust Regional Ethics Committee.

### **5.2.4 SPQ-B**

The SPQ –B was used to measure schizotypal traits, this scale was described in detail in Chapter 4, section 4.2.4. However to summarise, the SPQ yields a full score and scores for 3 sub-factors the Cognitive Perceptual factor which taps the positive aspects of psychosis which have also been used to specifically explore delusion proneness; Ideas of Reference Odd beliefs / Magical Thinking Unusual Perceptual Experiences/ Paranoid Ideation, the Interpersonal factor which is related to negative schizotypal characteristics such as social anxiety and few close friends and the Disorganised factor which reflects strange speech and behavior.

### **5.2.5 WAIS SIMILARITIES**

The similarities subsection of the Wechsler adult intelligence scales (WAIS; 1981) was included in the study as a measure of concept formation and abstract verbal reasoning. In this task, participants are asked to identify how two items are similar. As the task progresses items become less concretely associated and more abstractly connected and the semantic distance between the concepts widens For instance, identifying the similarities between fork and spoon, egg and seed and enemy and friend are examples of simple, intermediate and difficult items respectively. Participant responses were scored in line with the original manual (WAIS, 1981). Pertinent general categorisations were given 2 points and more concrete naming of common properties or functions earned 1 point. For example, identifying that the similarity between ‘eye and ear’ is that they are senses would score 2 points, whereas a response that they are features on the head would score 1 point. Scores can range from 0 – 33.

### 5.2.6 *WASON CARD SELECTION*

Three Wason Card Selection Tasks (WST) problems, that were adapted from Cheng and Holyoak (1985) and Goel, Shuren, Sheesley and Grafman (2004) were administered to participants. The problems included WST1, an arbitrary rule (if a card has an ‘A’ on one side, then it must have a ‘4’ on the other side), WST2 an abstract permission schema (if one is to take action ‘A’ then one must first satisfy condition ‘P’) and WST3 a concrete permission schema (if a person is to drink alcohol, he or she must be at least 18). The reasoning behind all three tasks is essentially the same. However, the differing semantic content typically leads to linear gains in performance from WST1 to 3. The ordering of the three problems was counterbalanced within subjects. Participants were asked to ‘only tick the box under the cards that you need to turn over to check the rule is being followed’. For each WST task, responses are recorded as correct or incorrect.

The order of the SPQ-B, WSTs and Similarities tasks was counterbalanced within and across participants.

### 5.2.7 *RESULTS*

The means, standard deviations and ranges for age, education and SPQ-B total and sub factor scores for all participants can be found in Table 5.1.

Table 5.1. Means (standard deviations; ranges) for demographic and SPQ-B variables.



		Full Group (N = 315)	
		M	(SD; Range)
Age		29.74	(11.67 18-54)
Education		15.10	(2.69; 9-25)
Similarities	(0-32)	21.93	(4.49; 8-32)
SPQ-B	(0-22)	7.98	(4.814 0-22)
Cognitive/ Perceptual	(0-8)	2.83	(1.97; 0-8)
Interpersonal	(0-8)	3.17	(2.33 0-8)
Disorganised	(0-6)	2.01	(1.91; 0-6)

Pearson correlation analyses (not shown) for the whole group revealed significant correlations between all SPQ-B total and factor scores that were consistent with those reported in the previous chapter. However, the only one of these factors that was associated with the reasoning tasks was the positive schizotypy factor which was negatively associated with performance on the similarities task  $r = 0.20$ ,  $p < 0.01$  and on WST3  $r = 0.20$ ,  $p < 0.01$ . All reasoning tasks were positively intercorrelated with one another. Age and handedness were not correlated with any of the reasoning tasks, however sex was negatively correlated with all reasoning tasks except WST1 and education was positively associated with performance in all reasoning tasks. Consequently partial correlation analyses, controlling for sex and education were computed for Similarities, all WSTs and the Cognitive Perceptual measure of positive schizotypy, the results of which can be found in Table 5.2. When sex and education were controlled for the association between Similarities and WST1 became non significant however, all other correlations reported above remained significant, in the same direction and Pearson's  $r$  did not rise or fall by more than 0.02. When only the highest cut-off

schizotypy scorers were included in the analysis this result became positive and increased to 0.46.

Table 5.2. Partial correlations between Positive Schizotypy scores, and reasoning tasks, (controlled for sex and education).

	Similarities	WST 1	WST 2	WST 3	SPQ-B	Cognitive Perceptual
Similarities		<b>0.10</b>	<b>0.20**</b>	<b>0.27**</b>	<b>-0.09</b>	<b>-0.19**</b>
WST 1	<b>0.10</b>		<b>0.31**</b>	<b>0.18**</b>	<b>-0.02</b>	<b>-0.04</b>
WST 2	<b>0.20**</b>	<b>0.31**</b>		<b>0.49**</b>	<b>-0.02</b>	<b>-0.10</b>
WST 3	<b>0.27**</b>	<b>0.18**</b>	<b>0.49**</b>		<b>-0.13*</b>	<b>-0.19**</b>
SPQ-B	<b>-0.09</b>	<b>-0.02</b>	<b>-0.01</b>	<b>-0.13*</b>		<b>0.71**</b>
Cognitive Perceptual	<b>-0.19**</b>	<b>-0.04</b>	<b>-0.10</b>	<b>-0.19**</b>	<b>0.71**</b>	

\*\* Correlation is significant at the .01 level (2-tailed)

\* Correlation is significant at the .05 level (2-tailed)

In order to identify differences between high positive Schizotypy (HPS) and low positive schizotypy (LPS) participants, individuals with SPQ-B Cognitive Perceptual scores which fell within the 5% high-low cut-off were identified. The cut-off scores in this group were consistent with those reported in Chapter 4, whereby those who scored 7-8 on the SPQ-B Cognitive Perceptual scale fell in the highest and those who scored 0 fell in the lowest 5% cut off. The demographic and Similarities scores for the high and low positive schizotypy (PS) groups can be seen in Table 5.3. Independent t-tests revealed that there was a small but significant difference in Similarities scores between the groups  $t(57) = 2.10$ ,  $p < 0.05$ , no significant differences between HPS and LPS participants in terms of age or education were identified. Independent t-tests revealed a significant

difference between the LPS and HPS groups for WST3  $t(69.73) = 2.73, p < 0.05$ .

The performance of each group across the three WST tasks can be seen in Figure 5.1.

Table 5.3. Means and standard deviations for demographic and Similarities scores for high and low PS groups.

	High PS (n = 17) (8 Male, 9 Female)		Low PS (n = 42) (19 Male, 22 Female)	
	M	SD	M	SD
<b>Age</b>	<b>28.00</b>	<b>10.87</b>	<b>33.43</b>	<b>12.66</b>
<b>Education</b>	<b>15.88</b>	<b>3.06</b>	<b>15.48</b>	<b>3.29</b>
<b>Similarities</b>	<b>21.47</b>	<b>4.06</b>	<b>23.81</b>	<b>3.79*</b>

\* Difference is Significant at the 0.05 level (2-tailed)

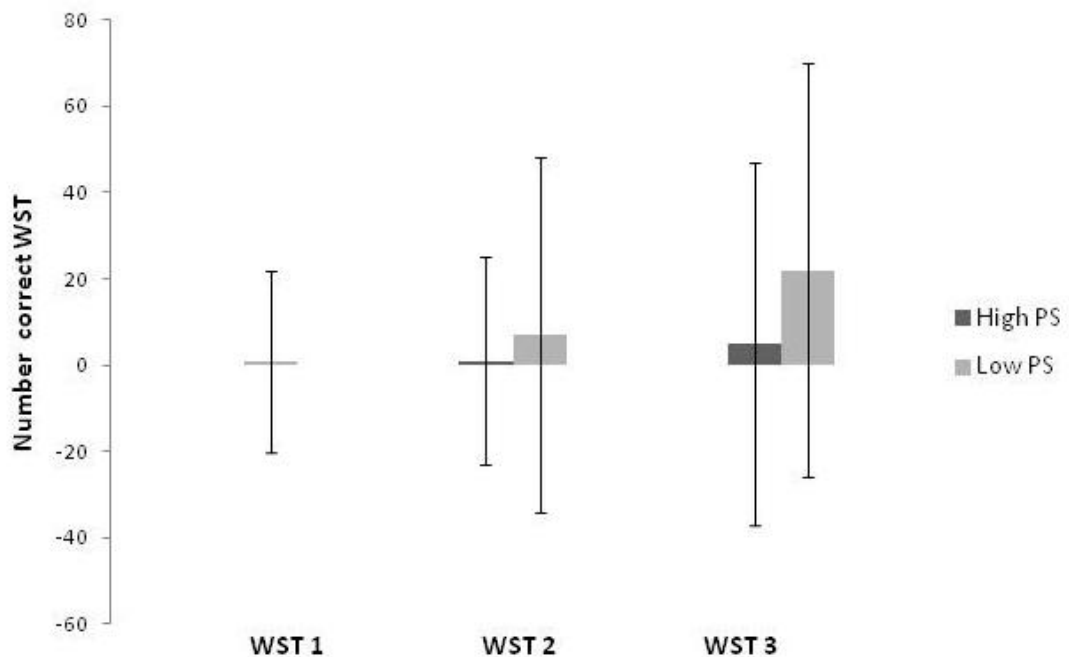


Figure 5.1. HPS and LPS WST performance.

In a model where Similarities scores were identified as the dependent variable, step-wise multiple regression analyses revealed a significant model of 3 predictors that explained the variance in Similarities scores ( $F[3,311] = 20.03, p = 0.001$ ). In this model WST3 explained 11 % ( $F[1,313] = 37.95, p = 0.001$ ), education explained 3% ( $F[1,312] = 12.10, p = 0.001$ ) and a negative direction of Cognitive Perceptual scores explained a further 2 % ( $F[1,311] = 7.61, p = 0.01$ ) of the variability in Similarities scores.

Further stepwise multiple regression analyses were computed for individuals in the highest 10% PS cut-off as there was insufficient variance of PS scores in the 5% cut off. A significant model emerged whereby only HPS scores on the Cognitive Perceptual factor explained the variability in Similarities scores ( $F[1,26] = 7.05, p = 0.01$ ), HPS scores accounted for 21% of the variance in the dependent variable. This regression can be seen in Figure 5.2.

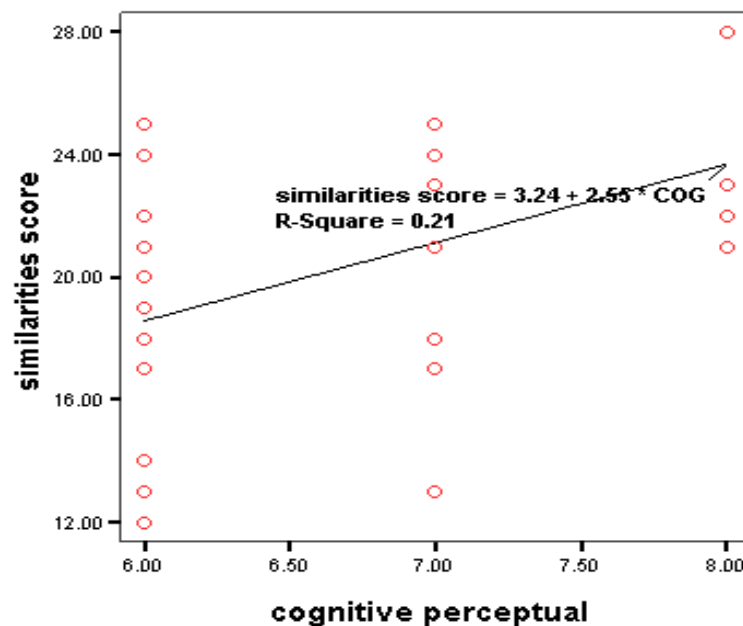


Figure 5.2. Relationship between PS and Similarities in the highest 10% of PS scorers.

### **5.2.8 CONCLUSION**

For both groups, reasoning performance improved as a function of the increased semantic facilitation from arbitrary content to abstract content to concrete content in the WSTs; this performance is in line with previous studies that have employed these tasks (Cheng & Holyoak, 1985; Goel, et al., 2004). The significant difference between HPS and LPS on WST3 reflects the fact LPS are superior at concrete reasoning than HPS participants. The lack of significance between PS group and WST1 and 2 is most likely due to the fact that both groups performed poorly on these tasks.

The associations found between similarities and the three WSTs whereby the strength of correlation increased as the tasks became easier from WST1 (arbitrary condition) to WST 2 (abstract condition) to WST3 (concrete condition) demonstrates that as similarities scores increase, correct responses on the WST's increase. The strength of the correlation between the WSTs and Similarities increases as a function of reduced task complexity and increased semantic transparency.

Due to the strong relationships sex and education frequently held with other variables, these variables were partialled out of the analysis. For both groups the SPQ-B and its factors remained strongly intercorrelated, these were not reported in this study as they entirely converge with the data presented in Chapter 4 and the standardisation literature. After the partial analysis, Similarities was no longer correlated with WST1 which suggests more years of education and male gender were largely responsible for the original correlation. However, Similarities was still positively correlated with WST2, and WST3 when sex and education were

controlled for. In addition, the inverse association between Similarities scores with the Cognitive Perceptual factor  $r = -0.19$ ,  $p < 0.01$  remained significant.

Similarly, independent t-tests revealed slight but significant differences between the LPS and HPS participants on Similarities scores, whereby LPS participants achieved higher mean scores than the HPS group. In addition, in a stepwise multiple regression computed for the full group lower scores on the PS measure predicted improved similarities performance. The other predictors included WST3 (which reflects concrete reasoning facilitated by semantic content) and education. These predictors make sense as Similarities is a reasoning task that is frequently employed as a measure of verbal IQ (WAIS, Wechsler 1981). In total, the model suggests improved reasoning ability, more years of education and lower PS traits are associated with performance in the similarities task and converges with previous findings that poorer performance in verbal reasoning is associated with HPS (Voglmaier et al., 2000).

In contrast, in correlation analyses of the 10% highest PS cut-offs, the previously negative association between Similarities and PS became positive and increased to 0.46. This suggest that whilst the HPS score lower than LPS individuals, within the very highest of the PS scorers Similarities increases as PS increases. In convergence with this correlation, when separate stepwise multiple regression analyses were conducted with the highest 10% PS cut-off group, high positive schizotypy emerged as the only significant predictor explaining 22% of the variance in Similarities scores.

This finding is contrary to the full group results, whereby performance in Similarities was predicted by concrete reasoning ability, more years of education and fewer PS traits. The fact that reasoning ability and education do not serve an explanatory function in high PS's semantic reasoning ability suggests that for high PS individuals a different mechanism may be involved in completing the task to that which is related to task performance in the full group. So whilst they are not performing as highly as the low PS group, in the absence of aid from reasoning ability (as suggested by its lack of predictive ability in this model and through the negative associations between HPS and WST3), and without the transfer of advantage from years of education, within the high PS group performance on this task improves as a function of higher positive schizotypal traits. In the context of the full group, PS is negatively associated with reasoning skill, but within PS individuals higher positive traits confer some advantages in Similarities performance. It is also worth noting that whilst significant, the difference between Similarities scores is small  $t=2.1$  and may be due to the larger number of individuals in the low compared with the high group.

One way to interpret this result is that in the Similarities task, high positive schizotypal individuals are making associations between concepts that increasingly become less concretely associated because of their well documented propensity to over-associate disparate concepts and events. This is compatible with the theory that disinhibition within semantic networks may underlie delusional belief formation (Voglamier, Seidman, Niznikiewicz et al., 2000). This is also convergent with literature that suggests an abnormal facilitation of the spreading activation within semantic networks underlies the remote associations and referential ideas that characterise schizophrenic delusions (Mohr, et al., 2001).

Which may explain why HPS participants performed less well than LPs participants, as abnormalities in the way in which concepts activate one another in the semantic memory of schizotypal individuals has been associated with decreased use of context to activate related items and inhibit unrelated items (Kiang & Kutas, 2005) and from a failure to use semantic information to constrain thought and language (Honey et al., 2008). In addition, individuals with elevated positive schizotypal traits have been found to judge loose associations as being more closely related and to consider unrelated words as more closely associated than participants with lower PS scores (Mohr, et al., 2001). Whilst the tendency to relate uncommon concepts to one another may be the basis of paranormal and paranoid ideation, it is often implied as essential for creative thought. However, it may also represent a preclinical vulnerability indicator to the more bizarre associations generated by individuals with delusions (Mohr et al., 2001).

Although more studies are necessary to understand why high delusion-prone schizotypies differ from low PS participants on this task a tentative theory may suggest that the task is facilitated by different mechanisms, networks or even hemispheres in these groups. In line with evidence that abnormalities of hemispheric asymmetry may underlie schizophrenia, patterns of cognitive hemispheric asymmetries, assessed by left and right hemisphere language tasks have been examined in relation to schizotypal symptoms and associations have been found between schizophrenic syndromes and the absence of a clear pattern of hemispheric dominance for language. The current finding could be a result of the pronounced semantic asymmetries and right brain language dominance that has been evidenced in schizotypal individuals (Nunn & Peters, 2001; Leonhard & Brugger, 1998). For instance, studies attempting to resolve the extent to which



paranormal belief formation may be related to spreading activation characteristics within semantic networks have found that strong believers' close semantic relations between distant concepts are processed by the right hemisphere, which is specialised in coarse as opposed to focused semantic processing (Pizzagalli, Lehmann & Brugger, 2001). In addition in terms of laterality, the left hemisphere has been found to be specialised for recognising close associates whereas the right hemisphere is superior at recognising more remote associates (Rodel et al., 1992). Similarly, the right pre frontal cortex has been found to be involved in the processing of incomplete information and the left more specialised for the processing of complete information (Goel et al., 2007).

Weinstein and Graves (2001) suggest higher schizotypy may partly arise from a lowering of criteria for evidence due to a reliance on processing strategies that are more dependent on the right cerebral hemisphere. This line of reasoning may also explain differences between high PS and low PS performance in the Similarities task as over reliance on the right hemisphere would reduce the role of the left hemisphere's specialism in verbal and logical processes that could control overt responding (Gellatly, 1985). Such dominance failure is often observed in patients with acute signs of psychosis (Leonhard & Brugger, 2001) and it may facilitate the emergence of paranormal and delusional ideas by way of right hemisphere associative processing characteristics. Furthermore, as a characteristic of schizotypal thinking, the development of paranormal beliefs has been related to spreading activation characteristics within semantic networks as participants who held fixed paranormal beliefs have been observed to demonstrate stronger indirect semantic priming effects after left visual field stimulation (Pizzagalli, Lehmann and Brugger, 2001). However, whilst compatible with the current findings these

interpretations are at present speculative. Further empirical evidence is necessary to ascertain whether semantic spreading due to a right hemisphere processing bias is mediating the associative reasoning performance of HPS participants.

### ***5.3 EXPERIMENT 2 – SEMANTIC AND PHONOLOGICAL FLUENCY***

Disorganisation in the way in which concepts are interconnected in semantic memory is thought to mediate the loosening of associations that schizophrenic individuals demonstrate on measures of categorisation and association such as the Category Generation Test (CGT; Green et al., 2004). Such evidence that semantic memory may be idiosyncratically organised in schizophrenia (Goldberg et al 1998, Sumiyoshi et al 2001, Elvevag et al 2002, Green et al 2004) is conceptually compatible with theories which suggest storage or access disorders underlie semantic memory impairments in schizophrenia. However, evidence that schizophrenic patients demonstrate reasonably preserved performance on naming tasks compared with a consistently impaired performance on semantic association tests (Al-Uzri et al., 2004; Barrera et al., 2005) suggests that the semantic deficit is not due to lexical impairments but occurs when connections between concepts must be made. If concept representations are organised differently, it follows that an idiosyncratic memory network will produce less coherent semantic categories with more unusual associations between concepts. However, the extent to which semantic networks are developmentally formed idiosyncratically or whether there is an impaired retrieval system which leads to the atypical recovery of concepts is not fully understood.

Various semantic processing impairments have been interpreted as being central to cognitive abnormalities in schizophrenia (Rosell et al., 2000) and have furthered arguments that delusions are manifestations of semantic deficits (Rosell et al., 1999; Morgan et al., 2006). On word association tests, schizophrenic patients have been found to produce responses that are less typical than those generated by patient controls (Johnson & Shean, 1993). According to Spitzer (1997) the unusual associations demonstrated by schizophrenic individuals are due to an increased range of semantic spreading activation where an item creates a normal activation for its strong associates and a disproportionately high activation for items that are weakly associated with it.

Research which has concentrated on qualitative differences in semantic memory has also demonstrated that semantic categories are idiosyncratically organised in schizotypal individuals when compared to the organisation of semantic memory in controls (Chen et al 1994, Green et al 2004). HPS has also been associated with the production of more frequent utterances of idiosyncratic words compared with LPS performance despite the fact that these individuals demonstrated equal verbal intelligence (Coleman, Levy, Lenzenweger & Holzman, 1996). Similarly, normal participants with high magical ideation and perceptual aberration scores produce more unusual and fewer typical responses than those produced by controls (Miller & Chapman, 1983). Similarly, in a category fluency task, high SPQ total scores were associated with less typical responses for the fruit category (Kiang & Kutas, 2006). This finding was interpreted as evidence that high schizotypal individuals demonstrate functionally altered semantic memory organisation (Kiang & Kutas, 2006) and that the association between schizotypy and lower typicality of responses is related to a difference in the extent to which a concept activates the

neural representation of items that are weakly related compared to those which are strongly associated with it. This effect has also been observed in individuals with schizophrenia (Spitzer, 1997) and may help to explain why individuals with high schizotypy are more likely to produce weakly related items in word association tests (Kiang & Kutas, 2006). This is also compatible with the sheer inhibition hypothesis which posits that lack of control over the mechanisms which should inhibit spreading activation in semantic networks leads to activation spreading more diffusely (Spitzer, 1993). However increased activations of weakly related representations were not associated with schizotypy in a subsequent study which found the typicality of responses did not differ as a function of schizotypy (Hori et al., 2007).

According to Kiang (2009), as fluency tasks have frequently been employed to reveal important information concerning the organisation of semantic memory (Aloia et al., 1996; Paulsen et al., 1996; Rossell et al., 1999; Sumiyoshi et al., 2001) they may provide salient indices of idiosyncratic language in schizophrenia and schizotypy. In the current study, participants with various PS scores were asked to generate words for several phonemic and semantic fluency tasks. In similar tasks, schizophrenic patients have been found to produce fewer responses than controls (Allen et al., 1993; Aloia et al., 1996; Paulsen et al., 1996; Rossell et al., 1999; Sumiyoshi et al., 2001; Giovannetti et al., 2003). Poor total performance on verbal fluency tasks has especially been associated with negative symptoms of schizophrenia (Allen et al., 1993; Howanitz, Cicalese, & Harvey, 2000) a finding which has been replicated in individuals with negative schizotypal traits (Tsakanikos & Claridge, 2004). On the contrary, in studies which have distinguished negative from positive symptomatology in schizophrenia, positive

psychotic symptoms have been associated with increased verbal fluency performance (Lindamer & Whitman, 1997; Kerns, Berenbaum, Barch, Banich & Stolar, 1999). This has also been demonstrated in individuals with high levels of positive schizotypy (O'Reilly, Dunbar & Bentall, 2001, Weinstein & Graves, 2002). This latter finding has been interpreted as evidence that psychosis is a consequence of increased automatic spreading activation in semantic networks (Weinstein & Graves, 2001; David, 1994; Hoffman & McGlashan, 1997, Tsakinikos & Claridge, 2004). It is important to note that evidence for associations between schizotypal traits and abnormal fluency performance would suggest fluency irregularities are primary psychotic features because they are also expressed in healthy non-clinical individuals with genetic vulnerabilities to psychosis (Tsakanikos & Claridge, 2004). This would indicate that irregular fluency performance is a cognitive endophenotype of psychosis proneness (Tsakanikos & Claridge, 2004). This line of reasoning is more in line with the theory that schizotypy should be interpreted within a quasi-dimensional rather than a fully dimensional model. However, other evidence has failed to reveal associations with negative traits and impoverished verbal fluency (Barrentes-Vidal et al., 2002, O'Reilly et al., 2001; Weinstein & Graves, 2002) or between positive schizotypy and improved fluency performance (Hori et al., 2008; Kiang & Kutas, 2006).

