Neuropsychological and Electrophysiological Biomarkers of the Schizophrenia Spectrum

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ABSTRACT

Schizophrenia is a neuropsychiatric disorder lying at the extreme of a spectrum of disorders that possibly share a common abnormality in neural connectivity. Efforts to reverse the core cognitive manifestations of schizophrenia using drug treatments have so far been unsuccessful. This thesis investigates the cognitive abnormalities and their electrophysiological correlates across the schizophrenia spectrum in order to identify and validate biomarkers for proof of concept studies of cognitive enhancers. Such studies in milder disorders of the schizophrenia spectrum such as schizotypal personality trait may be a crucial method in identifying new effective compounds, as reviewed in Chapter 3, and tested in Chapter 4. The latter features the results of a large three-centre study which probed the sensitivity of several neuropsychological measures to the schizotypy phenotype, as well as to the effects of amisulpride, risperidone and nicotine. Schizotypal volunteers showed impaired performance only on the more difficult tasks. The most consistent pharmacological finding was that amisulpride tended to improve performance in the high schizotypy group but to impair it in the average schizotypy controls. One interpretation is that the ability of low dose amisulpride to enhance dopamine function in frontal cortex reversed an impairment of dopamine function present in the high schizotypes which is thought to occur in schizophrenia. Chapter 5 explored the methodological question of whether low or average schizotypy individuals should be used as controls in cognitive comparisons versus high schizotypy. The results suggest that low schizotypes have the most intact cognitive performance and are therefore the control group of choice. Chapters 6, 7 and 8 tested the hypothesis that cognitive deficits are part of a larger information processing abnormality in the schizophrenia spectrum. In accordance, both high schizotypy and schizophrenia patients exhibited reduced amplitude of an early visual evoked potential P1 (Chapters 6 and 8, respectively) and disruptions of the underlying evoked neural oscillations (Chapters 7 and 8). The pattern of abnormalities suggested an inefficient top-down modulation of perception in the schizophrenia spectrum. These data argue that cognitive abnormalities and their electrophysiological correlate may be sensitive biomarkers of the core dysconnectivity deficit in schizophrenia. This thesis supports their use in proof of concept studies to foster the development of cognitive enhancers.

DECLARATION

that no portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning;

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THE AUTHOR

The author completed his medical training in 2007 at the Medical University in Sofia before being awarded a Manchester University Strategic Studentship in 2008 to pursue a PhD. During the past 3 years, the author was involved in translational research in the context of clinical neuroscience at the Neuroscience and Psychiatry Unit, the University of Manchester and the Wellcome Trust Clinical Research Facility, Manchester. After his PhD, the author plans to start specialist medical training with a view of combining academic and clinical practice.

RATIONALE FOR SUBMITTING THE THESIS IN AN ALTERNATIVE FORMAT

There were four experiments that contributed to this thesis and their results were written up as scientific articles shortly after the studies' completion. The option of using these articles in the current thesis allowed the author to concentrate on the preparation of the outstanding chapters. In addition, the peer review process of the submitted articles provided critical feedback that was used for the chapters that are yet to be submitted for publication. Overall, the option for alternative format submission was a major contributing factor to the accomplishment of the author's target of completing the PhD programme within 3 years of its initiation.

The final thesis format includes the traditional chapters of introduction, methodology and general discussion. The core of the thesis is formed by one article providing a review of previous research in the field of investigation and five original papers derived from the data of four experiments.