Inconsistent findings between studies in terms of associations between positive schizotypy and increased verbal fluency could be due to the use of different fluency tasks, as previous studies have employed either phonological or semantic fluency tasks. As these tasks may involve disproportionate executive (Lezak, 1995) and lexical retrieval (Tsakinikos & Claridge, 2004) demands in the current

study, clarification was sought through the administration of both types of fluency task. The lack of statistical significance in the relationship between PS and number of words generated in the phonological fluency was explored in Chapter 4, and taken for evidence that PS individuals do not exhibit impairments in executive function. To further explore the executive demands of fluency tasks, perseverations, intrusions and neologisms were recorded for both tasks. Due to conflicting evidence in the literature, in the current study it is difficult to predict whether quantitative differences in the number of words generated in the Semantic fluency task will be demonstrated between individuals with differing levels of schizotypy.

However, it was predicted that qualitative differences would be evident between high PS and low PS on several linguistic parameters. Consequently, the words produced by each participant in the phonological and semantic fluency tasks were subsequently rated by a separate group of participants for their typicality, familiarity, frequency and imageability. These ratings were then applied to the original participant's fluency data in order to see whether these individuals demonstrate an increased spreading facilitation in their semantic networks (Kiang & Kutas, 2006), sheer inhibition (Spitzer, 1993), and whether semantic memory is more idiosyncratically organised in participants with higher PS traits (Kiang & Kutas, 2006). However, rather than defining typicality as the relative frequency of production (Kiang & Kutas, 2006), in the current study, typicality norms for each word will be separated from frequency and provided by raters of the same age, education and mean PS score in terms of how typical the exemplar is of its' category (Mervis et al., 1976). If higher typicality reflects strong links between the category and the exemplar in semantic memory (McCloskey and Glucksberg,

1978; Kiang, 2009) then lower typicality would represent weaker links and be suggestive of sheer inhibition (Spitzer, 1993). Lower typicality scores would also be indicative of a more idiosyncratic semantic memory system. Therefore, in line with Kiang & Kutas (2006) it is predicted that HPS will produce less typical words in each task than LPS individuals. By the same logic, HPS participants should also generate words that are less frequent, familiar and, based on the finding that imageability facilitates the production of less frequent words (Seidenberg, 1995; Strain & Herdman, 1999), HPS participants are also predicted to produce words with higher imageability ratings than the LPS individuals.

### ***5.3.1 PARTICIPANTS AND SPQ***

The participants in the current experiment are the same as those who participated in experiments 2 and 3 in Chapter 4. Please refer to sections 4.3.1, 4.3.2 and 4.3.3 for details of the participants, the general health questionnaire and the full SPQ.

### ***5.3.2 FLUENCY TASKS***

For the semantic fluency task (SFT), participants were asked to verbally generate as many names as possible for 3 separate categories; fruits, animals and cities. Participants were given one minute for each category. As described in Chapter 4, in the phonemic fluency task, participants were asked to verbally generate as many words as possible beginning with 3 separate letters; P, F and L; participants were also given one minute for each letter. For the total semantic and phonological fluency tasks the total number of words generated, perseverations, intrusions and neologisms were recorded.

### ***5.3.3 FLUENCY RATING STUDY***

### **5.3.3.1 WORD SAMPLE**

In total 1327 words (397 P, 219 L, 300 F, 64 fruits, 160 cities and 186 animals) were produced by the participants in the phonemic and semantic fluency tasks that were described in section 5.3.2.

### **5.3.3.2 PARTICIPANTS**

Forty participants were recruited for this study, they were all native English speakers. The sample was comprised of 15 males and 25 females, of whom 36 were right and 4 were left handed. Their mean age was 21.48 (SD, 3.64), mean years of education was 14.7 (SD, 1.62) and their mean SPQ-B Cognitive Perceptual scores was 2.93 (SD, 2.13).

### **5.3.3.3 RATING TASKS**

As typicality is related to how well an exemplar is representative of its category, typicality ratings were only undertaken for animals, cities and fruits in the semantic task. Imageability ratings were requested for P, F, L, animals and fruits but not for cities. Familiarity and Frequency ratings were undertaken for all phonemic and semantic tasks. Separate booklets were compiled for each task, the words were randomly ordered, printed in Times New Roman font at 24pt and were presented in the centre of the page alongside a blank box for ratings. The order of booklet assignment to each participant was randomised using a Latin Square procedure. Each participant rated the different lexical attributes of words for 2 hours. If after this period a booklet was left incomplete, the completed ratings were removed and the remainder of the booklet was assigned to a new participant in the next study group. Participants were tested in groups of 10 in a large room and were given detailed instructions for each task and an informed consent form to complete prior to participation. Before leaving the experiment,



participants were also asked to complete the SPQ-B (described in detail in Chapter 4, section 4.2.4). Ethics approval for the current study was granted by the joint University and NHS Trust Regional Ethics Committee.

For each lexical parameter, ratings were in line with a 7-point Likert scale with 7 representing the most typical, imageable, frequent or familiar and 1 the least typical, imageable, frequent or familiar words. For typicality, the instructions were based on those provided by Larochelle, Richard and Souliers (2000). For imageability, the instructions were very similar to those provided by by Toggia and Battig (1978), Paivio, Yuille, and Madigan (1968) and Cortese and Fuget (2004) except a less Americanised example was provided. Familiarity rating instructions were in line with those of Marques, Fonseca, Morais and Pinto (2007) and Frequency instructions were based on those provided by Kučera and Francis (1967).

#### ***5.3.4 RESULTS***

The mean age education and SPQ-B Cognitive Perceptual scores for participants in the fluency study and rating study can be seen in Table 5.4. Independent t-tests revealed that there were no significant differences between these participants in terms of age, education or SPQ-B Cognitive Perceptual scores.

Table 5.4. Demographic and SPQ-B Cognitive Perceptual scores for the participants in the fluency and rating studies.

	<b>Fluency (n = 75)</b> <b>(26 Male, 49 Female)</b>		<b>Raters (n = 40)</b> <b>(15 Male, 25 Female)</b>	
	<b>M</b>	<b>SD</b>	<b>M</b>	<b>SD</b>
<b>Age</b>	<b>20.69</b>	<b>5.06</b>	<b>21.47</b>	<b>3.64</b>
<b>Education</b>	<b>14.27</b>	<b>1.61</b>	<b>14.70</b>	<b>0.82</b>
<b>SPQ-B Cognitive Perceptual</b>	<b>3.52</b>	<b>2.72</b>	<b>2.92</b>	<b>2.13</b>

The mean total responses, perseverations, intrusions, neologisms, frequency, typicality, imageability and familiarity scores for the words generated in the semantic and phonological fluency task for each group of SPQ Cognitive Perceptual scorers and the total group can be found in Table 5.5. Separate one way ANOVA analyses computed for each dependent variable revealed that there were no significant differences between any of the groups of SPQ Cognitive Perceptual Scorers.

Table 5.5. Semantic and Phonological means and stand deviations for task performance and lexical attributes for each group of SPQ-B Cog Per scorers.

Cog Per Score	Low Group						High Group				Total	
	0		1-2		3-4		5-6		7-8		Total	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
Phonemic Fluency	40.33	11.70	38.40	10.92	44.40	12.05	41.73	10.89	38.53	10.33	40.68	11.12
Semantic Fluency	52.13	10.85	53.73	10.20	56.6	8.91	53.66	9.54	50.33	9.30	53.29	9.74
Phonemic Frequency	3.13	0.38	3.10	0.60	3.21	0.42	3.31	0.47	3.23	0.43	3.20	0.46
Semantic Frequency	3.13	0.34	2.96	0.36	3.10	0.32	3.00	0.36	3.03	0.24	3.04	0.32
Phonemic Familiarity	4.04	0.52	4.01	0.75	4.20	0.58	4.19	0.52	4.21	0.53	4.13	0.57
Semantic Familiarity	4.58	0.42	4.36	0.46	4.59	0.50	4.46	0.49	4.48	0.40	4.49	0.45
Phonemic Imageability	2.85	0.32	3.00	0.30	2.97	0.39	2.93	0.26	2.71	0.29	2.89	0.32
Semantic Imageability	5.47	0.64	5.54	0.78	5.41	0.56	5.48	0.63	5.29	0.66	5.44	0.65
Typicality	4.41	0.49	4.23	0.44	4.31	0.44	4.26	0.44	4.28	0.14	4.30	0.45
Phonemic Word Length	4.68	0.49	4.78	0.47	4.77	0.43	4.64	0.27	4.86	0.57	4.75	0.45
Semantic Word Length	5.62	0.31	5.74	0.28	5.61	0.20	5.56	0.14	5.57	0.28	5.62	0.25
Phonemic Intrusions	0.23	0.54	0.40	0.74	0.40	0.83	0.60	0.63	0.40	0.51	0.40	0.66
Phonemic Perseverations	0.40	0.51	0.80	1.15	0.73	0.88	0.33	0.49	0.47	0.64	0.56	0.78
Phonemic Neologisms	0.13	0.52	0.00	0.00	0.33	0.62	0.20	0.56	0.07	0.26	0.15	0.46
Semantic Intrusions	0.07	0.26	0.60	1.12	1.47	1.92	1.07	1.39	0.60	0.91	0.76	1.30
Semantic Perseverations	0.40	0.63	0.73	0.96	0.40	0.63	0.33	0.62	0.53	0.74	0.48	0.72
Semantic Neologisms	0.00		0.00		0.00		0.00		0.00		0.00	

As reported in Chapter 4, education was inversely associated with the total number of words generated for Phonemic fluency. Pearson correlation analyses revealed that the Disorganised factor of the SPQ was inversely associated with

semantic frequency  $r = -0.23$ ,  $p < 0.01$ . This association remained after partial correlation controlled for age sex and education.

### **5.3.5 CONCLUSION**

For the semantic fluency task there were no differences between the number of words produced by individuals with different levels of positive schizotypy. This finding is contrary to studies which have found PS to be associated with elevated fluency performance. It is however, consistent with studies of semantic fluency in schizotypy which have found no differences between HPS and LPS in the number of words generated (Kiang & Kutas, 2006, Hori et al., 2007) this finding, in combination with the lack of differences between HPS and LPS on the phonological fluency task (Presented in the previous chapter) also suggests that unlike individuals with schizophrenia, there appears to be no phonological or semantic retrieval problems, no degradation of connections in the semantic network (Aloia et al., 1996; Paulsen et al., 2006; Rossell et al., 1999; Kiang & Kutas, 2006) or impaired executive functions (Giovannetti et al. 2003; Kiang & Kutas, 2006) in individuals with high positive schizotypy. The lack of association with HPS, intrusions, perseverations or neologisms also implies that these participants can maintain task rules on-line, monitor their performance and inhibit inappropriate responses (Lezak, 1995; Tsakanikos & Claridge, 2004). Accordingly Kiang and Kutas (2006) suggest that the normal category fluency, in terms of the total number of words generated, demonstrated by individuals with high schizotypal traits may reflect the presence of prefrontal compensatory mechanisms that have been associated with protection against decompensation in individuals with a genetic susceptibility to schizophrenia (Siever & Davis, 2004). This may also account for the way in which negative schizotypal traits were not

associated with any fluency variable. Similarly, in another study there were no differences between high and low schizotypal individuals on the behavioural measure of number of categories generated (Hori et al., 2007). However, in the highly schizotypal individuals, letter fluency task performance was found to be related to predominantly right asymmetry in prefrontal activation (Hori et al., 2007). This is consistent with the theory that decreased prefrontal control may lead to impairments in the ability to maintain contextual representations in working memory which could subserve the unusual associations observed in schizophrenia (Cohen & Servan-Schreiber, 1992; Kiang, 2009). More complex tasks are necessary in order to obtain behavioural evidence for this in healthy persons with high schizotypy.

Based on the findings of Kiang and Kutas (2006), it was predicted that lexical attributes such as typicality should vary between HPS and LPS individuals. This prediction was also extended to incorporate related lexical parameters including frequency, familiarity and imageability. However, contrary to these predictions there was no evidence that HPS participants produced words that were more idiosyncratic than those produced by LPS participants as all groups produced words that were equally frequent, familiar, imageable and typical, in the semantic and phonological fluency tasks. Whilst this is the first study to explore familiarity, frequency and imageability as a function of HPS, the lack of association with typicality is consistent with the findings of Hori et al. (2007).

Furthermore in the study which reported an association between schizotypy and typicality, this was only evident for the fruit category. Based on the current finding that participants in the fluency study produced words for only 64 fruits

compared with 160 cities, 184 animals and between 219 and 397 words for the letter fluency task, it appears that there is much lower variability in the fruit category. This effect was also demonstrated by the Kiang and Kutas' (2006) sample and in several similar studies (Battig & Montague, 1969; Ruts et al., 2004; Yoon et al., 2004). Kiang and Kutas suggest that the lower variability in this category may reduce the signal to noise ratio thus making differences in typicality more obvious between high and low schizotypal individuals. However, a significant difference on this small category alone does not seem sufficient evidence to suggest that semantic memory is functionally altered in high schizotypies. Consequently, it was important in the current study to only separate tasks by semantic or phonological orientation and not by individual categories. The inability to find statistical significance in the current study may also suggest that using norms generated by a sample that is matched for age, education and independent variable (i.e. SPQ Cognitive Perceptual scores) reduces the risk of false positive results that could be due to the different linguistic experiences of raters versus generators.

One consideration is that the lack of significance reported here is due to differences in the measure of positive schizotypy used in the current study, although whilst some of the studies that reported positive associations between fluency and PS used measures such as the O-LIFE (Tsakanikos & Claridge, 2004) or the Chapman's scales (Weinstein & Graves, 2001) the study which found PS to be associated with lower typicality also used the SPQ (Kiang & Kutas, 2006). Furthermore, the magical ideation scores which were obtained for the same participants in a different experiment were not found to be associated with any of the fluency independent variables in the current study.

The inverse association between higher SPQ Disorganised traits and the generation of words that are less frequent in the semantic category suggests good construct validity for the sub-factor as one of the themes it reflects is odd speech. One could conjecture that in healthy individuals with no clinical manifestations of thought disorder, increased activations of less frequent concepts in semantic memory could be behaviourally manifest as unusual speech. Based on the finding from a study with exactly the same participants presented in Chapter 4, where Disorganised traits were not associated with impaired performance in the NART (Chapter 4 table 8 section 4.3.5), the current results are not likely to be due to differences in verbal IQ between higher and lower Disorganised participants.

In the current study, no evidence was found to support an association between HPS and an increased facilitation of the spreading activation within semantic networks. This may reflect that advanced education confers protective advantages in the cognitive areas that are related to psychotic features in individuals with a genetic vulnerability for psychosis or perhaps that those who demonstrate more obvious signs of semantic spreading which is more indicative of schizotaxic pathological processes are not well represented in higher education. The marked absence of executive impairments in these participants may also explain their normative performance. Previously, the way in which executive deficits have been found to lead to impairments in the ability to maintain contextual representations in working memory has been implied as a causative factor in the mediation of unusual associations observed in schizophrenia (Cohen & Servan-Schreiber, 1992; Kiang, 2009).

It is also important to consider whether the sample size for each group led to type II errors (Hori et al., 2000). However, whilst type II errors could be blurring possible differences between the lexical attributes of words generated by HPS compared with LPS participants, the whole group is quite large and there is sufficient variance in PS scores to demonstrate relationships in correlation analyses. The lack of evidence for disproportionately strong activation for weakly related words in the system suggests that semantic spreading may not be an appropriate endophenotype for investigation of psychosis proneness in a homogenous sample of healthy high schizotypies in higher education. It may also intimate that semantic spreading is more closely associated to schizophrenic breakdown processes along a quasi dimensional spectrum as opposed to vulnerabilities that may be present in individuals whose high positive schizotypal traits may only confer psychosis risk endophenotypically as a consequence of neuropathology. This is in line with evidence of the qualitative differences between delusions in schizophrenia and neurodegenerative diseases which may suggest that different cognitive correlates will be associated with the formation and maintenance of delusions with such distinct aetiologies. Finally, the current findings could also suggest executive function is the real endophenotype that confers schizophrenic breakdown risks and subserves semantic spreading. Thus executive function impairments may also prove to be an important variable in the distinction between individuals on the quasi-dimensional and fully dimensional schizotypy spectrum.



## CHAPTER 6

# AFFECTIVE INTERFERENCE, PERSONAL MEMORY AND ANATOMICAL CORRELATES OF POSITIVE SCHIZOTYPY

### *6.1 INTRODUCTION*

Whilst the studies thus far have focused on the way in which certain cognitive mechanisms may be related to positive schizotypal dimensions, the extent to which performance in aspects of cognition that are more emotionally and personally salient varies as a function of positive schizotypy will be investigated in the current chapter. Based on the extant schizophrenia literature the first study that will be presented investigated the relationship between affective processing in terms of inhibition, and informed by evidence which suggests false alarms in memory paradigms may be associated with a proneness to psychosis and from neurodegenerative research which has found associations between confabulations, impairments in episodic memory and delusions (Lee, Meguro, Hashimoto et al., 2007) a secondary paradigm was devised to assess the effect of affective content on recall and recognition memory in positive schizotypy. The second study explored personal semantic and episodic autobiographical memory organisation behaviourally in a group of participants with various positive schizotypy scores. In order to interpret these results within a neuroanatomical diathesis stress model of positive schizotypy and psychosis proneness, in a third experiment the findings

of this study will be compared with the structural correlates of positive schizotypal traits as defined by a voxel based morphometric study in normal individuals.

## ***6.2 AFFECTIVE INTERFERENCE & FALSE REMEMBERING***

Whilst the majority of schizophrenia research is concerned with the way in which impairments in the cognitive architecture may be involved in disturbances such as delusions and hallucinations (Mohanty, Herrington, Koven et al., 2005), more recent studies have begun to focus on the centrality of affective processes to manifestations of psychosis. Affective disturbances have been associated with the aetiology and clinical presentation of schizophrenia (Mohanty et al., 2005) and the disproportionate responses to negative affect which have frequently been observed in individuals with schizophrenia have also been found to be highly related to the exacerbation of positive symptoms (Docherty et al., 1994; Docherty, 1996; Mohanty et al., 2005).

Mohanty et al, (2005) suggest that affective disturbances may be related to psychotic symptoms because such disturbances inevitably lead to distortions in cognitive functions such as attention, perception, reasoning and language. Consequently, it has been proposed that dysfunctional relationships between affective and cognitive processes could factor in the aetiology and emergence of psychotic symptoms (Mohanty et al., 2005; Freeman, Garety, Kuipers et al., 2002). For instance, in addition to the well documented selective attention impairments that have been observed in schizophrenia and schizotypy (Braver, Barch & Cohen, 1999; Mohanty et al., 2005), recent studies have demonstrated that the way in which negative emotional valence exacerbates attentional

processing difficulties in these individuals may be related to the expression or potential for psychosis (Mohanty et al., 2005).

Similarly, Canli et al. (2004), have found dissociations between mood state and personality traits in the neural networks involved in cognitive affective tasks in normal individuals and have demonstrated that different personality traits can advance explanations of the variance reported in studies assessing brain activation to emotional stimuli (Canli et al., 2002). In behavioural studies, the performance of individuals with various personality types has been found to be related to variance in affective processing (Canli et al., 2004). As previously discussed, personality has been associated with between subject variance in attention to emotionally laden stimuli (Amin et al., 2004; Haas et al., 2006; Derryberry & Reed, 1994; Reed & Derryberry, 1995; Canli et al., 2001). Individual differences in personality structure have also been found to correspond with variation in emotional memory, (Bradley et al., 1992; Libkuman et al., 2004), however this process varies considerably between individuals (Rusting, 1999) and has yet to be studied as a function of positive schizotypy. However, in previous work an individual differences approach, has revealed differences in personality traits could explain considerable behavioural and brain functional variance in emotional memory facilitation (Haas & Canli 2008). For example, individuals with high neuroticism and trait anxiety have been found to respond with longer latencies to negative compared with neutral words on emotional Stroop paradigms (Derryberry & Reid, 1998; Canli et al., 2004).

The emotional Stroop task appears to be an especially effective means by which to explore the relationship between individual differences and interference in

cognitive affective processes. Using emotional Stroop paradigms, several studies have shown that for individuals with schizophrenia and schizotypy, positive symptoms predict greater interference from threat related words (Epstein, Stern & Silbersweig, 1999; Mohanty, Koven, Fisher et al., 2001). In addition, this threat related emotional Stroop interference effect appears to be limited to positive schizotypal symptoms as it does not appear to extend to the negative symptoms of the schizotypal spectrum (Mohanty et al., 2001; 2005). However, whilst a further study failed to replicate an association between positive schizotypy and elevated affective interference in the behavioural data, fMRI results suggested that for individuals with high schizotypal traits, different brain regions are involved in response to the emotional Stroop task than those which were activated by participants with lower positive schizotypal traits (Mohanty et al., 2005). In this task, positive schizotypy was associated with reduced left dorsolateral prefrontal cortex (DLPFC), increased right DLPFC and larger activations in the nucleus accumbens, hippocampus, amygdala and basal ganglia (Mohanty et al., 2005). These findings suggest that the brain mechanisms which subservise affective cognition are similar in schizotypy and schizophrenia (Mohanty et al., 2005). The lack of statistical significance between high and low schizotypies in the behavioural data, despite evidence of different neural activations in the neuroimaging data has previously been reported in a study of schizotypy and verbal fluency (Hori et al., 2005).

Whilst previous studies have predominantly focused on the way in which negative items exacerbate cognitive disruptions in persons with schizophrenia or schizotypy, in the current study the stimuli were chosen to be dimensionally salient to a predominantly positive schizotypal personality type. This approach is

in line with findings that attentional processes in psychosis prone individuals should be most attenuated when the stimuli are congruent with the context of psychosis (Rossell, Shapleske & David, 1998). For instance, findings from reasoning studies suggest that rather than reflecting global deficits (Kemp, Chua, McKenna & David, 1997), reasoning biases have been especially associated with delusional individuals when the content includes information that is emotionally salient or threat related (Kemp, Chua, McKenna & David, 1997) or associated with delusion-congruent stimuli (Rossell, Shapleske & David, 1998).

Furthermore, this task will enable discernment of whether healthy participants with high positive schizotypy display higher affective reactivity as demonstrated by cognitive disturbance on emotional Stroop accuracy or latencies and whether these words elicit automatic semantic processing which overrides attentional processes (Canli et al., 2004). According to Maher (2003), hyperactivity of association could be an artefact of impaired inhibition whereby activated associations arise more frequently and decay more slowly (Maher, 2003; Maher et al., 2005; Lezenweger et al., 2007). The current emotional Stroop task was devised to assess whether individuals with high levels of positive schizotypy are less able to inhibit the semantic content of words chosen to be emotionally relevant to their personality type compared with neutral words and with the performance of participants with lower positive schizotypy scores.

Due to the fact that persons with schizophrenia frequently demonstrate attentional deficits (Braver, Barch & Cohen, 1999; Barch, Carter, Braver et al., 2001) an original Stroop task will also be employed to assess whether potential differences on the emotional Stroop are due to the salience of the emotional words or whether they are an artefact of a more general attentional deficit arising from an inability

to maintain and process contextual task related information and inhibit information that is irrelevant to the task. Based on the non clinical status of the participants in this study it is predicted that performance on the original Stroop paradigm will not differ as a function of positive schizotypy.

In addition to the emotional Stroop, a secondary but related paradigm was devised to assess whether the affective salience of the emotional Stroop items leads to biases in immediate and delayed recall and recognition memory. In this surprise recall recognition paradigm, the emotional Stroop also acts as an incidental learning task where participants were asked to recall as many words as possible from the emotional Stroop task at two time intervals; immediately after the emotional Stroop and again after a ten minute delay. Subsequently, participants were asked to complete a recognition paradigm which was comprised of equal numbers of emotional and neutral words from the emotional Stroop and matched emotional and neutral words that were not included in the original emotional Stroop task. Participants were asked to indicate if the word was old (i.e. from the original emotional Stroop) or new.

The manifestation of psychotic symptoms such as delusions and hallucinations has frequently been linked to cognitive biases, and it has been suggested that these biases have a causal role in the formation and maintenance of psychosis (Lawrence & Peters, 2004). Patients with delusions have been found to require less evidence to reach a conclusion than controls (Garety et al., 1991) and those with hallucinations have also been found to demonstrate premature and unfounded judgements, misattributions of externality and false positive biases (Tsakanikos & Reed, 2005). The externality hypothesis (Garety et al., 2001) describes the

inclination to accept that an experienced event, such as a voice, is in fact externally generated rather than attributing it to an internally generated input (Tsakanikos & Reed, 2005). Similarly, Tsakanikos & Reed (2005) suggest that the common propensity to experience non existing events and non existing relationships between events in individuals with delusions and hallucinations may reflect a putative cross-modal cognitive mechanism which mediates positive symptoms and which may activate biased attributional processes in susceptible individuals in ambiguous situations. In light of such associations, the second paradigm was designed to assess whether biases such as jumping to conclusions, misattributions of stimulus origins and experiences of non-existent events in individuals with psychosis have salient analogies with a potential for false remembering in non clinical psychosis prone individuals.