ABBREVIATIONS

AS	Average Schizotypy
ADC	Analog to Digital Converter
BCL	Biconditional Learning
BESA	Brain Electric Source Analysis
BPRS	Brief Psychiatric Rating Scale
CANTAB	Cambridge Neuropsychological Test Automated Battery
CMS	Common Mode Sense
COMT	Catechol-O-amine Transferase
D2	Subtype 2 dopamine receptor
dB	Decibel
DDD	Defined Daily Dose
DRL	Driven Right Leg
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders – 4th edition
EEG	Electroencephalography
ERPs	Event-Related Potentials
FDA	Federal Drugs Agency
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-aminobutyric Acid
GFP	Global Field Potential
HS	High Schizotypy
Hz	Hertz
ICD-10	International Classification of Disease – 10th edition
IEDSS	Intra- and Extra-Dimensional Set Shift
IQ	Intelligence Quotient
ITC	Inter-Trial Coherence
LS	Low Schizotypy
LSD	Least Significant Difference
MATRICS	The Measurement and Treatment Research to Improve Cognition in Schizophrenia
MEG	Magnetoencephalography
MINI	Mini International Neuropsychiatric Interview
MMN	Mismatch Negativity
NMDA	N-methyl-D-aspartate
PAL	Paired Associate Learning
PET	Positron Emission Tomography
PLF	Phase Locking Factor
RT	Reaction Time
SAT	Salience Attribution Test
SCID	Structured Clinical Interview for DSM-IV
SPD	Schizotypal Personality Disorder
SPEM	Smooth pursuit eye movement
SWM	Spatial Working Memory task
TF	Time-Frequency
VEPs	Visual Evoked Potentials
VF	Verbal Fluency Task
WM	Working Memory

CHAPTER 1

GENERAL INTRODUCTION

1.1. Schizophrenia

Schizophrenia is a clinical syndrome based on the presence of a collection of mental and behavioural phenomena. These include the so-called positive (abnormal perceptions and delusions) and negative (emotional flattening, lack of drive and will) symptoms, as well as widespread cognitive abnormalities and behavioural disorganization (bizarre behaviour and thought disorder). However, none of these symptoms are patognomic and a variety of presentations are possible.

1.2. Aetiology of schizophrenia

Despite more than a hundred years of research, the factors that cause schizophrenia are still unclear. What we know is that it affects just under 1% of the general population and that it is characteristically rare before puberty reaching its peak incidence is in the early adulthood (Tandon et al. 2009). This implicates a vulnerability of the nervous system that becomes exposed only during late maturation of the brain. This key vulnerability is likely to be familial with genetic factors accounting for more than 80% of the liability to schizophrenia (Tandon et al. 2008). However, only a small fraction, around 5-10% of all first degree relatives of schizophrenia patients go on to develop schizophrenia in their life time. This indicates that a significant proportion of those at genetic risk remain unaffected. These genetically vulnerable individuals however have been shown to be more prone to certain psychiatric illnesses (schizoaffective disorder) and personality disorders (schizotypal, paranoid and schizoid personality disorders) that resemble schizophrenia (Kendler, McGuire et al. 1993; Kendler, McGuire et al. 1993; Kendler, McGuire et al. 1993). This has led to the hypothesis that schizophrenia-related personality and schizophrenia are the increasingly extreme manifestations of a continuously distributed dimension of risk (Meehl 1989; Lenzenweger 2006). It is plausible that the very same basic abnormality of the nervous system is present across this spectrum, but depending on its extent and the influence of other risk factors it might results in the symptoms of schizophrenia: its ultimate complication.

The importance of non-genetic factors in the development of schizophrenia has been highlighted by research into environmental risk factors. These have been generally divided into early and late ones. The former take place during pregnancy or birth and therefore have the potential of disturbing the neurodevelopment of the fetus. These include influenza infection (Sham et al. 1992) and malnutrition (Susser et al. 1992) in the first trimester. In addition, obstetric complications (Lewis et al. 1987) and premature birth (Geddes et al. 1999) have both been linked to higher incidence of schizophrenia in adult life. These environmental risk factors probably interfere with normal neurodevelopment in those with genetic vulnerability. The group of later factors encompasses circumstances of the childhood and early adulthood of the individual. The most important ones are: i) being reared in immigrant communities ('lack of culturalization') (Selten et al. 1997; Kirkbride et al. 2006); urban rearing (Lewis et al. 1992), childhood abuse (Janssen et al. 2004) and cannabis consumption (Henquet et al. 2005). This group of factors probably serve to increase the risk of schizophrenia in those with genetic or neurodevelopmental vulnerability. Additionally, other environmental factors such as negative life events (Birley et al. 1970) or living with high emotion expressing relatives increase the risk for relapse in the established disease (Leff et al. 1980). Both early and late environmental factors therefore probably interact with the genetic vulnerability to trigger and decompensate a neurodevelopmental abnormality that may manifest itself as schizophrenia.

1.3. Schizophrenia: Is it in the brain?

The validity of this theory of schizophrenia thus depends on a crucial question – is there any evidence for an organic abnormality, a primary neuronal deficit, in schizophrenia? If so, is a similar pattern detectable in the milder cases of the spectrum?

The answer to the first part of the question has been the subject of prolonged debate. This controversy dates back to Kraeplin, the first psychiatrist to define schizophrenia or dementia praecox, as he named it. As the name suggests, he saw the syndrome as a form of early onset dementia. At a time when interest in neuropathology was at a peak, he understandably hypothesized that dementia praecox has its own

neuropathological substrate. The search for post-mortem abnormalities in patients however has been notoriously futile and controversial at best (Powchik et al. 1998). This encouraged alternative explanations to the pathophysiology of the disease, linking it to abnormal early life experiences. This view was inspired by the development of psychoanalysis and was at the heart of a powerful anti-psychiatric movement in the middle of the 20th century.

1.4. The dopamine evidence

Three important developments in the second half of the 20th century aided the case for an organic cause of schizophrenia. The first one came with the advent of a class of drugs known as neuroleptics. The first agent, chlorpromazine was developed as an antihistamine to be used in surgery but in 1952 was reported to be particularly useful in controlling the symptoms of patients with schizophrenia. The efficacy of the new drug surpassed the other alternatives at the time so convincingly that it took only a few years before it had established itself as first line of treatment. In the early 1960s Avid Carlsson found that chlorpromazine blocked the behavioural effects of the dopamine-releasing agent amphetamine. He postulated the existence of dopamine receptors that mediate the effects of dopamine and that these are blocked by chlorpromazine and related drugs – the dopamine hypothesis of psychotic action (Carlsson 1978). These discoveries won Carlsson the Nobel Prize in Medicine. The corollary hypothesis that schizophrenia involves excessive dopamine release (Carlsson 1977) was stimulated by the clinical insight that amphetamine can trigger schizophrenia-like psychotic episodes (Connell 1958). The original dopamine hypothesis therefore states that the disorder is due to excess dopamine action in the brain, specifically along the mesolimbic dopamine pathways. Direct evidence of dopamine hyperfunction in schizophrenia emerged from the use of PET to quantify radioligand binding in living human subjects (Abi-Dargham et al. 2000). Abi-Dargham et al. used alpha-methyl-para-tyrosine to induce acute dopamine depletion in patients and controls. As the duration of the challenge was too short to cause D2 receptor up-regulation, the difference between D2 receptor availability at baseline and the depleted state was hypothesized to reflect the amount of receptors normally occupied by dopamine. The authors found that after dopamine depletion raclopride

binding was higher in patients relative to controls dopamine and this was interpreted as evidence for higher baseline D2 receptor stimulation in schizophrenia. These results build on previous reports that amphetamine administration displaces more D2 receptor ligands in patients than in controls (Breier et al. 1997; Abi-Dargham et al. 1998). Amphetamine increases endogenous dopamine release which competes with the D2 ligands for postsynaptic dopamine receptor binding sites thus causing a reduction in radioligand binding as measured by PET. That this happens more in patients than controls is indicative of greater endogeneous dopamine release in acute schizophrenia.

The dopamine hypothesis was revised in the 1990s to account for several converging lines of evidence of prefrontal cortex dysfunction in schizophrenia. Firstly, Ingvar and Franzen showed reduced prefrontal cortex blood flow in patients (Ingvar et al. 1974) that was linked to psychomotor poverty syndrome in schizophrenia (Liddle et al. 1992). Secondly, using functional neuroimaging methods schizophrenia patients were shown to have lower degree of prefrontal cortex activation during demanding cognitive tasks, such as the Wisconsin Card Sorting Test (Weinberger et al. 1986; Wolkin et al. 1992; Kawasaki et al. 1993). These two findings indicated that schizophrenia is characterized by a prefrontal cortex dysfunction. The next development came with the work in primates by Goldman-Rakic demonstrating that prefrontal cortex function is facilitated by dopamine (Goldman-Rakic 1987). This suggested that a hypodopaminergic state might be responsible for the prefrontal cortex abnormality in schizophrenia. The paradoxical implication of co-existing hypo- and hyper-dopaminergic states were reconciled by evidence that neurotoxin lesion of mesocortical dopamine rejections cause the remaining projections to be over-reactive (Pycock et al. 1980). The revised dopamine hypothesis therefore argues that the increased dopamine release in the striatum is secondary of an impairment of frontal dopamine function (Weinberger et al. 1988; Davis et al. 1991); the former mediating positive symptoms and the latter impaired cognition and negative symptoms.