According to Laws and Bhatt (2005), most schizophrenia memory research has concentrated on omission errors such as impairments in recall and recognition rather than commission errors such as false alarms in recall and recognition memory. However, whilst schizophrenia is characterised by mnemonic impairments in several memory domains (Aleman, Hijman, De Haan & Kahn, 1999; Laws & Bhatt, 2005) evidence suggests that these deficits do not generally extend to non-clinical individuals with high schizotypal traits. Based on evidence that delusions in schizophrenia may be associated with increased false memories (Moritz, Woodward, Cutler et al., 2004), a recent study (Laws & Bhatt, 2005) found that non clinical delusion prone individuals also had poorer recall and made more false alarm recalls than low delusion prone controls, they also reported greater confidence for the correctness of their false positive responses thus demonstrating a jumping to conclusions style bias (Garety & Hemsley, 1994). However, other

evidence suggests that individuals with high levels of schizotypy may be less likely to make false alarms in certain experimental conditions. For instance, in another study higher schizotypy was associated with greater accuracy (i.e. fewer false positive responses) for lures that were not presented in the original learning paradigm but that were semantically associated with the words that were presented (Fisher, Heller & Miller, 2007). This has been interpreted as arising from a schizotypal tendency to fail to adequately attend to contextual information because in such a task, the more one attends to the contextual details the more one is likely to make semantically plausible false alarms (Barch et al., 2004; Kiang, 2009). This finding could also suggest that individuals with positive schizotypy are less likely to make false positive errors in recognition as opposed to recall paradigms. This is in line with the evidence that impairments and false alarm responses have been reported in recall but not recognition memory in schizophrenia (Mathews & Barch, 2004) and in individuals with Specific Delusional Disorder (SDD), memory deficits have been evidenced in recall but not recognition conditions (Herlitz & Forsell, 1996).

Further evidence for an association between psychosis proneness and a tendency for false positive mnemonic errors can be found in the dementia literature.

Confabulation, which has been defined as falsification of memory in the context of organic amnesia (Berlyne, 1972) has frequently been observed in Alzheimer's disease (AD; Lee, Akanuma, Meguro et al., 2007; Cooper, Shanks & Venneri, 2006) and may be associated with psychiatric symptoms in dementia (Lee, Meguro, Tanaka et al., 2004). Whilst confabulations are rare in non amnesic individuals and difficult to experimentally provoke in healthy participants, the study of false alarms in recall and recognition memory in non clinical psychosis



prone individuals may provide a suitable analogy by which to further understand the association between a vulnerability to delusional beliefs and confabulatory response biases.

Based on the evidence presented thus far, it was hypothesised HPS participants would produce more false alarms for delusion congruent items in recall conditions than LPS participants, identification of whether HPS participants also make more false positive style responses on neutral items will explain the extent to which the affective content of the words biases incidental encoding and retrieval. However, based on the evidence for intact recognition memory in schizophrenia and SSD it is predicted that HPS participants will not produce more false positives than LPS participants in the recognition task. In terms of general accuracy, it is predicted that HPS participants' performance will not significantly differ from those with lower positive schizotypy scores.

### **6.2.1 *METHOD***

### **6.2.2 *PARTICIPANTS AND SPQ***

The participants in the current experiment are the same as those who participated in experiments 2 and 3 in Chapter 4 and experiment 2 in Chapter 5. Please refer to sections 4.3.1, 4.3.2 and 4.3.3 for details of the participants, the general health questionnaire and the full SPQ.

### **6.2.3 *EMOTIONAL AND STANDARD STROOP***

The emotional words were chosen from the subscales of the SPQ (Raine, 1991; ideas of reference, magical thinking, unusual perceptual experiences, and paranoid ideation) that combine to form the positive schizotypy Cognitive Perceptual

factor. Words or themes were chosen from each Cognitive Perceptual relevant item in the SPQ generating 57 words. In order to identify the words which would be most salient to HPS participants, the words were rated for relevance to the concept by 15 participants who were not involved in any other part of the study. For each set of words pertaining to each of the four subscales, participants were given an explanatory paragraph about the individual subscale before being asked to rate the words on an 8 point Likert scale (0 not at all relevant – 7 especially relevant). Thirty words with the highest ratings were included in the emotional Stroop paradigm. These words were matched with thirty neutral words found on the MRC Psycholinguistic Database (Retrieved, August 2008) based on syntactical categories, length, number of syllables, frequency of usage (Kucera & Francis, 1967) and where possible familiarity (Gilholy & Logie, 1980). As each emotional and control word was presented once in each of the four colours (red, blue, yellow and black), 120 emotional items and 120 neutral items were presented in total.

A traditional colour Stroop task was also used to demonstrate whether any differences between HPS and LPS participants in the emotional Stroop could be attributed to the attentional demands involved in a Stroop paradigm. This task consisted of a congruent and incongruent condition, whereby the participants had to simply identify the colour of the word (e.g. RED written in red) in the congruent condition, but in the incongruent condition, the semantic content of the colour name presented was incongruent with the colour in which the word was written (e.g. RED written in yellow). In total, thirty congruent and thirty incongruent items were presented in the same colours that were used in the emotional version.

For both the emotional and standard Stroop tasks to avoid colour blur, slides were presented in grey comprised of 50% white, 50% black, words were all capitalised and in 32pt bold type. In order to avoid problems associated with colour vision words were written in blue, red, yellow and black. Finally, to control for viewing position each word was written on the slide 4 times and their presentation was centred. A fixation cross preceded each slide to focus attention. Stimuli were presented for 250 milliseconds on a 14 inch monitor using E-Prime 2.0 and participants pressed the coloured buttons on the keyboard that corresponded to the colour in which the word was presented. Prior to the Stroop tasks participants completed a short practice trial to familiarise themselves with the coloured buttons on the keyboard. A mixed trial design was used for both types of Stroop task.

#### ***6.2.4 INCIDENTAL RECALL AND RECOGNITION***

Immediately after the emotional Stroop, participants were told that whilst it was not specifically a memory task, we were interested to know any words they could remember from the paradigm. In order to avoid interference from another verbal task, after recording the recalled words participants were administered the black and white version of Ravens Progressive Matrices. After 10 minutes, participants were again asked what words they could remember from the emotional Stroop paradigm, once these words were recorded the participants were then asked to complete the computerised recognition paradigm.

In this recognition paradigm, 10 randomly chosen positive schizotypy salient (PSS) words and their 10 neutral counterparts from the emotional Stroop were matched with 10 new PSS words which were then matched with 10 new neutral

words that were not included in the emotional Stroop. Again these words were matched using syntactical categories, length, number of syllables, frequency of usage and where possible familiarity (Kucera & Francis, 1967). Stimuli were presented on a 14 inch monitor and were compiled in E-Prime 2.0, using the keyboard participants were asked to press B (before) if the word displayed was from the previous experiment and N (new) if the word was new. When the recognition task was finished, the Raven's test was resumed if incomplete.

The order of the Stroop tasks and the experimental tasks described in Chapters 4 and 5 was counterbalanced within and across participants with three important exceptions, to avoid linguistic interference Raven's Progressive Matrices was always conducted in the delay between the emotional Stroop and the recall and recognition paradigms obviously always had to follow the emotional Stroop immediately and after a ten minute delay, finally to avoid demand characteristics the two schizotypy based psychometric questionnaires, the SPQ and MI were always administered at the end of the testing session.

### **6.2.5 RESULTS**

The demographic information (age, sex and education) for each group and the total group can be found in Table 4.6 in the Results section of Chapter 4, section 4.3.5.

#### **6.2.5.1 Emotional Stroop**

The mean number of correct responses for emotional and neutral Stroop items and their respective latencies for each positive schizotypy score group can be seen in Table 6.1.

Table 6.1. Mean (and standard deviation) accuracy and latencies for emotional and neutral Stroop items for each positive schizotypy group.

Cog Per Score	Low Group				High Group				Total			
	0		1-2		3-4		5-6		7-8		Total	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
<b>Emotional (120) % Correct</b>	112.69	3.61	114.28	1.72	110.73	6.81	112.92	2.81	113.81	3.29	112.88	4.13
	94%		95%		92%		94%		95%		94%	
<b>Neutral (120) % Correct</b>	115.31	4.51	116.79	2.49	114.93	4.31	115.64	2.71	115.56	3.82	115.63	3.93
	96%		97%		96%		96%		96%		96%	
<b>Emotional Time</b>	440.80	101.88	432.65	110.29	425.84	143.90	399.19	105.32	423.15	92.69	424.75	109.73
<b>Neutral Time</b>	434.46	97.84	433.86	118.48	429.51	119.13	399.10	108.81	424.49	91.78	424.63	112.10

Paired samples t-tests (2-tailed) revealed a significant difference between the number of correct responses made for emotional compared with neutral words ( $t(74) = -9.91, p < 0.001$ ) whereby participants demonstrated greater accuracy for neutral ( $M = 115.63, SD = 3.93$ ) than for emotional words ( $M = 112.88, SD = 4.13$ ). However, there were no significant differences between the latencies for emotional and neutral words. Separate one way ANOVA analyses revealed that there were no significant differences between any of the positive schizotypy score groups in terms of accuracy on emotional and neutral Stroop items or between emotional and neutral Stroop latencies.

### 6.2.5.2 Stroop

The mean number of correct responses for congruent and incongruent Stroop items and their respective latencies for each positive schizotypy score group can be seen in Table 6.2.

Table 6.2. Mean (and standard deviation) accuracy and latencies for congruent and incongruent Stroop items for each positive schizotypy group.

CogPer Score	Low Group						High Group				Total	
	0		1-2		3-4		5-6		7-8		Total	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
<b>Congruent (30)</b>	29.13	1.54	29.50	0.65	29.07	1.44	28.94	1.27	29.38	0.72	29.20	1.17
<b>% Correct</b>	97%		98%		97%		96%		98%		97%	
<b>Incongruent (30)</b>	29.38	0.72	28.86	1.92	28.73	2.52	28.27	1.48	28.50	1.51	28.75	1.71
<b>% Correct</b>	98%		96%		96%		94%		95%		96%	
<b>Congruent Time</b>	423.74	135.15	449.32	125.27	451.47	148.80	418.65	92.96	383.17	98.84	424.46	121.60
<b>Incongruent Time</b>	521.80	151.32	535.31	176.73	437.02	126.83	457.35	158.15	464.62	108.56	483.14	146.37

Paired samples t-tests (2-tailed) revealed a significant difference between the number of correct responses made for congruent compared with incongruent words ( $t(74) = 2.08, p < 0.04$ ) whereby participants demonstrated greater accuracy for congruent ( $M = 29.20, SD = 1.17$ ) than for incongruent items ( $M = 28.75, SD = 1.71$ ). Further 2-tailed paired samples t-tests revealed a significant difference between the latencies of congruent compared with incongruent words ( $t(74) = -5.07, p < 0.001$ ) where participants were faster for congruent ( $M = 424.46, SD = 121.6$ ) than for incongruent items ( $M = 483.14, SD = 146.37$ ). Separate one way ANOVA analyses revealed that there were no significant differences between any of the positive schizotypy score groups in terms of accuracy on congruent and incongruent Stroop items or between congruent and incongruent Stroop latencies.

### 6.2.5.3 Immediate Recall

The mean number of correct emotional and neutral words recalled in the immediate recall condition and the mean number of emotional and neutral false

alarms for each positive schizotypy score group can be seen in Table 6.3, significant findings are illustrated by Figures 6.1 and 6.2.

Table 6.3. Mean (and standard deviation) immediate recall correct responses and false alarms for emotional and neutral words for each positive schizotypy group.

Cog Per Score	Low Group						High Group				Total	
	0		1-2		3-4		5-6		7-8		Total	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
<b>Emotional</b>	3.00	1.60	4.13	1.96	4.33	1.68	4.33	2.32	5.13	1.81	4.19	1.96
<b>Neutral</b>	1.93	1.16	1.07	1.03	1.47	1.77	1.67	1.40	1.53	1.55	1.53	1.40
<b>Emotional False Alarms</b>	0.20	0.41	0.07	0.26	0.07	0.26	0.87	1.24	0.93	1.16	0.43	0.87
<b>Neutral False Alarms</b>	0.13	0.35	0.07	0.26	0.13	0.35	0.27	0.46	0.27	0.46	0.15	0.38

Separate one way ANOVA analyses revealed that there were no significant differences between any of the positive schizotypy score groups in terms of the number of neutral items recalled or for the number of neutral false alarms produced. However, individual one way ANOVA revealed that there was a significant difference between the groups for the number of emotional words recalled ( $F[4,70] = 2.47, p = 0.05$ ) and for the number of false alarms made for emotional words ( $F[4,70] = 4.45, p = 0.003$ ). Bonferroni post-hoc analysis comparisons of the five groups indicate that the mean number of emotional words recalled were significantly different between individuals in the highest 5 % cut off (scorers of 7-8) for positive schizotypy ( $M = 5.13, 95\% \text{ CI } [4.13, 6.13]$ ) and those in the lowest PS group ( $M = 3.0, 95\% \text{ CI } [2.11, 3.89]$ ).

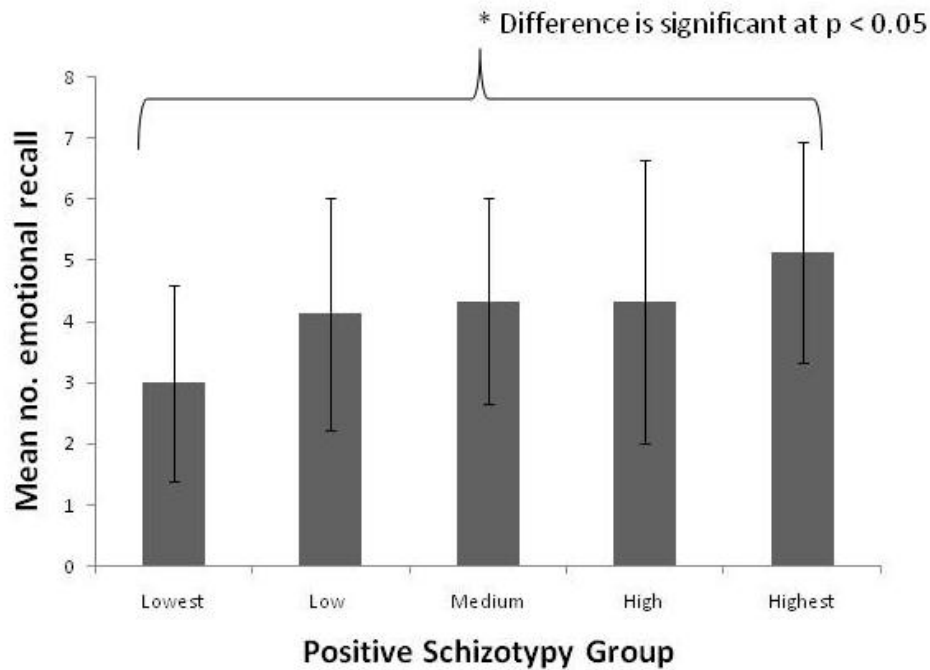


Figure 6.1. Mean number and standard deviation of emotional words recalled in the immediate recall condition.

Bonferroni post-hoc analysis comparisons of the five groups also indicated that the mean number of false alarms made for emotional words were significantly different between individuals in the highest 5 % cut off (scorers of 7-8) for positive schizotypy ( $M = 0.93$ , 95% CI [0.29, 1.58]) and those in the medium ( $M = 0.07$ , 95% CI [-0.08, 0.21]) and between the highest scorers and those in the second lowest PS group ( $M = 0.07$ , 95% CI [-0.08, 0.21]).



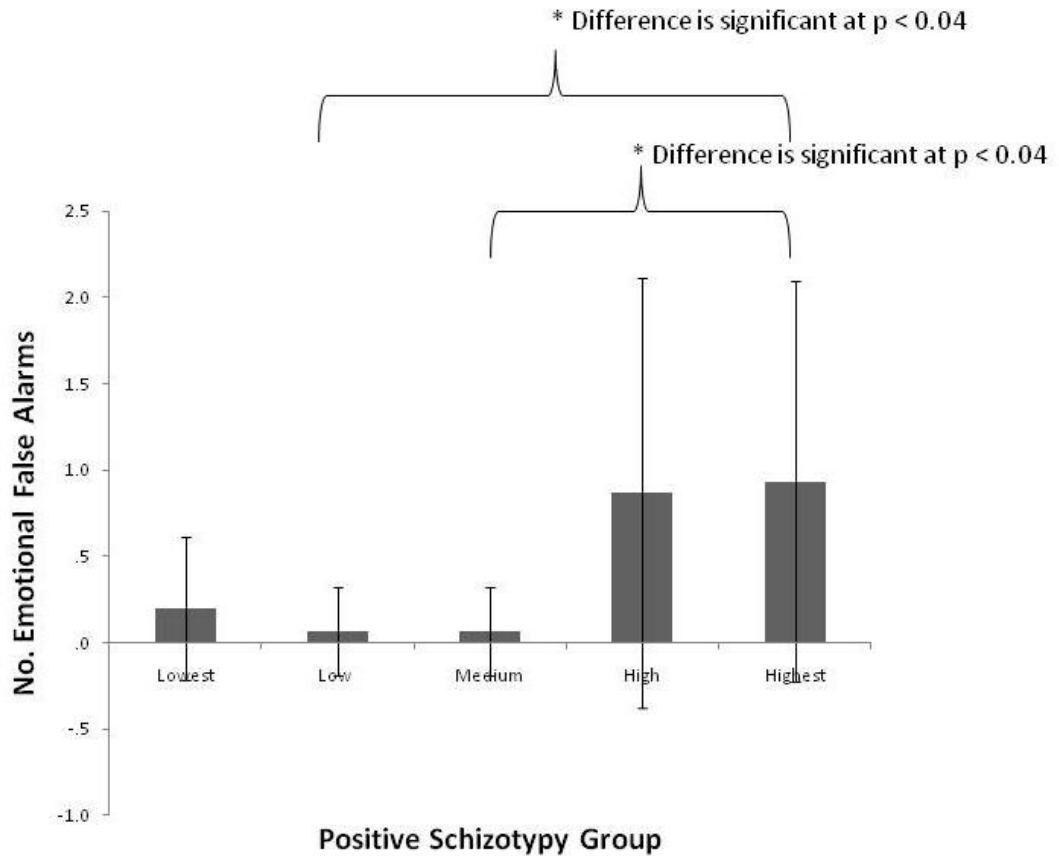


Figure 6.2. Mean number and standard deviation of emotional false alarms made in the immediate recall condition.

#### 6.2.5.4 Delayed Recall

The mean number of correct emotional and neutral words recalled in the delayed recall condition and the mean number of emotional and neutral false alarms for each positive schizotypy score group can be seen in Table 6.4, significant findings are illustrated by Figure 6.3.

Table 6.4. Mean (and standard deviation) delayed recall correct responses and false alarms for emotional and neutral words for each positive schizotypy group.

CogPer Score	Low Group						High Group				Total	
	0		1-2		3-4		5-6		7-8		Total	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
<b>Emotional</b>	3.27	1.71	3.67	1.63	3.67	1.71	3.93	1.86	4.81	1.97	3.86	1.81
<b>Neutral</b>	1.40	1.24	0.80	0.86	1.40	1.72	1.46	1.12	1.53	1.50	1.32	1.32
<b>Emotional False Alarms</b>	0.13	0.35	0.07	0.26	0.33	0.49	0.80	1.01	0.80	0.86	0.43	0.72
<b>Neutral False Alarms</b>	N/A		N/A		N/A		N/A		N/A		N/A	

No participants made false alarms for neutral words in the delayed recall condition. Separate one way ANOVA analyses revealed significant differences between the means of the positive schizotypy score groups in terms of the number of emotional false alarms produced in the delayed recall condition ( $F[4,70] = 4.29, p = 0.004$ ). Bonferroni post-hoc analysis comparisons of the five groups indicated that the mean number of false alarms made for emotional words in the delay condition were significantly different between individuals in the highest 5% cut off (scorers of 7-8) for positive schizotypy ( $M = 0.8, 95\% \text{ CI } [0.32, 1.28]$ ) and those in the second lowest PS group who scored 1-2 on the PS measure ( $M = 0.07, 95\% \text{ CI } [-0.08, 0.21]$ ). Significant differences were also evident between the second highest group of PS scorers (5-6) ( $M = 0.8, 95\% \text{ CI } [0.24, 1.36]$ ) and those in the second lowest PS group. A trend towards a significant difference ( $p < 0.07$ ) appeared to be emerging between those in the highest and high score groups and those in the lowest positive schizotypy score groups ( $M = 0.13, 95\% \text{ CI } [-0.06, 0.33]$ ).

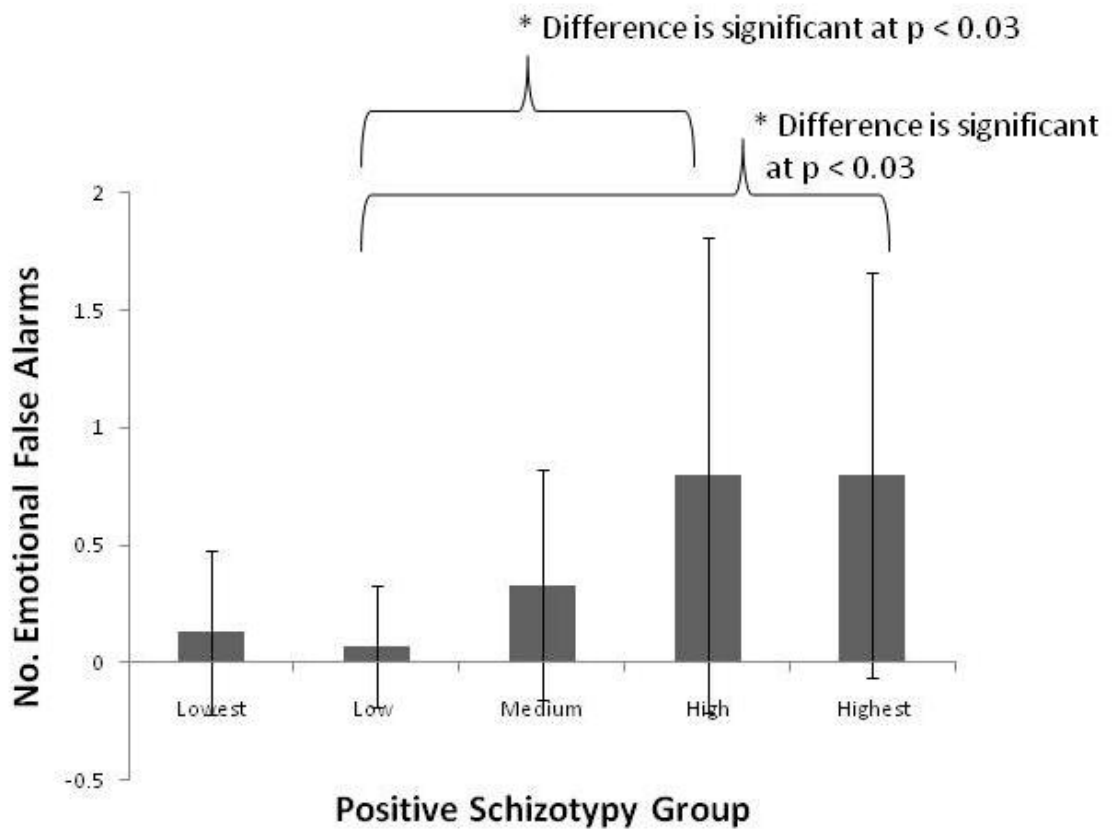


Figure 6.3. Mean number and standard deviation of emotional false alarms made in the delayed recall condition.

### 6.2.5.5 Recognition

The mean number of correct responses for emotional and neutral words, their respective latencies and the mean number of emotional and neutral false alarms made in the recognition paradigm for each positive schizotypy score group can be seen in Table 6.5.

Table 6.5. Mean (and standard deviation) recognition correct responses, latencies and false alarms for emotional and neutral words for each positive schizotypy group.