Whether this dopamine dysfunction characterizes only patients with psychosis or also the proposed milder forms of the schizophrenia spectrum is still an open question. The lack of overt psychosis in the latter group argues against excessive dopamine release in the mesostriatum. However, some evidence exists to suggest that people with high

levels of schizotypal personality traits (high schizotypy) have suboptimal activity in the prefrontal cortex (Koenigsberg et al. 2005). In support of this, a study administering a compound enhancing dopamine activity (a mixed D1/D2 dopamine receptor agonist) found improvement of prefrontal cortex function in patients with SPD (McClure et al. 2010). The improvement of function with dopamine enhancement appears to be specific to schizophrenia-related personality disorder as a study using amphetamine in patients with schizotypal and non-schizophrenia related personality disorders demonstrated (Kirrane et al. 2000). It is thus possible that one of the organic substrates of the schizophrenia spectrum is a sub-optimal dopamine prefrontal cortex function. This hypothesis was investigated in the current thesis by exploring the modulation of prefrontal cortex functions in schizotypy by agents affecting dopamine neurotransmission.

1.5. The structural evidence

The second major breakthrough came with the invention of an imaging technique, computer tomography (CT). It allowed for the first time the observation of the neuroanatomy of a living subject. A landmark study in schizophrenia patients revealed that there is an enlargement of the lateral brain ventricles (Johnstone et al. 1978). Such enlargement typically follows the loss of adjacent brain tissue and is a common finding in degenerative disease. This finding was replicated by numerous studies, including later ones which used a new class of imaging equipment, magnetic resonance imaging (MRI). It boasts the advantages of more precise delineation of the different brain regions, and lack of radioactivity-related side effects. The MRI data from schizophrenia patients has confirmed brain volume loss in multiple grey and white matter regions (Shenton et al. 2001).

Structural MRI studies have extended these findings to schizotypal personality disorder (Siever et al. 2002; Raine 2006). Schizotypy is also associated with lateral ventricle volume increase (Buchsbaum et al. 1997; Silverman et al. 1998), as well as gray matter reductions in the temporal lobe and thalamus (Dickey et al. 1999; Downhill et al. 2001). Compared to patients these structural abnormalities are generally of lesser magnitude and sparing some brain regions. Nonetheless, it appears

that structural brain abnormality is a feature associated with the risk for schizophrenia.

1.6. The cognitive evidence

The third development that aided the case for an organic abnormality in schizophrenia was the finding that impaired cognition is a core symptom domain (Green 2006). This is important as virtually all conditions that feature brain damage and degeneration feature cognitive impairment. In schizophrenia, the cognitive deficits typically predate the onset of the disease (Sorensen et al. 2006) and remain stable despite the symptom fluctuations and variance (Heinrichs 2005). The currently available antipsychotic medication has been shown to have at best only marginal impact on cognition, despite being broadly effective in controlling psychotic symptoms (Heinrichs 2005). They are also the single best predictor of functional and social outcome (Hofer et al. 2005; Milev et al. 2005). In fact, meta-analyses have shown that cognitive measures are the only research method that manages to distinguish a majority of schizophrenia patients from healthy individuals (Heinrichs 2005). It is thus increasingly likely that in the face of cognitive impairment schizophrenia research has found not only further proof of the organic nature of the disease, but also an objective and inexpensive measure of one of its core, currently unaffected by therapy features.

Cognitive impairment is also evident in schizotypy (Mitropoulou et al. 2002; Mitropoulou et al. 2005) and unaffected relatives of schizophrenia patients (Keefe et al. 1994; Sitskoorn et al. 2004). Similar to the structural abnormalities, these deficits are of lesser severity and affecting only a subset of the cognitive functions impaired in schizophrenia (Siever et al. 2004; Raine 2006). This data supports the suggestion that a subtle organic disruption of the nervous system unifies the schizophrenia spectrum disorders.