Cog Per Score	Low Group				High Group				Total			
	0		1-2		3-4		5-6		7-8		Total	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
<b>Emotional Accuracy</b>	13.07	2.01	13.33	2.05	13.60	2.47	14.27	1.44	13.80	2.60	13.61	2.14
<b>Neutral Accuracy</b>	12.67	1.95	13.80	2.08	13.07	1.91	13.73	2.15	13.60	1.80	13.37	1.98
<b>Emotional Time</b>	834.78	257.45	703.23	185.31	745.27	310.05	772.91	180.53	784.55	248.21	768.15	238.67
<b>Neutral Time</b>	815.40	200.63	708.39	211.10	715.25	248.51	768.01	232.75	754.55	199.03	752.32	216.80
<b>Emotional False Alarms</b>	2.87	1.99	3.13	1.64	3.93	1.58	3.07	2.12	3.87	2.03	3.37	1.88
<b>Neutral False Alarms</b>	1.40	1.05	1.13	1.06	1.13	1.06	1.40	1.35	1.33	0.82	1.28	1.06

Separate one way ANOVA analyses revealed that there were no significant differences between any of the positive schizotypy score groups in terms of the number of neutral or emotional items correctly recognised, for the time it took to undertake correct recognition of emotional and neutral words and for the number of neutral and emotional false alarms.

### 6.2.5.6 Correlation Analyses

Finally, Pearson correlation analyses were computed to assess the relationship between the cognitive perceptual measure of positive schizotypy and emotional recall and recognition in the immediate, delayed and recognition conditions.

These correlations can be seen in Table 6.6. As no associations between positive schizotypy and neutral recall, recognition or false alarms were manifest, only the correlations between positive schizotypy and emotional conditions will be presented.

As expected, many of the responses to emotional stimuli across the different conditions were positively correlated with one another. However, it is the associations between positive schizotypy and the dependent variables which are of particular interest to the current thesis. Positive schizotypal traits as measured by the Cognitive Perceptual sub-factor was positively associated with the accurate recall of emotional words in the immediate  $r = 0.26$ ,  $p < 0.05$  and delayed conditions  $r = 0.23$ ,  $p < 0.05$  and with the accurate recognition of emotional words  $r = 0.24$ ,  $P < 0.05$ . Positive schizotypal traits were also positively associated with increased false alarms in the immediate recall  $r = 0.37$ ,  $p < 0.01$ , and delayed recall conditions  $r = 0.39$ ,  $p < 0.01$

Table 6.6 Correlations between Cognitive Perceptual Traits and emotional immediate and delayed recall, recognition and false alarms.

	Cognitive Perceptual	Immediate Recall Emotional Accuracy	Immediate Recall Emotional False Alarms	Delay Emotional Accuracy	Delay Emotional False Alarms	Recognition Emotional Accuracy	Recognition Emotional Latency	Recognition Emotional False Alarms
Cognitive Perceptual		.26*	.37**	.23*	.39**	.24*	.03	.09
Immediate Recall Emotional Accuracy	.26*		.34**	.87**	.32**	.26*	-.07	-.03
Immediate Recall Emotional False Alarms	.37**	.34**		.32**	.83**	.09	-.07	-.04
Delay Emotional Accuracy	.23*	.87**	.32**		.26*	.33**	-.07	-.03
Delay Emotional False Alarms	.39**	.32**	.83**	.26*		.03	.05	.06
Recognition Emotional Accuracy	.24*	.26*	.09	.33**	.03		-.06	-.53**
Recognition Emotional Latency	.03	-.07	-.07	-.07	.05	-.06		-.10
Recognition Emotional False Alarms	.09	-.03	-.04	-.03	.06	-.53**	-.10	

\*Correlation is significant at the 0.05 level (2-tailed)

\*\* Correlation is significant at the 0.01 level (2-tailed)

### **6.2.6 CONCLUSION**

Whilst a significant difference was found between accuracy on emotional compared with neutral items across all participants contrary to the original hypothesis, performance on the emotional Stroop task did not vary between participants as a function of positive schizotypy. This demonstrates that the affective content of the emotional words was sufficient to interfere with accuracy for all participants but that it was not sufficient to cause specific cognitive disturbance (Mohanty et al., 2005) for participants with higher levels of positive schizotypy. Furthermore, the current results suggest that individuals with high schizotypy are able to inhibit the semantic content of words chosen to be emotionally relevant to their personality type. The lack of specificity of affective interference to participants with high positive schizotypal traits could be due to the theme of the emotional items. Whilst a previous study found affective content exacerbated cognitive disturbance in a Stroop task for participants with HPS (Mohanty, Koven, Fisher et al., 2001), the words in that study were related to threat rather than to psychosis proneness. Although biases have been found to be more pronounced in reasoning tasks using delusion-congruent stimuli (Rossell, Shapleske & David, 1998), it appears that the analogy made in the current study between delusion-congruent stimuli and individuals with delusions and positive schizotypal congruent stimuli and individuals with HPS is not sufficient to induce behaviourally manifest cognitive disturbances in the context of non clinical positive schizotypy. In light of previous findings of neural activation differences in HPS in the absence of behavioural differences (Mohanty et al., 2005, Hori et al., 2005), another interpretation could propose that whilst HPS participants do not appear to differ in response to affective content behaviourally, they are achieving this normative result through recruitment of quite different brain systems.

Unfortunately, it is impossible to verify this possibility as neuroimaging techniques were not utilised in the current study.

The lack of statistical difference between the behavioural responses to the emotional Stroop task demonstrated by individuals with high and low levels of positive schizotypy may also be consequent of methodology which may be masking possible emotional interference. One school of thought regarding the emotional Stroop effect is that emotional interference arises from slow effects of the current emotional trials on successive trials (McKenna & Sharma, 2004).

Whereas the methodology employed in the current study was based on an assumed fast effect of the current trial. The mixed design was chosen based on significant findings of emotional interference in previous work (Mohanty et al., 2001). However, more recent findings suggests that a mixed design Stroop is effective for fMRI but that this is not generalisable to behavioural studies where blocked designs should be employed. In fact recent work which has found fMRI effects in the absence of behavioural effects in mixed trial presentations such as that employed in the current study to be responses to emotional salience rather than emotional conflict (Haas, Omura, Constable & Canli, 2006; Taake, Jaspers-Fayer & Liotti, 2009). Whilst responses to emotional salience are more in line with the current hypothesis than are responses to emotional conflict, the mixed design method in the absence of brain imaging technology has made it unclear whether high PS participants are responding any differently than LPS participants.

The results of the original Stroop task were in line with the original hypothesis, and suggest that individuals with HPS do not share the attentional deficits that have frequently been associated with schizophrenia (Braver, Barch & Cohen,

1999; Barch, Carter, Braver et al., 2001). Whilst significant differences were found between accuracy and latencies for congruent compared with incongruent stimuli across all participants, no associations arose between positive schizotypy and either an inability to maintain and process contextual task related information or from issues with the inhibition of information.

Of interest however, are the findings from the incidental learning task used in this experiment. In the immediate recall condition, participants with HPS recalled significantly more emotional words than those with LPS. This is consistent with the positive correlation found between positive schizotypy and higher accuracy for emotional words in the immediate recall condition and is in line with evidence that individuals with HPS appear attentionally predisposed to attend to delusion congruent stimuli (Rossell, Shapleske & David, 1998), although as the emotional Stroop data suggest, this predisposition does not impair cognitive performance. However, whilst the lack of statistical significance identified by the ANOVA analysis suggests this bias decayed over time as the number of emotional words produced by HPS participants after a ten minute delay did not significantly differ from the number produced by any other positive schizotypy score group, correlational analysis demonstrated that positive schizotypy is positively associated with higher emotional recall accuracy in the delayed condition. This heightened accuracy for emotional stimuli extends to the recognition condition as a significant positive association between positive schizotypy and increased accuracy for emotional words was also evident in the recognition condition.

In line with the original hypotheses, in both the immediate and delay conditions significant differences were evident between the number of false alarms made by



participants with the highest positive schizotypy traits and those in the medium and low groups, and between the highest and low and the high and low groups respectively. For both conditions there also appeared to be a trend emerging for a significant difference between the highest and lowest groups. Correlational analyses were consistent with this trend and evidenced that positive schizotypy is positively associated with increased false alarms for emotional words in both immediate and delayed recall conditions. These findings are consistent with a previous study which found participants with high scores on a psychometric measure of delusional ideation demonstrate an increased proclivity for making false positive responses to memory tasks (Laws & Bhatt, 2005). However whilst Laws and Bhatt's (2005) study also found associations between delusional ideation and poorer overall memory, no evidence for such an association was established in the current study. On the contrary, the fact that HPS participants made no false alarms on neutral items suggests that false positive errors on emotional items do not arise from impaired memory but are mediated by a different mechanism. The current findings, in combination with evidence that false memory in schizophrenia may subserve delusions (Moritz et al., 2004), suggest a similar mechanism may underlie the association between false positive memory biases and delusion susceptibility in non clinical positive schizotypy.

The results of the recognition paradigm concur with previous studies which have found that whilst individuals across the dimensional and quasi dimensional schizotypy spectrum appear to make more false positive errors in recall memory, this bias does not extend to recognition memory. Intact recognition memory has also been demonstrated in schizophrenia (Mathews & Barch, 2004) and SSD (Herlitz & Forsell, 1996). The fact that there were no differences between high

and low positive schizotypy in terms of recognition memory also suggests that HPS participants were paying sufficient attention to the task (Laws & Bhatt, 2005).

The current findings that high positive schizotypy is associated with false alarms in immediate and delayed recall is also in line with several studies from recall based experimental contexts. A growing body of evidence supports the association between false positive responses and schizotypal traits. For instance, several studies have demonstrated that psychometrically defined non clinical hallucination prone participants are more likely to report false experiences of voices (Bentall & Slade, 1985; Rankin & O'Carroll, 1995; Barkus, Stirling, Hopkins et al., 2007). Converging neuroimaging data suggests that the brain regions involved in these false alarms in non clinical hallucination prone individuals mirrors those which subserve auditory hallucinatory experiences in schizophrenic participants (Barkus et al., 2007). Novel word detection paradigms have also been used to demonstrate a detection bias in individuals with schizotypy, where high schizotypy has been associated with a tendency to report words that were not present in trials. Such results have been interpreted in relation to the schizotypal trait of translating internal experience into external experience (Tsakanikos & Reed, 2005). Similarly, Frith (1996) argues the inability to attribute appropriate agency to events or to distinguish between internally and externally generated events is due to a functional disconnection between frontal and posterior brain regions which are involved in action and perception respectively. It follows that along the schizotypy continuum such a disconnection may lead to false mnemonic alarms in non clinical psychosis prone individuals and to the manifestation of psychotic experiences in persons who are more clinically

susceptible. An alternative explanation of these results might suggest the association between HPS and increased false positive responses for emotional words in immediate and delayed recall is attributable to increased semantic spreading (Spitzer, 1997) whereby an abnormal facilitation of the spreading activation within semantic networks creates plausible but incorrect semantic associates of the words that were originally presented.

These findings may be best interpreted in light of what is known about the general effects of emotion and mood on memory in terms of mood-congruent memory bias in normal individuals. Studies in this area have demonstrated that in healthy participants there is a bias to have both greater recall of old memories for emotional words and also to produce more false memories for emotional words (Windman & Kutas., 2001). This has been described as a switch to a more liberal criterion for emotional memory in the context of emotional stimuli. Furthermore, it has been argued that this 'emotion based recognition bias' may be of some adaptive value. In addition there is some electrophysiological evidence that an emotion based recognition bias is accompanied by more frontal responses (Windman & Kutas., 2001). In the current study this bias was pronounced in the high positive schizotypy group compared to those with lower schizotypal traits, this suggests these individuals have an exaggerated emotion based recognition bias which mirrors the liberal acceptance bias which is one of the core cognitive biases that has frequently been observed in these individuals.

Finally, the way in which false positive memories of emotional words extends to the delayed condition in non clinical schizotypy may be analogous with the confabulations in episodic memory that have been associated with clinical

delusions (Lee et al., 2007). The way in which confabulations in episodic memory have been related to delusions in AD (Lee et al., 2007) and in SDD (Herlitz & Forsell, 1996) suggests that there may be a continuum whereby episodic memory systems may be more susceptible to false positive errors in non clinical psychosis prone individuals, whereas for pathological populations, greater impairments in such memory systems may be associated with full blown delusion formation and maintenance. Further studies are necessary to explore the extent to which an association between episodic memory, false memory, confabulation and delusion proneness or the relationship between semantic spreading and psychosis can advance explanations of the current findings.

### ***6.3 EXPERIMENT 2A - AUTOBIOGRAPHICAL MEMORY***

Ecologically valid paradigms have become increasingly popular in the study of cognitive processes, both at the behavioural and at the neural levels (Ivanoiu et al., 2006). Accordingly, a growing number of studies have investigated real-life autobiographical memory (ABM).

ABM paradigms are different from typical laboratory memory tasks that require the encoding and retrieval of experimentally generated stimuli. In studies of ABM, participants recall events from their own history that are more distinct and of greater personal significance than laboratory stimuli. This promotes the subjective re-experiencing of emotions, sensory characteristics, and temporal, spatial and perceptual context of events (Conway, 2001). Autobiographical memory (AM) entails a complex set of operations, including episodic memory, self-reflection, emotion, visual imagery, attention, executive functions, and

semantic processes. The heterogeneous nature of ABM poses significant challenges in capturing its behavioural and neuroanatomical correlates.

Episodic ABM refers to memories of events or incidents that happened in the past. These memories can be recalled in detail and are almost re-experienced like a form of ‘mental time travel’ (Tulving, 1983). We produce or reconstruct these specific memories through generative retrieval to form a memory that has an ‘if one was there nature’ (Nelson, 1993). In contrast, semantic ABM’s are comprised of personal factual information such as memory for addresses, names of friends etc.

As delusions involve alterations in personal meaning and belief, they have often been interpreted as manifestations of abnormal semantics. As our beliefs and personal salience are formed on the basis of prior knowledge, belief structures and personal experience, all of which are stored in semantic memory (Sellen, Oaksford & Gray, 2005), it follows that disruptions to this system may lead to delusional ideation. By nature, autobiographical memory (ABM) involves innately personal semantic memories and therefore the study of autobiographical memory (ABM) within individuals with high positive schizotypy may yield especially meaningful information regarding the mechanisms that may subserve semantic spreading and delusions.

Furthermore, the study of ABM should also facilitate investigation of the interplay between positive schizotypy and episodic memory. As previously emphasised, semantic memory abnormalities are well documented in the schizophrenia literature. However, episodic memory deficits are equally important for

understanding the mechanisms that underlie the formation of delusions. Episodic memory deficits are frequently reported in schizophrenia (Aleman et al., 1999; Danion et al., 2007; Lepage et al., 2007) and certain episodic memory biases have been related to delusional ideation (Lepage et al., 2007). However, whilst the association between impaired episodic memory and schizophrenia may appear robust, the results are not without equivocation and consequently the constituent cognitive, behavioural and neuroanatomical implications of an episodic memory deficit in schizophrenia have not been fully characterised (Leavitt & Goldberg, 2009).

Inconsistent findings are likely to be a consequence of the various ways episodic memory has been experimentally tested. Apart from needing to be contextualised into an episode (Tulving 1979), episodic memory must be highly self significant and attached to autobiographical structures (Conway, 2001). Consequently a comprehensive assessment of episodic ABM such as that provided by the autobiographical memory questionnaire (Ivanou et al., 2006) will be used to circumvent these issues. The structure of this instrument also facilitates parallel semantic ABM assessment and therefore, semantic and episodic ABM scores are more reliably commensurate.

Furthermore, as ABM is inherently associated with the self and personal identity (Riutort et al., 2003) it ought to provide salient insights into the memory mechanisms at play in individuals with a propensity for delusional ideation as delusions have been conceptualised as being ostensibly a neuropathology of the self (Fienberg & Keenean, 2005). In light of such a characterisation it will be of interest to understand more about the structure of personal episodic and semantic

memory in individuals whose personality type intrinsically suggests a propensity for an abnormal personal identity. This argument follows from findings that demonstrate impaired personal episodic and semantic memory and reduced autobiographical memory in individuals with schizophrenia (Riutort et al., 2003). Whilst the extent to which these deficits can be associated with abnormal personal identity is somewhat unclear, due to the cognitive deficits that obfuscate this interpretation, the assessment of non clinical psychosis prone individuals such as high positive schizotypies may help to clarify the relationship.

Furthermore, the study of semantic and episodic ABM in individuals with traits residing across the spectrum of positive schizotypy will be especially interesting in light of the findings reported in the previous study. Further investigation of separate episodic and semantic systems for personal memory may help to clarify the extent to which psychosis proneness is associated with altered semantic or episodic memory.

### ***6.3.1 METHOD***

### ***6.3.2 PARTICIPANTS AND SPQ***

The participants in the current experiment are the same as those who participated in experiments 2 and 3 in Chapter 4 and experiment 2 in Chapter 5. Please refer to sections 4.3.1, 4.3.2 and 4.3.3 for details of the participants, the general health questionnaire and the full SPQ.

### ***6.3.3 AUTOBIOGRAPHICAL MEMORY QUESTIONNAIRE***

The Autobiographical Memory Questionnaire (Ivanou et al., 2006) was used as the ABM measure in the present study. This questionnaire's structure distinguishes between cued and free semantic and episodic autobiographical

memories and provides separate scores for the two types of memory. In the current study, due to the heterogeneity in participant's ages only episodic and semantic questions from the childhood (age 4 – 16 years) and the recent period (the last 5 years) were included.

### 6.3.4 RESULTS

The mean scores for semantic and episodic ABM for child and recent periods in both cued and free retrieval conditions for the whole group of participants (N=75) can be found in Table 6.7.

Table 6.7. Mean scores for semantic and episodic ABM for both life periods for cued and free retrieval conditions.

	Semantic				Episodic			
	Child		Recent		Child		Recent	
	M	SD	M	SD	M	SD	M	SD
<b>Cued</b>	<b>20.60</b>	<b>2.45</b>	<b>19.33</b>	<b>2.59</b>	<b>19.69</b>	<b>4.60</b>	<b>19.10</b>	<b>4.77</b>
<b>Free</b>	<b>26.35</b>	<b>7.94</b>	<b>26.20</b>	<b>7.29</b>	<b>29.55</b>	<b>11.37</b>	<b>26.75</b>	<b>11.28</b>
<b>Total</b>	<b>46.95</b>	<b>8.42</b>	<b>45.53</b>	<b>8.31</b>	<b>49.24</b>	<b>12.48</b>	<b>45.85</b>	<b>12.95</b>

For semantic memory, paired samples t-tests (2-tailed) revealed a significant difference between the scores for childhood and the recent period in the cued condition ( $t(74) = 3.64, p < 0.001$ ) whereby participants retrieved more semantic detail for the childhood ( $M = 20.6, SD = 2.45$ ) than for the recent period ( $M = 19.33, SD = 2.59$ ). For the episodic memory condition, paired samples t-tests (2-tailed) revealed a significant difference between the scores for childhood and recent in the free condition ( $t(74) = 2.56, p < 0.01$ ) where participants retrieved



more episodic detail for the childhood ( $M = 29.55$ ,  $SD = 11.37$ ) than for the recent period ( $M = 26.75$ ,  $SD = 11.28$ ), this was also reflected in the episodic total scores where there was a significant difference between the total scores for the childhood compared with the recent period ( $t(74) = 2.53$ ,  $p < 0.01$ ) where participants again retrieved more episodic detail for the childhood ( $M = 49.24$ ,  $SD = 12.48$ ) than for the recent period ( $M = 45.85$ ,  $SD = 12.95$ ).

As there were no a priori hypotheses speculating that differences between childhood and recent ABM could be somehow related to positive schizotypal traits, further statistical analyses will focus on combined childhood and recent ABM scores. The combined childhood and recent ABM scores for semantic memory can be found in Table 6.8, those for episodic memory can be found in Table 6.9.

Table 6.8. Mean (and standard deviation) total semantic ABM scores for the cued and free conditions for each positive schizotypy group.

Cog Per Score	Low Group						High Group				Total	
	0		1-2		3-4		5-6		7-8		Total	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
<b>Cued</b>	<b>40.67</b>	<b>4.12</b>	<b>42.13</b>	<b>4.90</b>	<b>37.27</b>	<b>3.56</b>	<b>39.20</b>	<b>2.51</b>	<b>40.40</b>	<b>3.11</b>	<b>39.93</b>	<b>4.04</b>
<b>Free</b>	<b>52.20</b>	<b>14.68</b>	<b>50.87</b>	<b>14.16</b>	<b>54.80</b>	<b>12.34</b>	<b>55.27</b>	<b>13.55</b>	<b>49.60</b>	<b>11.29</b>	<b>52.55</b>	<b>13.09</b>
<b>Total</b>	<b>92.86</b>	<b>16.37</b>	<b>93.00</b>	<b>15.19</b>	<b>92.07</b>	<b>13.79</b>	<b>94.47</b>	<b>13.06</b>	<b>90.00</b>	<b>13.84</b>	<b>92.48</b>	<b>14.18</b>

Separate one way ANOVA analyses revealed that there were no significant differences between any of the positive schizotypy score groups in terms of the cued, free and total semantic ABM scores.

Table 6.9. Mean (and standard deviation) total episodic ABM scores for the cued and free conditions for each positive schizotypy group.

Cog Per Score	Low Group						High Group				Total	
	0		1-2		3-4		5-6		7-8		Total	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
<b>Cued</b>	<b>41.33</b>	<b>10.09</b>	<b>41.07</b>	<b>9.38</b>	<b>33.33</b>	<b>7.35</b>	<b>38.00</b>	<b>4.63</b>	<b>40.27</b>	<b>7.17</b>	<b>38.80</b>	<b>8.30</b>
<b>Free</b>	<b>41.87</b>	<b>14.47</b>	<b>49.87</b>	<b>18.14</b>	<b>57.73</b>	<b>20.79</b>	<b>63.47</b>	<b>12.60</b>	<b>68.53</b>	<b>25.01</b>	<b>56.29</b>	<b>20.59</b>
<b>Total</b>	<b>83.20</b>	<b>19.90</b>	<b>90.93</b>	<b>17.74</b>	<b>91.07</b>	<b>24.07</b>	<b>101.47</b>	<b>13.87</b>	<b>108.80</b>	<b>28.19</b>	<b>95.09</b>	<b>22.64</b>

Separate one way ANOVA analyses revealed that there was a significant difference between the groups for the episodic free retrieval condition ( $F[4,70] = 4.84, p = 0.002$ ) and for the total episodic score ( $F[4,70] = 3.32, p = 0.02$ ).

Bonferroni post-hoc analysis comparisons of the five groups indicate that the mean free episodic scores were significantly different between individuals in the highest 5 % cut off (scorers of 7-8) for positive schizotypy ( $M = 68.53, 95\% \text{ CI } [54.69, 82.38]$ ) and those in the lowest PS group who scored 0 on the PS measure ( $M = 41.87, 95\% \text{ CI } [33.85, 49.88]$ ). Bonferroni post-hoc analysis comparisons of the five groups also indicated that the mean total episodic scores were significantly different between individuals in the highest 5 % cut off (scorers of 7-8) for positive schizotypy ( $M = 108.80, 95\% \text{ CI } [93.19, 124.41]$ ) and those in the

lowest PS group who scored 0 on the PS measure ( $M = 83.20$ , 95% CI [72.18, 94.22]), as this significance is driven by the variance in the free episodic condition, the results for total episodic have not been illustrated.

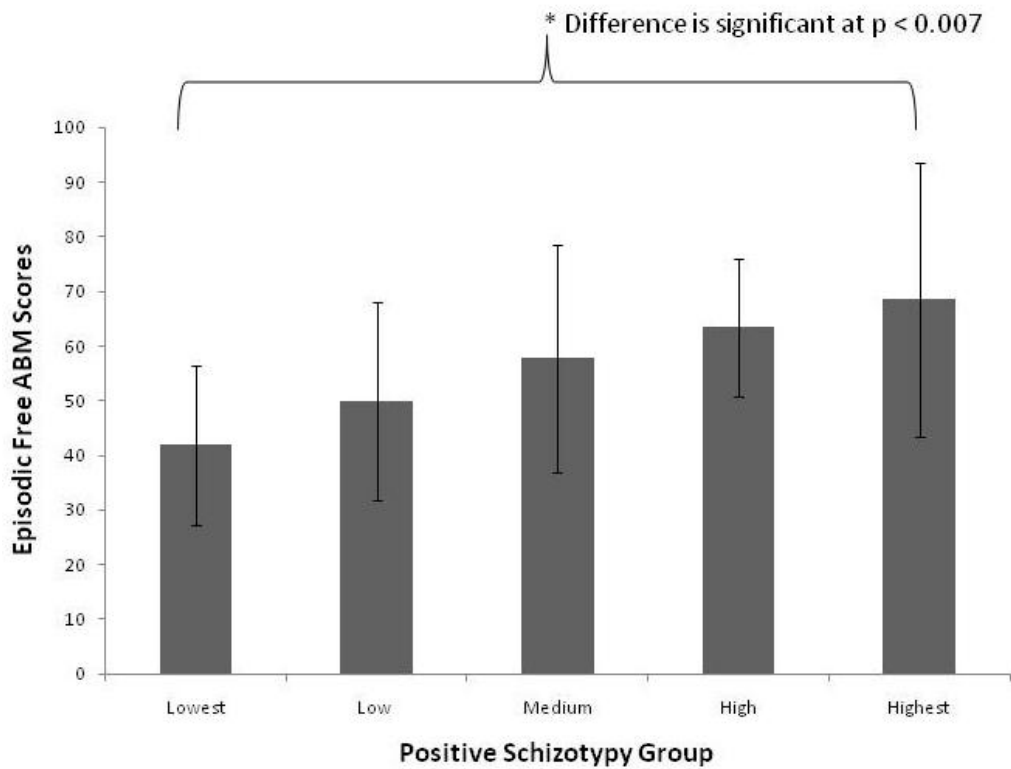


Figure 4.6. Mean (and standard deviation) episodic memory scores for the free retrieval condition for each positive schizotypy score group.

### **6.3.5 CONCLUSION**

No differences between any of the positive schizotypy score groups were manifest in any semantic autobiographical memory retrieval condition. This suggests that semantic ABM scores in persons with high levels of positive schizotypy are not behaviourally dissociable from the scores of individuals with fewer positive traits.

However, significant differences between those with the highest and lowest positive schizotypal traits were manifest on the scores for free retrieval of episodic

memory, whereby individuals with higher positive schizotypy achieved higher episodic memory scores in the free retrieval condition. This significance also drove the total episodic ABM (as the total is comprised of cued and free) scores to be significantly different between the highest and lowest PS groups. These results are somewhat contrary to the association of impaired episodic memory and schizophrenia (Aleman et al., 1999; Danion et al., 2007; Lepage et al., 2007; Leavitt & Goldberg, 2009). However, as episodic memories must be highly associated to the self in order to become connected to autobiographical structures (Conway, 2001), the current findings can be interpreted in light of the highly referential predisposition of individuals with high positive schizotypy. Further examination of the data revealed that rather than being due to the number of episodic memories in the free retrieval condition, the significant difference was most likely to be due to the fact that HPS participants produced memories that were more detailed and specific. It was also noted that several of the memories recalled by HPS participants in the episodic free condition were quite peculiar and reflected many core schizotypal themes. This may explain why there were no differences between HPS groups in the cued episodic memory condition, where responses are much more constrained by the initial cues. However, further qualitative analyses of these responses would be necessary to validate this claim. A further limitation of the current study is that whilst individuals with HPS produced more episodic free ABM's than those in the lowest HPS group, it is very difficult to verify the validity of these memories or to identify false memories or exaggerations. In fact, two participants in the HPS group spontaneously offered to recall memories that they had once firmly believed but now know to be false. Consequently, and without further investigation, it is difficult to know how to interpret these results.

However, the current findings in combination with the association between false positive memory and psychosis proneness in the prior study do appear to suggest that episodic memory is somewhat altered in HPS. Whilst further evidence is necessary to clarify exactly what this alteration means, a tentative hypothesis could be offered in light of the associations between episodic memory and the presence of delusions which has been reported in dementia research. In Alzheimer's disease, confabulations in episodic memory have been found to be associated with delusions (Lee et al., 2007). Similarly, in the prior study false alarms in the delayed paradigm were associated with delusion prone participants.

### ***6.4 EXPERIMENT 3 - NEUROANATOMICAL CORRELATES OF POSITIVE SCHIZOTYPAL TRAITS***

In the current study, a hypothesis proposing that biological asymmetry of the frontal lobes in positive schizotypy may be sufficient to justify the confabulatory behaviour evidenced in the first and possibly in the second study will be tested.

Recent neuroimaging advances have expanded explanations of individual differences in certain personality dimensions through the characterisation of the relationship between structural variance in specified brain structures and distinct personality traits (Gardini et al., 2009). Whilst non-clinical positive schizotypy has been identified as a vulnerability factor for schizophrenia, in the normal population, characteristic positive traits such as aberrant perceptual experiences and negative traits including anhedonia and disorganisation appear to be dimensionally expressed. Individual differences in the expression of schizotypal traits have been found to be heritable, to depend on genetic and neurobiological factors and to be associated with cognitive, behavioural and emotional functions.

However, the mechanisms which mediate the variation and expression of schizotypal traits are not well defined. The aim of the current study was to identify the neural substrates which subserve positive schizotypal personality dimensions.

As discussed in Chapter 2, in relation to schizotypy, studies have so far concentrated on the relationship between schizotypal traits and the brain in terms of; hemispheric asymmetry (Gruzelier & Doig, 1996; Leonhard & Brugger, 1998; Nunn & Peters, 2001; Weinstein & Graves, 2002), electrophysiology (Kidd & Powell, 1993; Kimble, Lyons, O'Donnell, et al., 2000), and neurotransmitter activity (Siever et al., 1993). In addition, positive schizotypy has independently been associated with variance in synaptic density (Gruzelier & Kaiser, 1996), neurochemical dopaminergic dysfunction (Siever et al., 1993) electrophysiological deficits (Perry et al., 1997; Salisbury et al., 1996) and with neurological soft signs (Barkus, et al., 2006).

Studies investigating grey matter differences in individuals with Schizotypal Personality Disorder have found sulcal enlargement (Cannon et al., 1994), reduced grey matter volume in the left superior temporal gyrus (Dickey et al., 1999) and larger ventricular brain ratios (Siever et al., 1995), which are consistent with neuroimaging results reported for schizophrenia. However, fewer studies have assessed the relationship between brain structure and schizotypy. Whilst an early study reported that reduction of prefrontal volume was associated with higher levels of trait schizotypy (Raine et al., 1992) a more recent study described positive associations between positive schizotypy and increased grey matter tissue volume in specific brain regions (Modinos et al., 2009). In this study, individuals

with high positive schizotypy, when compared with participants with low positive schizotypal traits were found to have larger global volumes and larger regional volume in the medial posterior cingulate and the precuneus (Modinos et al., 2009). Whilst differences in the posterior cingulate and precuneus have been reported in prior neuroimaging studies of schizophrenia patients (Mitelman, Shihabuddin, Brickman et al., 2005), persons with first episode psychosis (Koo, Levitt, Salisbury et al., 2008), individuals with at-risk mental state (Pantelis, Velakoulis, McGorry et al., 2003) and in people with SPD (Modinos et al., 2009) in contrast to Modinos et al.'s findings of increased grey matter, these studies all reported that *reduced* grey matter volumes in these regions were associated with schizophrenia and related spectrum disorders. A limited number of earlier studies have reported associations between increased grey matter volume and schizophrenia spectrum disorders (Shin. Lee, Kang et al., 2005; Philips, Velakoulis, Pantelis et al., 2002); however, in the majority of studies it is reduced grey matter volume which has been associated with schizophrenia and spectrum disorders. Modinos et al., (2009) propose that the association of increased grey matter volume in high positive schizotypy may be due to delayed synaptic pruning (Gotay, Giedd, Lusk et al., 2004).

Apart from the result that high positive schizotypy was associated with *increased* grey matter, based on the relationship between positive schizotypy and psychosis proneness, it is also surprising that no pre-frontal correlations were detected (Raine et al., 1992; Bruen et al., 2008; Pantelis et al., 2003). Especially in light of the neuroimaging and behavioural studies that have found evidence for frontal asymmetry in positive schizotypy (Gruzelier & Doig, 1996; Leonhard & Brugger, 1998; Nunn & Peters, 2001; Weinstein & Graves, 2002) and in anatomical studies

of delusions (Forstl et al., 1991; Staff et al., 1999; Venneri et al., 2000; Sulzer et al., 2003; Shanks & Venneri, 2004; Bruen et al., 2008). A putative relationship between positive schizotypy and frontal asymmetry would also be consistent with the results of the previous two studies because the higher false alarms for delusion themed words and the possible false or exaggerated personal episodic remembering could be justified in relation to this predominantly right sided asymmetry in right and left frontal structures. Moreover, evidence for the theory that altered episodic memory retrieval may contribute to delusion formation has been provided by behavioural (Lee et al., 2007) and neuroimaging studies demonstrating associations between delusions and hypoperfusion of (Staff et al., 1999; Venneri et al., 2000) and reduced cerebral grey matter (Bruen et al., 2008) in the right frontal lobe. As this structure is consistently related to episodic memory retrieval, it follows that dysfunctional episodic memory could subserve the emergence of delusions. Whereas in a non clinical presentation such as positive schizotypy such associations may be manifest as false positive remembering.

The results of the Modinos et al., (2009) study may also be due to the small sample size ( $n=38$ ) and the lack of variance between the high and low PS groups in terms of the positive schizotypy measure which was derived from the Community Assessment of Psychic Experiences (CAPE) scores as the low PS group ( $n=20$ ) had a mean of 1.12 ( $SD = 0.04$ , range 0 – 15) and the high PS group ( $n = 18$ ) had a mean of 1.75 ( $SD = 1.15$ , range 0 – 50), it seems the mean difference between the groups is small for a group differences neuroimaging study and looking at the range and the standard deviations, the significance appears to be driven by a few extreme outliers in the high group. Furthermore, the CAPE



assessment measure of positive schizotypy used in the Modinos study may be less sensitive to the detection of dimensionally continuous positive schizotypal traits as it is comprised of more 'pathological items' (Modinos et al., 2009, p.7) which may again explain the apparent lack of variance in the non-clinical population to which it was administered. To circumvent these issues in the current study the Cognitive Perceptual sub factor of SPQ (Raine, 1991) will be used to assess positive schizotypy in a large group of non clinical individuals, these scores will subsequently be regressed against the grey matter tissue values of each participant which will be treated as continuous variables in the general linear model. Positive and negative correlations will also be conducted. The incongruent results may also be an artefact of a more general methodological issue of adopting a group differences as opposed to a multiple regression approach. Whilst high-low differences may be appropriate for behavioural studies (Langdon & Coltheart, 2004) they may be less suitable for neuroimaging anatomical studies where greater variance may be needed to detect salient associations. Whilst it would have been advantageous to look at both whole group and high/low comparisons, because in the behavioural studies in the current thesis the significant effects are typically within participants in the high and low extremes, the individuals recruited for this neuroimaging study were an opportunity sample and as such there were insufficient numbers in the high and low cut offs to perform tests of difference between high and low scorers. Consequently multiple regression of the relationship between positive schizotypy and cortical gray matter volume was the only appropriate methodology.

The central purpose of the current study is to assess whether the specific regional associations found to be associated with delusions in previous studies may be due

to individual differences in structural genetic vulnerability (Bruen et al., 2008).

Thus in the current study the extent to which individual differences in schizotypal traits in normal individuals, are associated with variance in the brain regions which have been related to psychosis in previous studies will be assessed.

Consequently, in the current study it was predicted that positive schizotypy would be inversely associated with areas of less grey matter volume in the right and left frontal lobes and that this lower volume would be predominantly manifest as frontal asymmetry with a larger association in the right compared with the left frontal lobe. The hypothesis of the current study was informed by the anatomical and behavioural evidence for asymmetry of frontal structures in positive schizotypy, from the findings of such a pattern of frontal asymmetry in studies of delusions (Forstl et al., 1991; Staff et al., 1999; Venneri et al., 2000; Sulzer et al., 2003; Shanks & Venneri, 2004; Bruen et al., 2008) and from the behavioural and anatomical associations between delusions, confabulation and impairments in episodic memory (Lee et al., 2004; 2007; Bruen et al., 2008).

#### ***6.4.1 PARTICIPANTS***

In total, 80 young adult healthy individuals were recruited to participate in the current study. The group consisted of 36 males and 44 females with a mean age of 26.64, *SD* 6.38 and their mean number of years of education was 17.43, *SD* 2.96.

#### ***6.4.2 SCHIZOTYPAL PERSONALITY QUESTIONNAIRE***

Please refer to Chapter 4, section 4.3.3 for full details of the SPQ.

#### ***6.4.3 VOXEL BASED MORPHOMETRY***

The neuroimaging analysis technique of voxel-based morphometry (VBM) allows a voxel-by-voxel comparison of tissue concentration to enable analysis of focal differences in brain volume. The value of VBM lies in its unbiased objective scope for comprehensive measurement of differences throughout the whole brain rather than techniques which are biased to investigation of specific structures (Ashburner & Friston, 2000; 2001). Three dimensional T1-weighted MRI images were acquired on a 3 Tesla Philips Achieva MRI system with a Turbo Field Echo sequence. Voxel dimensions were 1 x 1 x 1 mm and field of view was 256 mm with a matrix size of 256 x 256 x 124. Total acquisition time was 4 minutes 41 seconds (TR 9.9 msec, TE 4.6 msec and flip angle 8°).

A number of preprocessing steps were carried out to isolate the grey matter from the 3D T1-weighted structural scans before performing the statistical analysis using SPM5 (Wellcome Department of Imaging Neuroscience, UCL, London, UK). To correct for global differences in brain shape, structural images were warped to standard stereotactic space (normalised to the brain template provided by the Montreal National Institute) and segmented to extract grey matter, white matter and cerebrospinal fluid. The grey matter segments obtained through this procedure were then modulated to correct for changes in volume induced by nonlinear normalisation and smoothed using a Gaussian filter set at 12mm to reduce possible error from between-subject variability in local anatomy and to render the data more normally distributed. Previous research suggests that smoothing with a 12 mm kernel reduces the risk of false positive findings (Rosen et al., 2005). Finally the pre-processed grey matter segments were entered into a series of voxel-based multiple regression analyses to investigate linear correlations between grey matter concentration and positive schizotypy scores as

defined by the Cognitive Perceptual sub factor of the SPQ. Age, sex and education were included in the model as covariates.

#### 6.4.4 RESULTS

Participant demographics and schizotypy scores for the total group and separated scores for males and females can be found in Table 6.10. Independent t-tests (based on Levene's test for equality of variances) revealed that the only significant difference between the sexes was age ( $t(75) = -2.33, p < 0.02$ ) where females ( $M = 28.05, SD 7.20$ ) were significantly older than the males ( $M = 24.92, SD 4.77$ ). Consequently, age was included in the regression model as a covariate.

Table 6.10. Mean (and standard deviation) demographic and Schizotypy scores for the full group and by gender.

	Full Group n=80		Males n=36		Females n=44	
	M	SD	M	SD	M	SD
Age	26.64	6.38	24.92	4.77	28.05	7.20
Education	17.43	2.96	16.89	2.93	17.88	2.94
SPQ	12.96	9.53	12.78	9.43	13.11	9.73
Cognitive Perceptual	4.64	4.29	3.83	3.64	5.30	4.70
Interpersonal	6.46	5.70	6.58	6.02	6.36	5.49
Disorganised	3.39	3.0	3.53	3.36	3.27	2.86

Correlations between demographic variables and schizotypal traits for the whole group can be seen in Table 6.11. Age was significantly positively correlated with education  $r = 0.28, p < 0.05$  and with sex  $r = 0.25, p < 0.05$ . Education was significantly inversely associated with Cognitive Perceptual traits  $r = -0.27, p < 0.05$ . Consequently alongside age, sex and education were included in the regression model as covariates. In line with the results from previous studies

including those within the current thesis the SPQ was very highly positively correlated with its sub factors and its sub factors were moderately significantly positively correlated with one another.

Table 6.11 Correlations between demographic and schizotypal traits for the full group n = 80.

	Age	Ed	Sex	SPQ	Cognitive Perceptual	Interpersonal	Disorganised
Age		.28*	.25*	.01	-.06	.06	-.01
Ed	.28*		.17	-.22	-.27*	-.20	-.19
Sex	.25*	.17		.02	.17	-.02	-.04
SPQ	.01	-.22	.02		.81**	.86**	.70**
Cognitive Perceptual	-.06	-.27*	.17	.81**		.59**	.41**
Interpersonal	.06	-.10	-.02	.86**	.59**		.40**
Disorganised	-.01	-.19	-.04	.70**	.41**	.40**	

\*Correlation is significant at the 0.05 level (2-tailed)

\*\* Correlation is significant at the 0.01 level (2-tailed)

Whilst participants completed the full SPQ, due to the focus of the current thesis, only the voxel based morphometric results for the Cognitive Perceptual sub factor will be presented. Whilst both positive and negative regressions were examined, only the inverse regressions were statistically significant. The brain regions where higher Cognitive Perceptual scores were discretely inversely associated with lower grey matter tissue volume can be seen in Table 6.12 and in Figures 6.7 and 6.8. All correlations reported were thresholded at 20 voxels and were significant at  $p < 0.01$ .

Table 6.12. Areas of significant inverse correlation with Cognitive Perceptual traits.

Brain area	Left/ Right	Brodmann area (BA)	Cluster size	Z value at local maximum	Taliarach Coordinates		
					x	y	z
Medial Frontal	R	10	286	3.51	12	41	13
		8	52	2.68	16	29	43
Inferior Frontal	R	45	158	3.35	48	20	14
				2.53	48	31	4
Superior Frontal	R	10	165	3.21	22	56	-10
		6	38	2.64	12	12	52
Middle Frontal	R	10	64	2.59	36	45	11
Precentral	R	9	28	2.57	38	6	44
Cingulate	R	24	174	3.18	12	-7	45
		32		2.74	8	8	42
Middle Temporal	R	39	20	2.75	38	-61	20
Inferior Frontal	L	47	54	2.65	-34	21	-14
Medial Frontal	L	9	35	2.59	-8	40	18
Superior Frontal	L	9	56	2.51	-20	40	33
Middle Frontal	L	8		2.5	-18	35	39
Cingulate	L	32	88	2.48	-6	15	32
				2.41	-8	6	42
Anterior Cingulate	L	33		2.36	-6	12	26

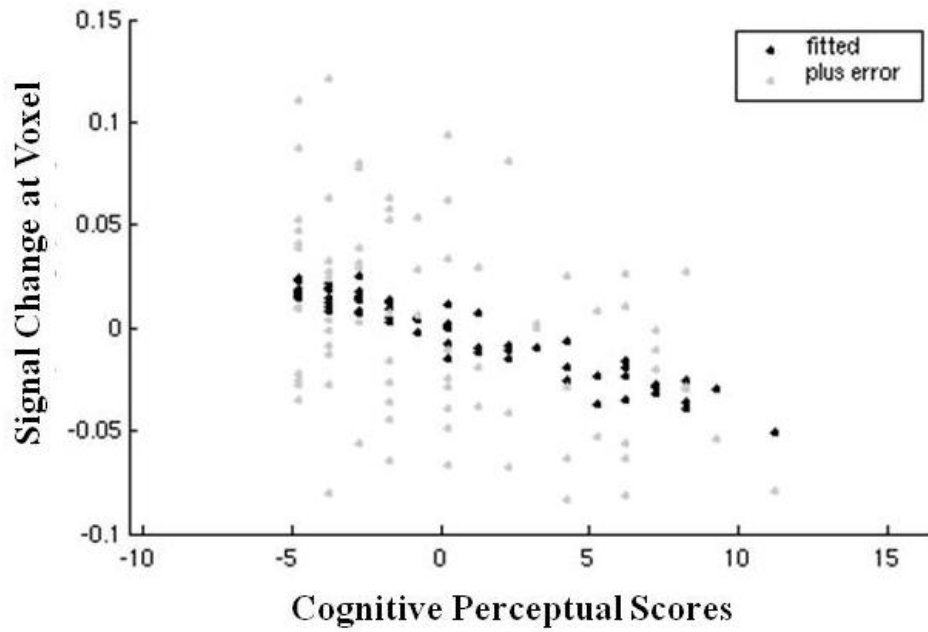


Figure 6.7. Scatter plot of grey matter volume and Cognitive Perceptual scores.

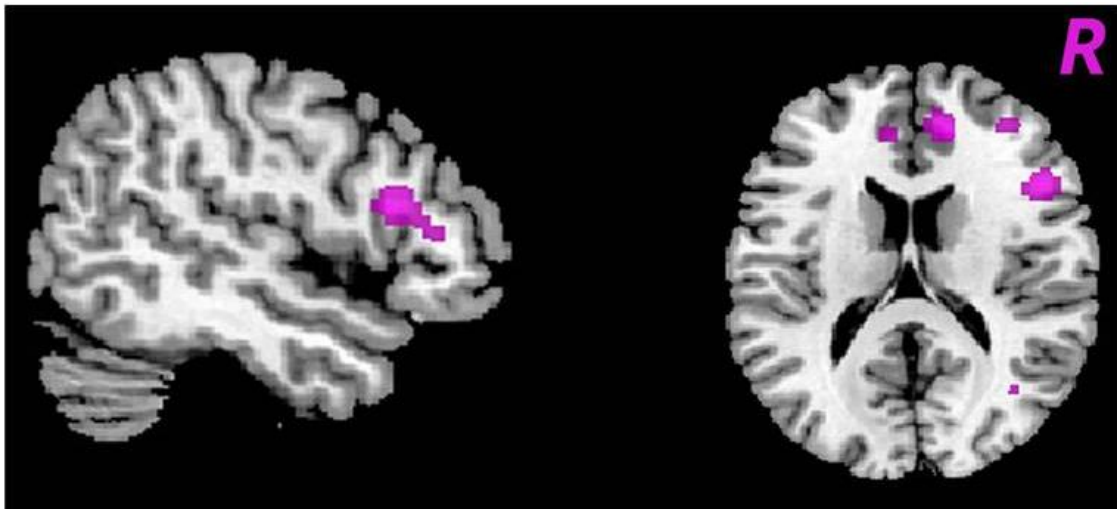


Figure 6.8. Areas of significant negative correlation between Cognitive Perceptual traits and regional grey matter volume in the inferior frontal gyrus (sagittal view) and in the medial, middle, inferior and superior frontal gyri (axial view).

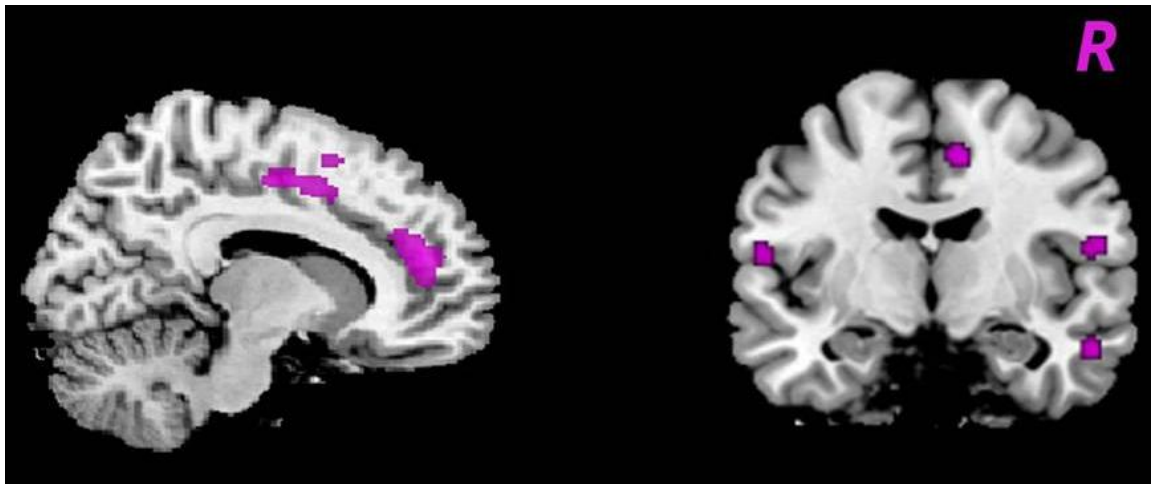


Figure 6.9. Areas of significant negative correlation between Cognitive Perceptual traits and regional grey matter volume in the ventral and dorsal anterior cingulate (sagittal view) and the right temporal lobe (coronal view).

#### **6.4.5 CONCLUSION**

Inverse voxel-based regression analyses revealed higher Cognitive Perceptual scores were discretely and significantly associated with specific regions of lower grey matter (GM) volumetric values. For this sub-factor, which assesses psychosis proneness, higher scores were associated with smaller GM volumes bilaterally in the frontal and cingulate cortices (although the extent of involvement of right sided areas was far greater than in the left) and in the right temporal lobe. In the frontal lobes this association was manifest in the medial, middle, inferior, precentral and superior gyri. In the cingulate cortex, lower GM volumetric values in the right ventral anterior cingulate cortex and bilateral dorsal anterior cingulate were associated with higher CP scores.

The bilateral yet asymmetrically right dominant associations between high positive schizotypy scores and specific regions of lower GM tissue volume in the frontal lobes are in line with the hypothesis and are consistent with findings from



schizophrenia studies (Pantelis et al., 2003), positive schizotypy findings (Gruzelier & Doig, 1996; Leonhard & Brugger, 1998; Nunn & Peters, 2001; Weinstein & Graves, 2002), neurodegenerative research of patients with psychosis (Forstl et al., 1991; Staff et al., 1999; Venneri et al., 2000; Sulzer et al., 2003; Shanks & Venneri, 2004; Bruen et al., 2008) and with the results from the previous studies which suggest confabulation and delusions are associated with structures which are also involved in episodic memory (Lee et al., 2004; 2007; Bruen et al., 2008). This may also help to explain why high positive schizotypy was associated with more false alarms and possibly with altered episodic personal memory in the previous studies as false beliefs may be associated with impairments in inferior prefrontal mechanisms which are important for reality monitoring (Richardson & Malloy, 2001). The asymmetry of frontal involvement may be especially relevant for justifying the association between positive schizotypy and false positive memories and suggests that false alarms in positive schizotypy presents a good non-clinical behavioural and anatomical analogy of pathological confabulations.

As these right dominant frontal structures, which have been associated with delusions in perfusion (Staff et al., 1999; Venneri et al., 2000) and structural studies (Bruen et al., 2008), are consistently related to episodic memory retrieval, it follows that dysfunctional episodic memory could be aetiologically relevant to the emergence of delusions. Converging behavioural evidence further supports the association between confabulations and delusions and impairments in personal episodic memory retrieval for late adulthood and recent life periods (Cooper et al., 2006; Lee et al., 2007). One interpretation of the relationship between confabulations in episodic memory and delusions is that confabulation and

psychosis occupy the same continua (Berrios, 1998; Lee et al., 2004) and that reality monitoring impairments in memory and beliefs subserved delusional and confabulatory symptoms (Johnson, Hashtroudi & Lindsay, 1993). In a group of patients with Alzheimer's disease, confabulations in episodic memory were associated with delusions and confabulations in semantic memory were associated with cognitive impairment (Lee et al., 2007). Similarly confabulations in autobiographical episodic memory have been reported in the presence of relatively intact personal semantic memory (Cooper et al., 2006). These findings suggest that different mechanisms are involved in episodically and semantically associated confabulations. This is consistent with Dalla Barba et al's. (1999) model whereby semantic confabulations reflect cognitive dysfunctions in 'knowledge consciousness' and episodic confabulations are associated with delusions due to impaired 'temporal consciousness' (Lee et al., 2007). The fact that these associations are both biologically and behaviourally manifest in individuals with high positive schizotypy provides validation for the conceptualisation of this personality type as a meaningful endophenotype for the emergence of delusions due to neuropathology. If individual differences in the expression of positive schizotypal traits are correlated with structural variance in the brain regions and behaviours that are associated with delusions in pathological populations, it follows that positive schizotypy could represent a structurally supported diathesis that remains latent unless elicited by sufficient neurological pathology.

The frontal lobes have frequently been found to be associated with psychosis and psychosis proneness and this association is especially true for delusional aspects of psychosis. In first episode psychosis, reduced grey matter volume has been

found in the dorsomedial frontal cortex (Whitford, Farrow, Williams et al., 2009) the authors suggest, contrary to the few paradoxical positive correlations reported between delusions and grey matter density, a level of structural neural atrophy is necessary for the emergence of delusions in first episode psychosis and that increased atrophy may be causal in the formation of more systematised delusions. Delusions have also been related to dysmetabolism of the frontal lobe in BA 10 and 8 and in further prefrontal and anterior cingulate regions (Sultzer et al., 2003). In addition, in dementia with Lewy bodies, delusions have been associated with hypometabolism of the right prefrontal cortex (Perneczky, Drzezga, Boecker et al., 2009). More specifically delusions of theft and persecution in dementia with Lewy bodies have been correlated with dysfunction in bilateral dorsolateral frontal cortex, right medial frontal and left medial superior frontal gyrus (Nagahama, Okina, Susuki, & Matsuda 2008). In line with such evidence it has been suggested that there is an 'aetiological' association between pathological changes in prefrontal function and delusions (McMurtray, Sultzer & Monserratt, 2008). The right middle and inferior frontal gyrus have also been consistently associated with inhibitory control and down regulation of emotion (Rubia et al., 2003; Aron et al., 2004), when such areas are structurally compromised impairments in inhibition and emotional regulation may contribute to delusion formation.

The cingulate cortex and right temporal lobe have also been associated with delusions in previous studies. In a task devised to characterise the neuroanatomical underpinnings of referential ideation in delusional individuals, activity in the cingulate cortex associated with normal participants' performance was absent from the activation patterns found in deluded participants. The authors

argue that abnormalities of the cingulate cortex could inhibit reflective processes from normalising self relevance and thus lead to delusional beliefs (Blackwood, Bentall, Ffytche et al., 2004). Furthermore, in patients with schizophrenia, default mode activity in the medial frontal, temporal, and cingulate has been associated with the severity of positive symptoms (Garrity, Pearlson, McKiernan et al., 2007). The anterior cingulate has also been involved in emotional processing where it has been found to act as an interface between cognition and emotion and it has also been found to be involved in emotional conflict (Bush, Luu & Posner, 2000). Further studies have suggested the anterior cingulate is essential for key aspects of error monitoring such as error detection and compensation (Van Veen & Carter, 2006). It follows that less gray matter volume in substrates which such important cognitive and emotional responsibilities may be critical to the mediation of delusional behaviour.

However, in line with a prior study which assessed the relationship between TPQ personality traits and brain structure, it could be anticipated that an alternative hypothesis would suggest that rather than neuroanatomical variance mediating variance in individual differences, it is the personality traits that cause the observed variance in brain regions (Gardini et al., 2009). In this account repeated behaviours and environmental contexts would cause specific morphological brain variability. However according to Gardini et al., there is more evidence from developmental behavioural genetics (Heiman, Stallings, Young, & Hewitt 2004) to support the initial hypothesis that variance in regional brain morphology is expressed phenotypically as individual differences in personality.

It is also important to acknowledge possible limitations of the method of VBM. Bookstein (2001) has criticised VBM for its failure to differentiate between changes in tissue volume and mis-registered images. However, by using methods such as tissue specific templates, the current procedure for the application of VBM reduces the effects of mis-registration. Another criticism of VBM is that it may not be sensitive to all types of relationships within the brain as VBM assumes linearity of variance. However, according to Rosen et al., (2005) whilst VBM might not produce data that is exactly the same as region of interest analyses (ROI) it is certainly comparable. Moreover, VBM makes no assumptions about location and size, whereas ROI has been criticised for not providing information outside of the ROI.

Finally it must be made explicit that the participants in the current VBM study are different from those who participated in the behavioural work that has been previously described in this thesis. As discussed if neuroimaging data were available for the original participants it would have been possible to run high/low comparisons as well as the multiple regression. It would also have been powerful to run correlations between region of interest (ROI) volumes and neuropsychological scores. This would have enabled more direct evidence that the behavioural effects are directly related to the regional anatomical substrates.

In conclusion, the results of the current study are in line with findings from schizophrenia and neurodegenerative research. Individual differences in schizotypal traits in normal individuals are associated with variance in some of the brain regions which have been related to psychosis in previous studies. This suggests that individual differences in positive schizotypy in normal individuals

are reflected endophenotypically in the structure of the brain. This may represent a predisposing structural liability to the emergence of delusions under different neurological and extreme environmental stressors.

As this brain behaviour correlation was found in healthy young individuals, it suggests that independent of aetiology, psychosis appears to be supported by dysfunction in these bilateral but predominantly right sided frontal and cingulate regions. The results suggest that, even in non-clinical persons, individual differences in positive schizotypal traits are reflected in the structural variance of the specific neural areas that are involved in psychosis. Most individuals with this atypical but dimensional trait will not decompensate. However, the endophenotype model of positive schizotypy proposed in this thesis suggests that if high positive schizotypal individuals are under the duress of a significant stressor, especially a neurologically based one, the prominent symptom will be psychosis. This inverse association between higher positive schizotypy scores and lower GM tissue volume suggests that these individuals possess a latent underlying structural vulnerability or diathesis to psychosis.

## CHAPTER 7

# VALIDATING THE ENDOPHENOTYPE IN CLINICAL POPULATIONS

### *7.1 INTRODUCTION*

Different personality profiles can indicate distinct vulnerabilities for psychotic decompensation. For instance, Low et al., (2002) assessed the contribution of caregiver rated pre-morbid personality on the NEP five factor inventory to psychosis in dementia and found higher pre-morbid neuroticism was predictive of delusions; higher agreeableness of hallucinations and aggressiveness of affective disturbance and overall behavioural disturbance. However as previously discussed, the finding which bears most relevance for the current thesis is that prior to dementia onset, Alzheimer's disease (AD) patients with psychosis have been found to have increased schizotypal symptoms (Eror et al., 2005). In light of such findings, Elise et al., (2005) have proposed a model in which genes that confer a small risk for psychosis may interact with the neurodegenerative illness to yield manifest psychotic symptoms during AD.

Such research may help us understand the emergence of organic psychosis in older adulthood and degenerative diseases and may further the assessment of the contribution of pre-morbid personality to the emergence of psychosis in AD, in non-demented older individuals and in the context of other forms of neurological illness. The association between schizotypal traits and the emergence of psychosis in AD confirms that schizotypy could be an ideal endophenotype for investigating

the aetiology of the emergence of psychosis due to neurological stress such as neurodegeneration. However, the current studies were designed with the objective of validating the endophenotype in various other clinical populations. In order to test the diathesis stress hypothesis that positive schizotypy is an endophenotype for the emergence of psychosis under various neurological stressors and to see how the endophenotype interacts with different neurological aetiologies, a series of single case studies will be reported in which we assessed whether patients presenting with psychotic symptoms as a consequence of different neurological illnesses such as AD, vascular dementia and Parkinson's disease (PD), severe emotional and environmental stressors and psychopharmacological treatment had a predictable personality profile of high positive schizotypy. In an additional experimental group study of patients with PD, the association between the presence of psychosis following levodopa treatment and high schizotypy will be also be tested. Subsequently, the endophenotype will be tested anatomically through a voxel based morphometric study of the neuroanatomical correlates of the psychotic symptoms in PD which were found to be behaviourally correlated with positive schizotypy in the first part of this study.

## ***7.2 EXPERIMENT 1- CASE STUDIES***

The three case studies that will be presented in this section were referrals from the Clinical Neuroscience Centre (CNC) at the University of Hull. Primarily, the CNC is a tertiary assessment centre and the majority of patients are referred for in depth clinical interview and neuropsychological testing to clarify diagnoses. The three patients reported in this study originally appeared to have similar psychiatric presentations including delusions and hallucinations. Their referring consultants originally thought these psychotic symptoms were associated with cognitive



decline due to neurodegenerative diseases. Based on the current diathesis stress hypothesis whereby positive schizotypy is conceptualised as a latent variable that is expressed as individual differences in personality unless significant neurological stress leads to its endophenotypic expression as psychosis, it is predicted that the three patients will have higher than average levels of positive schizotypal personality traits.

### ***7.2.1 ASSESSMENT OF PERSONALITY***

As in the previous experimental work in this thesis, the SPQ was used to measure schizotypal traits. The SPQ has previously been explained in full, please refer to Chapter 4, section 4.3.3 for full details of the SPQ's structure, scoring and administration. The Tri-dimensional personality questionnaire (TPQ; Cloninger, 1987) which assesses harm avoidance, novelty seeking and reward dependence was also administered to the patients, please refer to Chapter 4, section 4.4.3 for more detailed description of this instrument.

### ***7.3 CASE 1***

MD is a 65 year old male who is a retired Senior Instructing Officer at a secret base in the Navy. He has Parkinson's disease with impaired mobility and tremor for which he was being treated with Ropinerole. MD experienced a range of abnormal phenomena, sometimes with visual manifestations including fleeting hallucinations of children and adults which could trigger paranoid beliefs. He had persistent symptoms of delusional parasitosis, with stabbing and crawling sensations in his skin, which he attributed to insects, he believed he could see these parasites moving under his skin and claimed he could and had removed them. At the same time as the emergence of the parasitosis, MD began to react to noises and visual perceptions in a paranoid manner. This was especially apparent

after dark and caused immense distress. MD believed that groups of men gathered in his garden and loft and he believed he could hear them whispering and plotting. On such occasions, MD would often ask his wife to be silent so he could listen in to these ‘visitors’ and he would form plans to counter their possible attack. Often MD would search the house for assailants and burglars. This was frequently a time when his previous professional experience triggered security overload and MD reacted with anger and prepared himself for conflict. MD was aware that he did not see objects normally, and explained that these problems were especially evident at the periphery of his visual field. Whilst he was obsessional and repetitive about his infestation delusion, he had fleeting insight regarding the possibility that his intruders were imaginary however this insight was partial and he emphasised that they felt very real at the time. Olanzipine treatment for these symptoms was discontinued after he exhibited increased agitation and paranoia. The consultant who referred MD to the clinic suggested these psychiatric symptoms were likely to be associated with cognitive decline due to cortical Lewy body disease. Consequently MD was referred for neuropsychological testing to determine whether Lewy body disease was a likely candidate for the emergence of these delusional beliefs and hallucinatory experiences.

However, extensive neuropsychological testing revealed MD’s psychometric testing performance was well within normal age range and his MMSE was 28/30. Please refer to Table 7.1 for further details of MD’s neuropsychological test performance.

Table 7.1 Neuropsychological Profile for MD

Test		Patient	Controls	
		MD	Mean	SD
Mini Mental State Exam (MMSE)		<b>28/30</b>	28.6	1.6
Confrontational Naming		<b>20/20</b>	19.6	0.7
Verbal Paired Associates		<b>16/24</b>	14.1	4.5
Pyramids and Palm Trees		<b>52/52</b>	50.9	1.2
Rey's Complex Figure	Copy	<b>29/36</b>	33.2	2.9
	Delay	<b>5/36</b>	14.3	5.2
Semantic Fluency		<b>61</b>	54.5	13.3
Phonemic Fluency		<b>56</b>	44.6	14
Digit Span Forward		<b>7</b>	6.6	1.4
Digit Span Backward		<b>5</b>	4.9	1.3
Raven's Progressive Matrices		<b>27/36</b>	32.1	3.5
Stroop Task	Error	<b>0</b>	0.6	2.1
	Time	<b>23.5</b>	21.9	1.3
Digit Cancellation	Correct	<b>54/60</b>	53.6	5.3
Visuoconstructive Apraxia		<b>13/14</b>	13.5	0.7
Token Task		<b>36/36</b>	33.9	1.5
WAIS Similarities		<b>22/33</b>	21.4	6.1
Logical Memory	Immediate	<b>7/25</b>	No Norms	
	Delayed	<b>19/25</b>	No Norms	

Red- Impaired by > 2 SD's

Blue – Normal Range

Controls (N=34), Mean age 66.1 (9.5), males 10, right handed 31, mean years of education 13.2 (3.0)

The only abnormality found was evidenced on a specific provoked confabulation questionnaire (Cooper et al., 2006 where MD systematically responded in a confabulatory and self-referential manner. However, as there was no evidence of cognitive decline his symptoms do not seem likely to be associated with cortical Lewy body dementia.

MD's personality profile for the SPQ and TPQ can be seen in Tables 7.2 and 7.3 respectively. Interestingly, this personality screening revealed MD has high positive schizotypal traits and that he is highly reward dependent.

Table 7.2. SPQ profile for MD

		<b>MD</b>	<b>Age Matched</b>
		<b>Scores</b>	<b>Control</b>
			<b>M (SD)</b>
<b>Total SPQ</b>	<b>Full Score</b>	<b>15</b>	<b>15.6 (11.1)</b>
	<b>(74)</b>		
<b>Cognitive perceptual</b>	<b>Total</b>	<b>10</b>	<b>6.06 (6.96)</b>
	<b>(33)</b>		
<b>Interpersonal Factors</b>	<b>Total</b>	<b>4</b>	<b>8.08 (8.03)</b>
	<b>(33)</b>		
<b>Disorganised Factors</b>	<b>Total (16)</b>	<b>2</b>	<b>2.89 (3.45)</b>

Controls (N=118), Mean age 52 (SD 4.4, Range 47-79), males 59 (Badcock & Dragovic, 2006)

Table 7.3. TPQ profile for MD

		Maximum score	MD Score	Percentiles
Novelty Seeking	Exploratory	9	4	44.44
	Impulsive	8	0	0.00
	Extravagant	7	0	0.00
	Disorderly	10	3	30.00
	Novelty Seeking total	34	7	20.59
Harm Avoidance	Pessimistic	10	4	40.00
	Fearful	7	4	57.14
	Shy	7	0	0.00
	Fatigable	10	2	20.00
	Harm Avoidance total	34	10	29.41
Reward Dependence	Sentimentality	5	4	80.00
	Attachment	9	6	66.67
	Persistence	11	4	36.36
	Dependence	7	3	42.86
	Reward Dependence total	32	17	53.13

### 7.3.1 COMMENT

The findings that MD has high positive schizotypy and high reward dependence, in combination with the dopamine agonist Ropinerole is in line with the hypothesis that high positive schizotypy can lead to psychotic symptoms under neurological stress, which in this case is pharmacologically based. In addition, MD's performance and behaviour on certain semantic tasks mirrored the performance that has been observed in individuals with schizophrenia, whereby MD exhibited an inability to inhibit responses to semantic naming and associative tasks which may be due to the Ropinerole's facilitation of an abnormal spreading activation within semantic networks. MD's positive symptoms and loosening of associations could also make sense in light of studies that have used ketamine to further explore delusional behaviour (Honey et al., 2008). As Ketamine has been found to provoke symptoms that are characteristic of delusions and hallucinations

in normal individuals it has been used as a drug model of delusional psychosis to relate presymptomatic physiology to symptom outcome. Honey et al. (2008) assessed brain responses, to a sentence completion task which was used to engage brain regions associated with semantic processing. In schizophrenic patients with delusions and in healthy participants under a sub-clinical dose of ketamine the middle temporal gyrus, left inferior frontal gyrus and left superior temporal gyrus were associated with thought disorder. MD's Ropinerole was gradually reduced and changed to Co-careldopa and his psychotic symptoms were lessening with Ropinerole reduction.

#### ***7.4 CASE 2***

AS is a 75 year old Spanish born Lady, who has been a UK resident since she married her English husband 50 years ago. A prominent presenting symptom was AS's experience of the uncanny feeling that she could hear the voices of her two nieces calling her. As this increased, AS reported that they began to talk and argue with her, AS argued back demanding to know why they were in her house. She could not see these nieces and believed they must be 'covered up', she also responded to them behaviourally leaving them food and cups of tea. She dated these unusual experiences from the death of husband and sister. She also reported that other deceased family members visited her home and she believed her deceased husband slept in her bed and talked to her. This, unlike the invasion of her nieces, was welcomed by AS. AS did not like to be alone and often felt lonely and was taking the antidepressant Imipramine. As she is also diabetic and hypertensive her consultant referred her for tertiary assessment with a suspected early vascular dementia. Clinical interview revealed the importance of understanding the context of AS's lived experiences, her personality and

background. AS has always had spiritualist beliefs (as confirmed by her son) and her parents were psychics who were in demand in their town to transmit messages to the dead. AS believed she had also always had this gift and remembered seeing and communicating with her grandparents after they had died when she was about 5 years old. However her family noted a clear differentiation between such beliefs and her current hallucinations. The neuropsychological profile for AS can be seen in Table 7.4.

Table 7.4. Neuropsychological profile for AS

Test		Patient	Controls	
		MD	Mean	SD
Mini Mental State Exam (MMSE)		<b>24/30</b>	28.4	1.4
Confrontational Naming		<b>9/20</b>	19.5	0.7
Verbal Paired Associates		N/A	13.6	4.3
Pyramids and Palm Trees		N/A	50.9	1.2
Rey's Complex Figure	Copy	<b>10.5/36</b>	33.3	3.5
	Delay	<b>2/36</b>	13.8	6.99
Semantic Fluency		<b>34</b>	53.3	12.6
Phonemic Fluency		<b>14</b>	41.4	15.6
Digit Span Forward		<b>3</b>	6.8	1.4
Digit Span Backward		<b>2</b>	5.4	1.3
Raven's Progressive Matrices		<b>17/36</b>	31.08	3.8
Stroop Task	Error	N/A	0.6	3.9
	Time	N/A	24.1	11.51

<b>Digit Cancellation</b>	<b>Correct</b>	<b>43/60</b>	<b>51.2</b>	<b>5.7</b>
<b>Visuoconstructive Apraxia</b>		<b>11/14</b>	<b>13.5</b>	<b>0.7</b>
<b>Token Task</b>		<b>N/A</b>	<b>33.9</b>	<b>1.5</b>
<b>WAIS Similarities</b>		<b>N/A</b>	<b>21.4</b>	<b>6.1</b>
<b>Logical Memory</b>	<b>Immediate</b>	<b>N/A</b>	<b>No Norms</b>	
	<b>Delayed</b>	<b>N/A</b>	<b>No Norms</b>	

Red- Impaired by > 2 SD's

Blue – Normal Range

Controls (N=52), Mean age 77.2 (5.4), males 24, right handed 52, mean years of education 14 (3.78)

Whilst there appear to be a number of abnormal scores in her profile, when adjusted for language competence AS's psychometric scores were normal (MMSE 24) except for a measure of focused attention. AS also displayed retained episodic memory, knowledge of current affairs and reasoning. Further personality screening tests were undertaken for the SPQ and TPQ, the results of which can be seen in Tables 7.5 and 7.6 respectively. The personality screening protocol revealed AS to have high traits for positive schizotypy and to be highly reward dependent.

Table 7.5 SPQ profile for AS



		AS Scores	Age Matched Control M (SD)
<b>Total SPQ</b>	<b>Full Score (74)</b>	<b>17</b>	<b>15.6 (11.1)</b>
<b>Cognitive perceptual</b>	<b>Total (33)</b>	<b>14</b>	<b>6.06 (6.96)</b>
<b>Interpersonal Factors</b>	<b>Total (33)</b>	<b>4</b>	<b>8.08 (8.03)</b>
<b>Disorganised Factors</b>	<b>Total (16)</b>	<b>1</b>	<b>2.89 (3.45)</b>

Controls (N=118), Mean age 52 (SD 4.4, Range 47-79), males 59 (Badcock & Dragovic, 2006)

Table 7.6 TPQ profile for AS

		Maximum score	AS Score	Percentiles
Novelty Seeking	Exploratory	9	2	22.22
	Impulsive	8	2	25.00
	Extravagant	7	2	28.57
	Disorderly	10	2	20.00
	Novelty Seeking total	34	8	23.53
Harm Avoidance	Pessimistic	10	2	20.00
	Fearful	7	6	85.71
	Shy	7	2	28.57
	Fatigable	10	1	10.00
	Harm Avoidance total	34	11	32.35
Reward Dependence	Sentimentality	5	4	80.00
	Attachment	9	8	88.89
	Persistence	11	6	54.55
	Dependence	7	2	28.57
	Reward Dependence total	32	20	62.50

### 7.4.1 COMMENT

The neuropsychological testing was adapted to suit AS's linguistic competence, scoring also accounted for linguistic and grammatical ability in her second

language. In this context AS demonstrated retained episodic memory, reasoning ability, semantic competence and verbal fluency. It must be noted that when adjusted for language, her borderline scores (when compared with the scores of age matched English native speakers) were normal apart for focused attention. There was therefore no indication of global cognitive decline either secondary or due to neurodegeneration. AS was referred for reassessment two years later and her cognitive profile remained unchanged. One formulation of AS's psychotic symptoms is that her personality composition of high positive schizotypy and high reward dependence may be a diathesis that when combined with several bereavements, her depressive state and loneliness, and family conflict led to psychotic decompensation with persistent hallucinosis and delusional beliefs.

### **7.5 CASE 3**

GS is a 71 year old male who is a retired Mathematician. After a radical prostatectomy in 2006, GS developed a clouded psychotic state which evolved into mania and GS displayed pressure of speech, loosening of associations and grandiose, paranoid and elaborate delusions. The diagnosis at this time was organic affective psychosis which was supported by subtle right frontal ischemic changes. However, in 2007 GS became more forgetful and neuropsychiatric symptoms re-emerged. Displaying a residual tendency to confabulation, false memory reduplication and misidentification of his wife, and believing other people were in his house and garden. These episodes also appeared to be triggered by physical stress. This also elicited behavioural responses which included GS laying extra places at the table and making drinks for these visitors. More generally, GS had also been observed to be more forgetful and to have 'slowed

up' mentally. GS was referred for further clarification of whether vascular or neurodegenerative processes were contributing to his cognitive slowing and neuropsychiatric symptoms. The neuropsychological profile for GS can be seen in Table 7.7, his MMSE was 25/30 and semantic association was age abnormal as were the times to complete the Stroop, digit cancellation, token test.

Table 7.7. Neuropsychological Profile for GS

Test		Patient	Controls	
		MD	Mean	SD
Mini Mental State Exam (MMSE)		25/30	28.4	1.4
Confrontational Naming		19/20	19.5	0.7
Verbal Paired Associates		9/24	13.6	4.3
Pyramids and Palm Trees		48/52	50.9	1.2
Rey's Complex Figure	Copy	36/36	33.3	3.5
	Delay	10/36	13.8	6.99
Semantic Fluency		40	53.3	12.6
Phonemic Fluency		38	41.4	15.6
Digit Span Forward		6	6.8	1.4
Digit Span Backward		4	5.4	1.3
Raven's Progressive Matrices		31/36	31.08	3.8
Stroop Task	Error	0	0.6	3.9
	Time	35.32	24.1	11.51

<b>Digit Cancellation</b>	<b>Correct</b>	<b>46/60</b>	<b>51.2</b>	<b>5.7</b>
<b>Visuoconstructive Apraxia</b>		<b>14/14</b>	<b>13.5</b>	<b>0.7</b>
<b>Token Task</b>		<b>30/36</b>	<b>33.9</b>	<b>1.5</b>
<b>WAIS Similarities</b>		<b>20/33</b>	<b>21.4</b>	<b>6.1</b>
<b>Logical Memory</b>	<b>Immediate</b>	<b>7/25</b>	<b>No Norms</b>	
	<b>Delayed</b>	<b>7/25</b>	<b>No Norms</b>	

Red- Impaired by > 2 SD's

Blue- Normal Range

Controls (N=52), Mean age 77.2 (5.4), males 24, right handed 52, mean years of education 14 (3.78)

The personality profile for GS on the SPQ and TPQ can be found in Tables 7.8 and 7.9 respectively.

Table 7.8. SPQ profile for GS

		<b>GS</b>	<b>Age Matched</b>
		<b>Scores</b>	<b>Control</b>
			<b>M (SD)</b>
<b>Total SPQ</b>	<b>Full Score</b>	<b>29</b>	<b>15.6 (11.1)</b>
	<b>(74)</b>		
<b>Cognitive perceptual</b>	<b>Total</b>	<b>9</b>	<b>6.06 (6.96)</b>
	<b>(33)</b>		
<b>Interpersonal Factors</b>	<b>Total</b>	<b>9</b>	<b>8.08 (8.03)</b>
	<b>(33)</b>		
<b>Disorganised Factors</b>	<b>Total (16)</b>	<b>13</b>	<b>2.89 (3.45)</b>

Controls (N=118), Mean age 52 (SD 4.4, Range 47-79), males 59 (Badcock & Dragovic, 2006)

Table 7.9. TPQ profile for GS

		Maximum score	GS Score	Percentiles
Novelty Seeking	Exploratory	9	5	55.56
	Impulsive	8	6	75.00
	Extravagant	7	3	42.86
	Disorderly	10	6	60.00
	Novelty Seeking total	34	20	58.82
Harm Avoidance	Pessimistic	10	1	10.00
	Fearful	7	3	42.86
	Shy	7	3	42.86
	Fatigable	10	3	30.00
	Harm Avoidance total	34	10	29.41
Reward Dependence	Sentimentality	5	4	80.00
	Attachment	9	4	44.44
	Persistence	11	3	27.27
	Dependence	7	3	42.86
	Reward Dependence total	32	14	43.75

### **7.5.1 COMMENT**

Clinical interview revealed GS's knowledge of current affairs was vague and lacked the detail expected from one of his level of education and professional background. Neuropsychological testing mostly demonstrated performance that was within normal age limits; however, his verbal learning and confrontation naming were only just above cut off. Mini Mental State Examination (MMSE), semantic association execution time on the Stroop, digit cancellation and token task were all age abnormal. A specific provoked confabulation test (Cooper et al., 2006) also revealed a tendency to form confabulatory memories. In addition, personality assessment revealed higher than average positive schizotypy and novelty seeking personality traits. The profile, in the context of GS's preserved everyday skills and independence were taken as indications of a clinical diagnosis of multi domain mild cognitive impairment. The way in which GS's premorbid

cognitive ability, educational achievements and professional attainments may mean the testing materials lack the sensitivity to detect subtle deficits in other domains must also be considered. GS's high level of cognitive reserve might have enabled him to achieve scores in the normal age range which would lead to overestimation of his cognitive ability and the degree of disease related changes.

The cognitive abnormalities that were detectable suggest impaired functioning of several brain systems. Therefore, it seems unlikely that any changes in GS can be attributed to the progression of his focal frontal ischemic damage.

In light of the current hypothesis, it appears that in 2006 GS's predisposing personality features were a diathesis that when combined with the neurological stress of frontal lobe ischemic damage led to his original brief organic psychosis. The association between the subtle frontal lobe ischemic changes is interesting in light of the results of the VBM study presented in the previous chapter which found high positive schizotypy in young healthy individuals to be related with lower grey matter volume predominantly in the right frontal lobe. This, in combination with findings that decreased grey matter in the right frontal cortex has previously been associated with delusions (Staff et al., 1999; Venneri et al., 2000; Sultzer et al., 2003; Shanks & Venneri, 2004; Bruen et al., 2008), further validates the construct of schizotypy as an endophenotype for neurological psychosis through the traits' relationship with an anatomical vulnerability. It appears that subsequent damage to this network disrupts the regions functional role in aligning mental contents with veridical reality. The region of correlation, especially in the frontal lobe, involves areas which are relevant for personal

episodic memory retrieval and behavioural studies have shown episodic memory deficits predict confabulation and delusional belief.

However contemporarily, there appears to be a global underlying process of cognitive decline as revealed by neuropsychological assessment. GS's high cerebral reserve and vulnerability of frontal lobe functions to symptoms of false memory and confabulation is somewhat obscuring his multi-domain mild cognitive impairment.

## ***7.6 CONCLUSION***

These case histories describe patients who originally appeared to have similar presentations including delusions and hallucinations. Their referring consultants originally thought these psychotic symptoms were associated with cognitive decline due to neurodegenerative diseases or due to organic psychosis. They were therefore referred to the Clinical Neuroscience Centre for tertiary assessment. However, very different natural histories emerged after comprehensive neuropsychological exam and detailed personality screening. In line with recent research it seems positive schizotypal personality traits may be a vulnerability indicator to psychiatric decompensation in combination with stressors as observed in these patients in the form of dopamine agonists, bereavement and depression, and focal ischemic insult and neurodegeneration. Such findings further validate the anatomical and behavioural evidence for positive schizotypy as an endophenotype in a diathesis stress model of neurological psychosis.

A limitation which must be noted is the fact that these case studies are all retrospective and whilst the patients and their caregivers suggested that schizotypal traits preceded psychotic breakdown, we have no empirical prospective evidence for the premorbid status of schizotypal traits. Consequently, whilst schizotypy is considered a trait, it also correlates with delusions in this study which suggests it may be modulated by the neuropathological condition.

### ***7.7 EXPERIMENT 2 - VALIDATING THE ENDOPHENOTYPE BEHAVIOURALLY AND NEUROANATOMICALLY IN PARKINSONS DISEASE***

Neuropsychiatric symptoms frequently emerge as a consequence of treatment in some patients with Parkinson's disease (PD) (Rascol, Brooks, Amos et al., 2000; Holyroyd, Currie & Wooten, 2001), however, their psychological and biological correlates have yet to be fully characterised. In other neurodegenerative conditions, the emergence of these symptoms has been associated with reduced grey matter (GM) volume in specific brain regions (Rosen et al., 2005; Bruen et al., 2008) and it has been suggested that there might be a predisposing biological vulnerability that makes some patients more liable to develop neuropsychiatric symptoms than others.

Similarly although there is a large corpus of literature which has associated the emergence of psychosis in PD to treatment with dopaminergic medication, not all PD patients treated with such agents experience psychosis (Holyroyd, Currie & Wooten, 2001), suggesting that there may be predisposing susceptibility factors involved in the emergence of psychosis in PD following treatment. In line with evidence that psychosis prone personality traits, such as high schizotypy, could be



latent vulnerability or susceptibility markers which express themselves endophenotypically when significant neurological damage occurs (Erer et al., 2005; Elise et al. 2005; Bruen et al., 2008), the aim of this study was to determine whether positive schizotypy was associated with psychosis related neuropsychiatric symptoms due to Levodopa medication in individuals with PD. The aim of the current experiment is to examine possible associations between psychosis in PD and high positive schizotypal traits. More specifically, it is predicted that positive schizotypy will be positively associated with psychotic symptoms such as delusions in Levodopa treated PD patients.

The rationale behind this study is consistent with the way in which Canli et al. (2001) have proposed that an individual differences approach can explain why certain neuropharmacological drugs can have such markedly different effects on people. For example, Canli et al. (2001) suggest an individual differences model can explain the differential effects of procaine, a drug which has been found to produce both intense fear and euphoria in different individuals (Ketter et al., 1996; Canli et al., 2001). Canli et al., have found that these quite polarised reactions may be explained by variance in personality traits whereby highly extraverted individuals appear likely to react to the drug with euphoria and highly neurotic individuals seem more predisposed to have an intense fear reaction (Canli et al., 2001). For the current studies, the theory that individual differences in personality could potentially moderate pharmacological effects may suggest implications for the positive schizotypy endophenotype. Whilst certain drugs such as ketamine and L-Dopa are known to produce psychotic symptoms in some people, the individual differences model could perhaps explain why these drugs do not induce psychosis in everyone. This model would predict individuals with psychosis prone

personalities may be more vulnerable to develop psychosis due to these drugs than in those with less predisposing traits.

In order to test this model experimentally, a voxel based regression analysis of the neuropsychiatric psychotic symptom that was behaviourally associated with positive schizotypy will be presented. This will enable the neuroanatomical diathesis stress model of positive schizotypy to be tested in a population that is clinically psychotic due to neuropharmacological stress in the form of Levodopa medication.

To further establish the construct validity of positive schizotypy as an endophenotype for neurological psychosis a separate correlational analysis will be computed between grey matter tissue volume and apathy because, whilst it is a frequent neuropsychiatric in PD, there is no evidence or logic for it to be associated behaviourally or anatomically with positive schizotypy

### ***7.7.1 PARTICIPANTS***

In total, 40 PD patients were recruited for the current study. They were selected from referrals to the outpatient clinical for Parkinson's disease at the San Camillo Research Hospital in Venice, Italy. The group was comprised of 18 females and 22 males, their mean age was 65.78, (SD 9.67), mean education 11.28, (SD 4.42), and their mean MMSE score was 26.82, (SD 2.47). All patients were treated with a combination of levodopa and variable doses of dopamine agonists.

### **7.7.2 NEUROPSYCHIATRIC INVENTORY**

The frequency and severity of delusions and apathy were assessed with the Italian version of the Neuropsychiatric Inventory (NPI-12; (Cummings et al., 1994). The NPI is a caregiver-based behavioural rating system developed and validated for the assessment of mental state and behavioural abnormalities in dementia. The NPI records the presence or absence, severity (rated 1–3) and frequency (rated 1–4) of 12 symptom fields. An index of severity is created for each behavioural variable by multiplying the frequency and severity scores.

### **7.7.3 SPQ**

The Italian version of the SPQ was used to measure schizotypal traits in the current study, please refer to Chapter 4, section 4.3.3 for full details of the SPQ's structure, scoring and administration.

### **7.7.4 VOXEL BASED MORPHOMETRY**

Three dimensional T1-weighted MRI images were acquired on a 1.5 Tesla Philips Achieva MRI system with a Turbo Field Echo sequence. Voxel dimensions were 1 x 1 x 1 mm and field of view was 256 mm with a matrix size of 256 x 256 x 124. Total acquisition time was 4 minutes 41 seconds (TR 9.9 msec, TE 4.6 msec and flip angle 8°). Following pre-processing (described in detail in Chapter 6, section 6.4.3), grey matter segments were correlated with scores for delusions and with apathy. Analyses were conducted in SPM5. Age, education and total intracranial volume (TIV) were included in the model as covariates.

### **7.7.5 RESULTS**

The demographic information, schizotypy and NPI scores for the full group of participants, and separated scores for males and females can be found in Table

7.10. Independent t-tests revealed that there were no significant differences between males and females on any of these variables.

Table 7.10. Demographic, Schizotypy and NPI scores for the full group and by gender.

	Full Group n=40		Males n=22		Females n=18	
	M	SD	M	SD	M	SD
Age	65.78	9.67	66.81	8.97	64.50	10.58
Education	11.28	4.42	12.41	4.77	9.89	3.61
MMSE	28.13	1.79	27.69	1.78	28.67	1.68
Cognitive Perceptual	3.43	4.08	2.42	3.80	4.67	4.17
Delusions	0.33	0.94	0.27	0.77	0.39	1.14
Apathy	1.93	3.23	1.59	2.94	2.33	3.60

Correlations between demographic variables, schizotypal traits, NPI behaviours and apathy for the whole group can be seen in Table 7.11. Age was significantly negatively correlated with Cognitive Perceptual scores  $r = -0.44$ ,  $p < 0.01$ . Most interestingly, delusions were positively correlated with the Cognitive Perceptual factor  $r = 0.36$ ,  $p < 0.05$  and as expected, there were no significant relationship between apathy and positive schizotypal traits. In line with the results from previous studies, including those within the current thesis, the SPQ was very highly positively correlated with its sub factors, and its sub factors were moderately significantly positively correlated with one another (not shown).

Table 7.11. Correlations between demographic, schizotypal traits and NPI scores for the full group n = 40

	Age	Sex	Education	MMSE	Cognitive Perceptual	Delusions	Apathy
Age		.12	-.04	-.14	-.44**	-.22	.15
Sex	.12		.29	-.28	-.28	-.06	-.12
Education	-.04	.29		.27	-.06	-.02	-.21
MMSE	-.14	-.28	.27		.11	-.06	-.28
Cognitive Perceptual	-.44**	-.28	-.06	.11		.34*	-.04
Delusions	-.22	-.06	-.01	-.06	.34*		.28
Apathy	.15	-.126	-.21	-.28	-.04	.28	

\* Correlation is significant at the 0.05 level (2-tailed)

\*\* Correlation is significant at the 0.01 level (2-tailed)

Due to the significant correlation between schizotypy and delusions, a voxel based correlation analysis in which the participant's grey matter volumes were regressed against their NPI delusion scores was computed. The anatomical results of this analysis can be seen in Table 7.12 and Figures 7.1 and 7.2. Higher severity and frequency product scores for delusions were associated with lower grey matter volume in bilateral, but predominantly right, frontal and limbic structures (superior, inferior and precentral frontal gyri). Significant clusters were also found in right posterior cingulate, and in left orbitofrontal cortex and inferior parietal lobule and bilaterally in the inferior semi-lunar lobule of the cerebellum. All correlations reported were thresholded at 20 voxels and were significant at  $p < 0.02$ .

Table 7.12. Areas of significant inverse correlation with delusion scores.

Brain area	Left/ Right	Brodmann area (BA)	Cluster size	Z value at local maximum	Taliarach Coordinates		
					x	y	z
Inferior Semi-Lunar Lobule	R		946	3.17	42	-77	-35
Superior Frontal	R	8	476	2.39	4	32	50
	L	8		2.11	-14	37	42
	R	8		2.02	2	39	46
Precentral Gyrus	R	6	91	2.31	51	-14	28
Inferior Frontal Superior Frontal	R	11	273	2.19	24	34	-22
				2.17	28	44	-19
Cingulate Gyrus	R	31	38	2.03	14	-41	39
Pyramis	L		423	2.54	-6	-81	-23
Inferior Semi-Lunar Lobule	L		343	2.80	-40	-77	-35
Superior Temporal Gyrus	L	42	68	2.43	-67	-25	7
Orbital Gyrus	L	47	108	2.15	-20	30	-23
Inferior Frontal	L	46	28	2.03	-46	43	13
Inferior Parietal Lobule	L	40	57	2.01	-34	-50	4

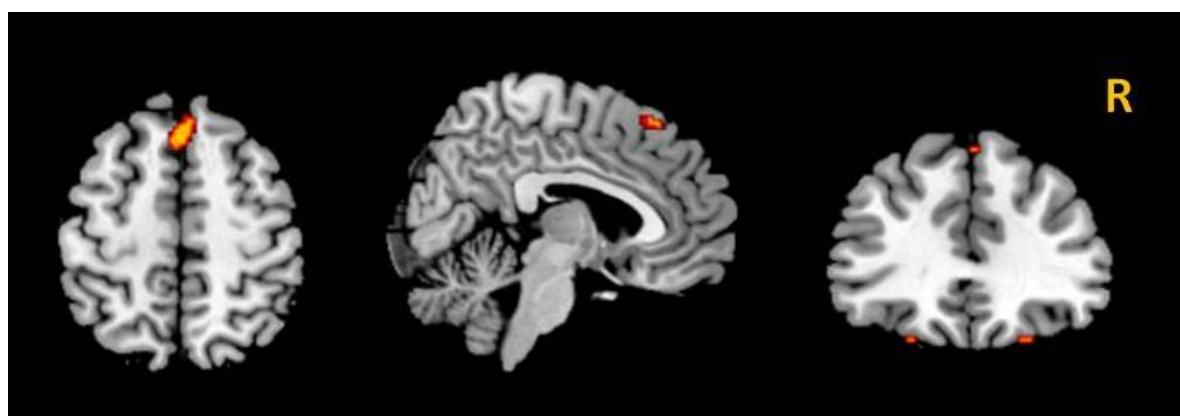


Figure 7.1. Areas of significant negative correlation between delusion scores and regional grey matter volume in the bilateral but predominantly right sided superior frontal gyrus.

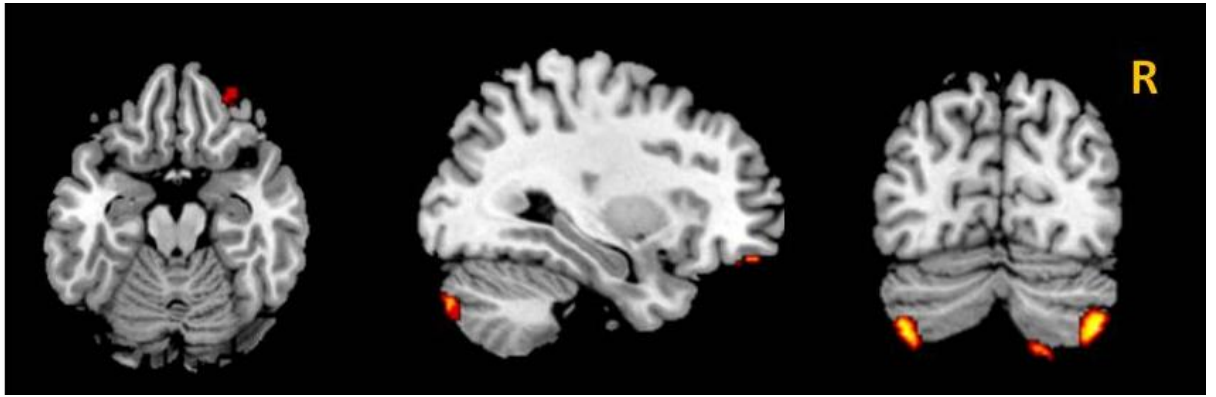


Figure 7.2. Areas of significant inverse correlation between delusion scores and regional grey matter volume in the inferior frontal gyrus (axial and sagittal view) and in the bilateral cerebellum (coronal view)

Conversely, due to the fact that apathy was not associated behaviourally with positive schizotypy a voxel based correlation analysis in which the participants' grey matter volumes were regressed against their NPI apathy scores was also computed. The anatomical results of this analysis can be seen in Table 7.13 and Figures 7.3 and 7.4. Higher severity and frequency product scores for apathy were associated with lower grey matter volumes in the left inferior parietal and right post central and precuneus of the parietal lobes, the right lingual gyrus and the right inferior and middle occipital gyrus of the occipital lobe the right thalamus and in bilateral superior frontal lobes.

Table 7.13. Areas of significant inverse correlation with apathy scores.

Brain area	Left/ Right	Brodmann area (BA)	Cluster size	Z value at local maximum	Taliarach Coordinates		
					x	y	z
Superior Frontal Gyrus	R	9	21	2.73	10	56	32
Postcentral Gyrus	R	5	42	2.42	8	-45	63
Precuneus	R	7	51	2.25	24	-67	49
			26	2.10	14	-47	37
Thalamus	R		26	2.03	6	-29	9
Inferior Occipital Gyrus	R	19	83	1.92	38	-70	-5
Middle Occipital Gyrus	R			1.82	36	-80	2
Lingual Gyrus	R	18	75	1.90 1.86	16	-72	4
Inferior Parietal Lobe	L	40	190	2.60	-38	-41	39
Inferior Frontal	L	47	42	1.99	-40	15	-4

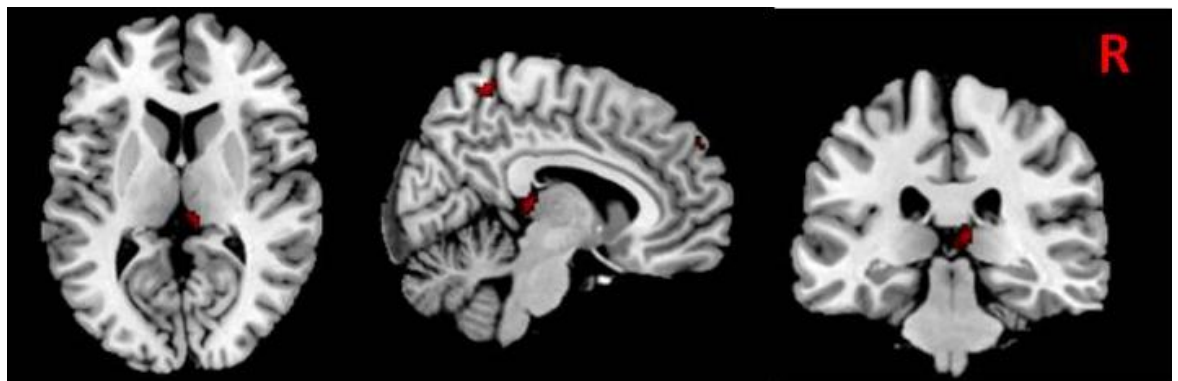


Figure 7.3. Areas of significant inverse correlation between apathy scores and regional grey matter volume in the right thalamus and in the right precuneus (sagittal view).



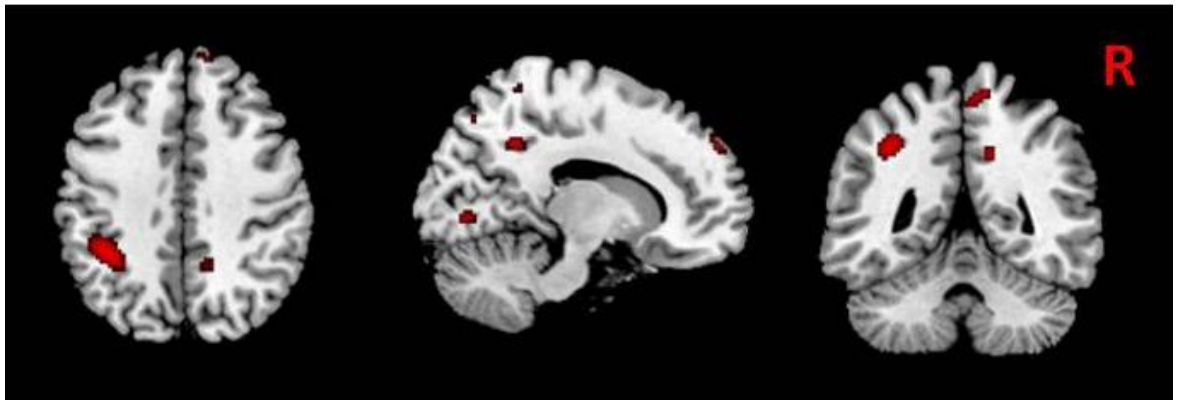
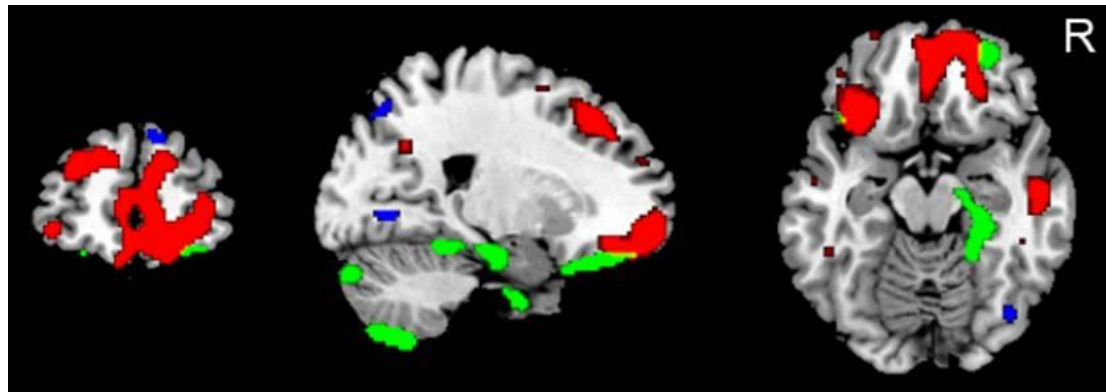


Figure 7.4. Areas of significant inverse correlation between apathy scores and regional grey matter volume in the left inferior parietal lobe (axial and coronal view) and in the right superior frontal (sagittal and coronal view) and the right inferior occipital gyrus (sagittal view).

To illustrate the topographical relationship between areas of significant correlations with delusions and apathy in PD and the regions that were found strongly related to high positive schizotypy, the maps of significant correlations were overlaid all on the same high resolution structural MRI volume (see Figure 7.5). While there were regions of overlap between some of the significant clusters associated with high positive schizotypy and those associated with high delusion scores in PD, no overlap was found between any of the areas showing significant correlations with schizotypy and the clusters of significant correlations found associated with high apathy scores.



Red = Positive schizotypy  
 Green = Delusions  
 Blue = Apathy  
 Yellow = Overlap between positive schizotypy and delusions

Figure 7.5. Areas of overlap between positive schizotypy and delusions. The areas of correlation between grey matter and apathy were uniquely related to this symptom only.

### 7.7.6 CONCLUSION

The behavioural result for delusions, whereby higher delusion frequency and severity was positively associated with positive schizotypal traits was consistent with the hypothesis. This significant association suggests that positive schizotypy is an appropriate endophenotype for explaining the aetiology of delusional psychotic symptoms in a PD neuropharmacological model.

Furthermore the lack of association between apathy and positive schizotypy demonstrates that positive schizotypy is selectively associated with delusions. This suggests that rather than being a susceptibility marker for all neuropsychiatric symptoms, positive schizotypy has a unique relationship to delusional aspects of psychosis. This finding is especially salient when compared with the neuroanatomical regions that were found to be involved in non clinical positive schizotypy as a personality construct in the previous chapter. Whilst the regions that appear to support positive schizotypal traits have remarkable

convergence with regions that have been reported to be involved in delusions in previous studies, and indeed the current study, they do not however suggest that a reciprocal structural behavioural relationship between positive schizotypy and propensity to develop apathy is at all likely. As the voxel based morphometric results for apathy in the current study demonstrate, there is no physical overlap between the neuroanatomical regions and circuitry involved in apathy and those which subserve schizotypal personality traits and delusional symptoms (please see Figure 7.5). As the relationship between behaviour, brain structure and apathy was included to highlight the anatomical and behavioural specificity of positive schizotypy to delusional psychosis, the structural correlates will not be discussed in further detail in the current thesis.

The neuroanatomical correlates for delusions in this PD sample are in line with the results of the previous study where higher positive schizotypy scores were associated with smaller GM volumes bilaterally in the frontal (the medial, middle, inferior, precentral and superior) and cingulate cortex. As demonstrated by Figure 7.5 there is overlap between the brain regions which are associated with the predisposing personality type and the expression of delusional psychosis. The current results are also consistent with the neuroanatomical evidence for delusions from other studies in terms of the laterality of the frontal systems as the frontal involvement is bilateral but predominately right sided (Forstl et al., 1991; Staff et al., 1999; Venneri et al., 2000; Sulzer et al., 2003; Shanks & Venneri, 2004; Bruen et al., 2008) and more generally, the involvement of the frontal lobes (Sultzer et al., 2003; McMurtray, Sultzer & Monserratt, 2008; Nagahama, Okina, Susuki, & Matsuda 2008; Whitford, Farrow, Williams et al., 2009; Pernecky, Drzezga, Boecker et al., 2009). The cingulate cortex and temporal lobe have also

been associated with delusions in previous studies (Blackwood, Bentall, Ffytche et al., 2004; Garrity, Pearlson, McKiernan et al., 2007) and with positive schizotypal personality traits in Experiment 3 in chapter 6. The association between delusions and the right inferior parietal lobe has also been reported in a prior study (Bruen et al., 2008). The link between the parietal lobe and the bilateral cerebellum and delusions could be interpreted in light of a dysfunctional cerebellar parietal network which has been implied in delusions (Blakemore, Oakly & Frith, 2003) and hypothesised to lead to the misattribution of external agency (Spence 1997; Blakemore, 2003). In fact, previous work has identified the cerebellum as being a central component of the neural basis of agency (Yomogida, Sugiura, Sassa et al., 2009). Cerebellum activation has also been associated with delusion, persecutory ideation and suspiciousness in a prior fMRI study (Whalley, Gountouna, Hall et al., 2007).

The findings are also convergent with the predictions based on Canli et al's. (2001) individual differences model of the differential effects of specific drugs on individuals with certain personality profiles. In the current study, variance in individual differences in positive schizotypal personality traits is associated with psychotic reactions to Levodopa medication.

In summation, these findings indicate that delusional neuropsychiatric symptoms in PD are associated with lower regional grey matter volumes predominantly in right hemisphere and that they are more likely to emerge following treatment in those patients who have a predisposing biological and psychological vulnerability.

## ***7.8 GENERAL CONCLUSIONS***

In the current chapter, single case studies and behavioural and neuroimaging experiments were presented in order to test the hypothesis that predisposing personality traits represent a diathesis that corresponds to a latent variable that is manifest quite normally as individual differences in personality unless interaction with neurological or significant environmental stressors lead to its endophenotypic expression as delusional psychosis.

In each of these studies, the conceptualisation of positive schizotypy as an endophenotype for psychosis in a diathesis stress model was validated behaviourally and anatomically. In the single case studies, schizotypal traits predicted psychotic decompensation due to severe affective and environmental stressors, previous focal ischemic insult and neurodegeneration and PD medication. The hypothesis was then validated experimentally in a behavioural neuropharmacological study which found positive schizotypy to be exclusively related to psychotic manifestations of PD treatment with Levodopa. Furthermore, in a neuroanatomical neuropharmacological study of the same Levodopa treated PD patients, the psychotic manifestation that was behaviourally associated with positive schizotypy was also anatomically associated with regions which are also involved in the personality construct of positive schizotypy in young healthy individuals.

## CHAPTER 8

### DISCUSSION

The impetus of the work undertaken for this thesis was to establish whether the fully dimensional expression of positive schizotypal personality traits represents a psychological and biological diathesis that predicts psychotic decompensation in states of neurological stress. To our knowledge, this is the first piece of work to fully reconcile a predispositional psychological and biological susceptibility within a diathesis stress model of neurological psychosis. Whilst previous studies have assessed psychological or biological vulnerabilities to the development of psychotic symptoms in neurodegenerative and functional models, to date no individual study has theoretically or experimentally combined these features.

The initial behavioural studies served the function of establishing positive schizotypy firmly within a fully dimensional account as the performance of individuals within the highest positive schizotypy cut-off was identified to be neuropsychologically normal. This furthers the fully dimensional argument that positive schizotypy should be distinct from a psychotic disease model and also from the schizophrenia continuum. It is central to the current hypothesis that individuals with high positive schizotypy are not expected to be excessively liable to decompensate into psychosis and that their future potential for psychotic breakdown should be entirely distinct from schizophrenia spectrum breakdown processes. Individuals who are imminently vulnerable to psychotic breakdown in

the absence of severe neurological stress would be better conceptualised on the schizotaxic spectrum of the quasi dimensional continuum and as such are considered to be quantitatively and qualitatively distinct from those high positive schizotypal individuals on the fully dimensional personality spectrum.

Consequently, the model which informs the hypothesis of the current thesis would predict that individuals who are genetically at risk for psychosis, are so at a level that is protective against decompensation and that such psychotic breakdown processes are only predicted for these individuals if a significant amount of neurological stress occurs. Such a distinction may explain how the majority of individuals with high dimensional positive schizotypy remain healthy (Kwapil, Barrantes-Vidal & Silva, 2007), because this dimension is quite separate from a disease context.

High positive schizotypies should, however, be liable to manifest psychotic symptoms through a neurodegenerative process such as AD (Erer et al., 2005) or through any other significant neuropathological, neuropharmacological or extreme biopsychosocial environmental developments. In this explanation, the aetiology of the early emergence of delusional psychosis in the individuals with mild AD that were described in Chapter 1, could be due to a predisposing, pre-pathological structural genetic liability which remained latent until expressed endophenotypically through interaction with neurodegeneration.

This hypothesis arose from the results of an earlier study which investigated the neuroanatomical correlates of neuropsychiatric symptoms in a group of patients with mild Alzheimer's disease (AD; Bruen et al., 2008), from retrospective

studies related pre-symptomatic schizotypal traits to delusions in AD (Elise et al., 2005; Eror et al., 2005) and was also based on the convergence demonstrated between an association between delusional symptoms within this group of patients and specific brain region in other neurological illnesses (Staff et al., 1999; Sultzer et al., 2003; Forstl et al., 1991; Feinberg et al., 1999; Shanks and Venneri, 2002). Such neuroanatomical and behavioural convergence despite different aetiological background was hypothesised to be due to a reflection of individual differences in structural genetic vulnerability and/or neurodevelopmental susceptibility.

The aims of the thesis were novel in that an individual differences approach was adopted to test the endophenotype on a level that successfully validated the predictive ability of positive schizotypy in neurological psychosis on neuroanatomical, psychological, emotional, cognitive and symptomatic levels. The interdependence of these components has further legitimised the theoretical basis for assessing the vulnerability which positive schizotypy confers for neurological psychosis. For instance, the hypothesis was firmly rooted in the neuroanatomical correlates that have been reported to be involved in delusional psychosis in prior neuroimaging studies. In order for the construct to meaningfully represent a latent genetic liability for psychosis under neurological stress it was deduced that such psychosis prone personality traits would be reflected genetically as individual differences in brain structure in those brain regions which are involved in clinical psychosis, and that reflexively these regions would be associated with personality and neuroanatomically related delusion prone neurocognitive processes. Consequently, it was necessary to demonstrate that positive schizotypy is theoretically compatible with models of the cognitive and



physiological contributions to the development of psychosis (Shanks & Venneri, 2004; Ellis & Lewis, 2001; Frith, 1999).

Accordingly a hypothesis was constructed to reflect the way in which positive schizotypy appears to be a multidimensional construct that is comprised of multiple cognitive, emotional and biological mechanisms (Vollema, Sitskoorn et al., 2002; Yaralian et al., 2000), which appear to operate throughout the lifespan (Badcock & Dragovic, 2005) and to be related at the subsyndromal level to the cognitive, emotional and biological mechanisms which have been associated with psychosis.

In the first chapter which was devised to test the endophenotype's validity at a cognitive level, accounts of the association between an abnormal spreading activation in semantic networks and the formation and maintenance of delusions in schizophrenia was explored in relation to positive schizotypy. Whether this semantic spreading facilitation extended to participants with positive schizotypy was evaluated with reference to semantic reasoning and fluency. In the associative semantic reasoning experiment a model emerged which suggested improved reasoning ability, more years of education and lower positive schizotypal traits predicted higher performance in the similarities task. However, for the positive schizotypal individuals in the highest cut-off only high positive schizotypal traits explained their associative performance, unlike the other participants, reasoning ability and education conferred no explanatory function. This finding may suggest, that for individuals with high positive schizotypy a different mechanism may be involved in completing the task to that which is related to task

performance in the full group. Although more studies are necessary to understand why high delusion-prone schizotypies differ from low positive schizotypal participants on this task a tentative theory may suggest that the task is facilitated by different mechanisms, networks or even hemispheres in these groups.

Unfortunately, it was concluded that whilst compatible with the current findings, until further experimental work had been undertaken, these interpretations are at present merely speculative. Further empirical evidence is necessary to ascertain whether semantic spreading due to a right hemisphere processing bias is mediating the associative reasoning performance of HPS participants.

In a further study designed to explore the relationship between positive schizotypy and semantic spreading activation, it was predicted that lexical attributes such as typicality frequency, familiarity and imageability should vary between high and low positive schizotypal individuals. However contrary to these predictions, no evidence was established to suggest that high positive schizotypal participants produced words with significantly different frequency, familiarity, imageability and typicality in the semantic or phonological fluency tasks. Whether these null results represent type II errors due to lack of power or that advanced education confers protective advantages in the cognitive areas that have been found to be related to psychotic features in individuals with a genetic vulnerability for psychosis were discussed. However, the lack of evidence for disproportionately strong activation for weakly related words in the system could intimate that semantic spreading may not be an appropriate endophenotype for investigation of psychosis proneness in relation to neurological stress model. This may suggest that semantic spreading is more closely associated to schizophrenic breakdown

processes along the quasi dimensional spectrum as opposed to vulnerabilities that may be present in individuals whose high positive schizotypal traits may only confer psychosis risk endophenotypically as a consequence of neuropathology.

This theory is compatible with evidence that the qualitative differences between delusions in schizophrenia and neurodegenerative diseases suggest that different cognitive correlates will be associated with the formation and maintenance of delusions with such distinct aetiologies. Consequently, subsequent studies assessed the relationship between positive schizotypy and different cognitive correlates that were hypothesised to be more analogous to those which appear to be involved in neurological psychosis. Firstly, the relationship between positive schizotypy and a threshold for affective interference was examined with an emotional Stroop task that was designed to comprise the delusional prone themes on which positive schizotypal traits are conceptually based. However, whilst the affective content of the emotional words was sufficient to interfere with accuracy for all participants, it was not sufficient to cause specific cognitive disturbance. The demonstration of an ability to inhibit the semantic content of words chosen to be emotionally salient to positive schizotypy again supports the contention that semantic spreading may not be as relevant for delusion proneness in fully dimensional persons as it is for those on the quasi dimensional spectrum.

Whilst it was hypothesised that perhaps the words were not as emotionally salient to positive schizotypal participants as anticipated, the results from the related incidental learning paradigm suggested that despite the normative emotional Stroop performance, these emotional words were being processed differently by individuals with high positive schizotypy as they were recalling more emotional

words than participants with lower positive schizotypy scores. Most interestingly, high positive schizotypal participants were also making significantly more false alarms for emotional words than made by those with lower traits. The fact that high positive schizotypal participants made no more false alarms on neutral items than controls, and their intact recognition memory suggests that false positive errors on emotional items do not arise from impaired memory but are mediated by a different mechanism. Moreover, such findings may intimate a similar mechanism may underlie the association between false positive memory biases and delusion susceptibility in non clinical positive schizotypy. These findings converged with other recent studies that have found false alarms across several paradigms and cognitive and perceptual domains to be associated with positive schizotypy and have been interpreted in line with the externality hypothesis and jumping to conclusions bias demonstrated by personas with full blown psychotic delusions. False mnemonic alarms in non clinical psychosis prone individuals appear to be continuous with the manifestation of psychotic experiences in persons who are more clinically susceptible.

Two hypothesis were proposed to interpret the association between false alarms for emotional words and positive schizotypy. Firstly an abnormal facilitation of the spreading activation within semantic networks (Spitzer, 1997) could have created plausible but incorrect semantic associates of the words that were originally presented. Secondly, the way in which false positive memories of emotional words extends to the delayed condition in non clinical schizotypy may be analogous with the confabulations in episodic memory that have been associated with clinical delusions (Lee et al., 2007). A continuum was proposed whereby episodic memory systems may be more susceptible to false positive

errors in non clinical psychosis prone individuals, but for pathological populations, greater impairments in such memory systems may be associated with full blown delusion formation and maintenance. However, further studies are necessary to explore the extent to which an association between episodic memory, false memory, confabulation and delusion proneness or the relationship between semantic spreading and psychosis can advance explanations of the current findings and more generally of the correlates of psychosis proneness in non-clinical positive schizotypy.

The rationale behind the neuroimaging studies was based on the hypothesis surmised from the results of the voxel based regression of delusions in AD (Brien et al., 2008), that the specific regional associations we found may be due to individual differences in structural genetic vulnerability. Thus the neuroimaging studies in the current thesis assessed whether individual differences in schizotypal traits in normal individuals, were associated with variance in the brain regions which have been related to psychosis in previous studies. This should facilitate identification of whether variance in individual differences in positive schizotypy in normal individuals is reflected endophenotypically in the structure of the brain and the extent to which schizotypy may represent a predisposing structural liability for the emergence of delusions under different neurological and extreme environmental stressors.

Due to the fact that understanding the mechanisms which mediate the variation and expression of non-clinical positive schizotypal traits may reveal latent variables that could advance explanations of the aetiology of psychosis, a voxel based morphometric study of the neuroanatomical correlates of positive

schizotypy was conducted. Inverse voxel-based regression analyses revealed higher positive schizotypy was discretely and significantly associated with specific regions of lower grey matter (GM) volumetric values bilaterally in the frontal and cingulate cortices (although the extent of involvement of right sided areas was far greater than in the left) and in the right temporal lobe. The bilateral yet asymmetrically right dominant associations between high positive schizotypy scores and specific regions of lower GM tissue volume in the frontal lobes are in line with the hypothesis and are consistent with findings from schizophrenia studies (Pantelis et al., 2003), positive schizotypy findings (Gruzelier & Doig, 1996; Leonhard & Brugger, 1998; Nunn & Peters, 2001; Weinstein & Graves, 2002), neurodegenerative research of patients with psychosis (Forstl et al., 1991; Staff et al., 1999; Venneri et al., 2000; Sulzer et al., 2003; Shanks & Venneri, 2004; Bruen et al., 2008) and with the results from the studies which suggest confabulation and delusions are associated with structures which are also involved in episodic memory (Lee et al., 2004; 2007; Bruen et al., 2008). The way in which the anatomical correlates may explain the behavioural manifestation of false alarms in the previous studies was found to be especially important for a hypothesis which suggests that structural variance in normal individuals confers a latent susceptibility for psychosis under neurological stress. It follows that if this vulnerability which is behaviourally manifest as individual differences in schizotypal personality is represented in the structure of the brain in normal individuals, and if the structures involved are in the same regions that are related to psychosis in clinical populations, then it would be logical to predict that analogous brain behaviour relationships, qualitatively comparable but quantitatively less pronounced than those that are associated with the full

endophenotypic expression of psychosis, should be behaviourally manifest in the prodromal phase.

The way in which individual differences in schizotypal traits in normal individuals were found to be associated with variance in some of the brain regions which have been related to psychosis in previous studies offers validation to the original hypothesis that individual differences in positive schizotypy in normal individuals are reflected endophenotypically in the structure of the brain. Whilst some accounts would suggest repeated behaviours and environmental contexts that are related to specific personality traits cause the variance in brain regions, according to Gardini et al., (2009) the evidence from developmental behavioural genetics (Heiman, Stallings, Young, & Hewitt 2004) provides a compelling account to support the interpretation that variance in regional brain morphology is expressed at the behavioural level as individual differences in personality.

The way in which this brain behaviour correlation is expressed in the brain structure of healthy young individuals, intimates that independent of aetiology, psychosis appears to be closely related to dysfunction in bilateral but predominantly right sided frontal and cingulate regions. As the result of this study demonstrate, even in non-clinical persons, individual differences in positive schizotypal traits are reflected in the structural variance of the specific neural areas that are involved in psychosis. According to the neurological stress hypothesis, it is predicted that most individuals with this atypical but dimensional trait will not decompensate. However, should high positive schizotypal individuals succumb to the duress of a significant stressor, especially a

neurologically based one, the prominent symptom will be psychosis. This inverse association between higher positive schizotypy scores and lower GM tissue volume suggests that these individuals possess a latent underlying structural vulnerability or diathesis to psychosis. Whether this neuroanatomical expression represents a valid predisposing structural liability to the emergence of delusions under different neurological and extreme environmental stressors was tested in the final experimental chapter within a clinical population and in a series of single case studies of patients with various psychotic presentations with distinct aetiologies.

In these studies, the conceptualisation of positive schizotypy as an endophenotype for psychosis in a diathesis stress model was validated behaviourally and anatomically. In the single case studies, schizotypal traits predicted psychotic decompensation due to severe affective and environmental stressors, previous focal ischemic insult, neurodegeneration, and PD medication. These studies contributed to a picture that suggests that, despite different natural histories for the emergence of psychosis, positive schizotypal personality traits nevertheless reliably predict psychiatric decompensation in combination with severe stressors such as dopamine agonists, bereavement and depression, and focal ischemic insult and neurodegeneration. These studies contribute to the validity of the anatomical and behavioural evidence for positive schizotypy as an endophenotype in a diathesis stress model of neurological psychosis.

The hypothesis was then validated experimentally in a behavioural neuropharmacological study which found positive schizotypy to be exclusively related to psychotic manifestations of PD treatment with Levodopa. Furthermore,



in a neuroanatomical neuropharmacological study of the same Levodopa treated PD patients, the psychotic manifestation that was behaviourally associated with positive schizotypy was also anatomically associated with regions which are also involved in the personality construct of positive schizotypy in young healthy individuals. The way in which higher delusion frequency and severity was positively associated with positive schizotypal traits at the behavioural level was also reflected at the neuroanatomical level. The behavioural and anatomical contingency of these significant associations suggests that positive schizotypy is a valid endophenotype for explaining the aetiology of delusional psychotic symptoms in a PD neuropharmacological model.

These results can also be extended to make predictions in light of a threshold account for the way in which differing quantities and combinations of positive schizotypal traits might interact with differing levels of neuropathology or neuropharmacological inputs to explain individual differences in the threshold for psychotic decompensation. As positive schizotypy reflects sufficient variance in individual differences to explain its differential contribution to a liability for psychosis (Kuntsi, Andreou, Ma et al., 2005) and given the fact that these differences are heritable and expressed between and within individuals reliably throughout the lifespan (Kuntsi, Andreou, Ma et al., 2005), the validity of regarding schizotypy as an endophenotype for psychosis is increased. Similarly, the individual differences aspect of the endophenotype also has explanatory power for the findings that psychosis in Alzheimer's disease or psychotic presentations following certain neuropharmacological treatments in other diseases do not result in psychosis in all individuals (Paulsen et al., 2000; Forstl et al., 1994; Canli et al., 2001). For instance, the fact that some individuals express an Alzheimer's disease

phenotype at an early stage compared with others may reflect variance in the extent to which the endophenotype is expressed within individuals. This would also indicate that the threshold of AD, or other neurodegenerative pathology required to reveal the phenotype would vary considerably amongst individuals as a function of individual differences in endophenotypic expression. In light of the hypothesis, these disparities are not inevitable and nonspecific concomitant of increased disease severity (Sweet et al., 2003) or drug administration but are due to individual differences in the expression of positive schizotypy.

The conceptualisation of positive schizotypy as an endophenotype for neurological psychosis could enhance the prospect of earlier detection of at risk individuals and improve diagnostic predictive ability. It should also help to guide more effective and specific interventions and preventative actions. For instance positive schizotypy could be used as a screening measure to identify patients who may be unsuitable for certain pharmaceutical interventions or suggest that some persons may need more careful monitoring when certain drug therapies are administered. Future studies are required to further the predictive and ameliorative potential of the construct.

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