1.7. Pathogenesis: Theories

The accumulated evidence of disruptions in various neural processes and morphological changes in schizophrenia has indicated that it is increasingly unlikely

for the core disruption to affect a single region, such as the prefrontal cortex. Instead current theories favour a more distributed pathogenesis. On the assumption that the separate symptom domains can be attributed to specific brain regions one prominent theory likens schizophrenia to systemic diseases such as multiple sclerosis or cerebral lupus where discrete lesions in different sites produce a heterogeneous and varied clinical syndrome (Carpenter et al. 1985; Andreasen 1986). Another one implicates a dysfunction in the processes that mediate neuronal communication (Friston 2005). Such a primary abnormality in the connectivity or "wiring" of the brain will also produce multiple heterogeneous deficits depending on the neural circuits it affects. The advent of imaging techniques that allow the investigation of functional connectivity such as functional MRI (fMRI), positron emission tomography (PET) and time-frequency analysis using electroencephalography or magnetoencephalography lent support to the latter hypothesis. Studies in patients using these methods have demonstrated disruptions in neural connectivity during cognitive tasks and in resting state.

1.8. Status quo: Operational diagnostic criteria

Despite these advances in our understanding of the neuropathological underpinnings of schizophrenia, from diagnostic point of view it is still a functional, syndrome-based disorder. In fact, known sufficient organic causes of the schizophrenia syndrome automatically exclude the diagnosis of schizophrenia. Instead, the current operational definitions of schizophrenia (laid out in the tenth revision of the International Classification of Diseases, ICD-10, and the fourth revision of the Diagnostic and Statistical Manual of Mental Health Disorders, DSM-IV) put the accent on the presence of psychotic symptoms for sufficiently long period of time as well as some degree of functional impairment. Despite providing a much needed consensus regarding the characteristic features of schizophrenia (Kendler et al. 1994; Kety et al. 1994), DSM-IV and ICD-10 diagnoses suffer from inherent fundamental problems. Firstly, the overreliance on psychotic symptoms introduces diagnostic ambiguities both in respect to other conditions that feature psychosis (Tandon et al. 2009), as well as when drawing the line between schizophrenia, personality disorders and even healthy volunteers (Kendler et al. 1996). In addition, longitudinal studies have shown

that psychotic symptoms are poor at predicting the course of the disease and response to drugs (Jansson et al. 2007). Finally, basing the diagnosis solely on the patients' reports and clinician's observations introduces a subjective element that could account for the operational diagnoses' modest reliability (Jansson et al. 2007). This is perhaps most relevant in regards to schizophrenia spectrum research, where all the key features are based on the clinician's judgement (Jones et al. 2006). The drawbacks of the operational schizophrenia diagnosis have wide ranging implications, affecting the reliability of fundamental and clinical research. In respect to genetic studies for example, none of the identified risk genes are specific to schizophrenia, but rather indicate general vulnerability to mental health disorders or personality psychopathology (Allan et al. 2008).

1.9. Towards mechanism-based understanding of schizophrenia: Biomarkers

The search for an aetiology-based rather than syndrome-based definition of schizophrenia has stimulated research into biological correlates of disease process in schizophrenia. The NIH Biomarker Definitions Working Group defines biomarkers as quantifiable outcomes which are modified by the disease and therapeutic intervention. Defining the neurobiological substrate of schizophrenia through biomarkers can help negate the drawbacks of the currently used operational criteria.

In terms of diagnosis reliability, successful biomarkers could help delineate it from its related disorders or subtype the condition into distinctive disorders that are currently grouped together by the DSM-IV and ICD-10 criteria. It has been argued that subtyping of schizophrenia could lead to significant empowerment of genetic and other basic research (Stober et al. 2009).

The benefits of an ideal biomarker go further than improving diagnosis and include predictive power for disease course and treatment outcome. Such property will improve patient management by informing the time, type and course of interventions. In the context of drug development, such predictive power can help reduce the size and duration of clinical trials by substituting traditional clinical end points with

biomarker measurements. Also, a successfully developed biomarker would provide an insight into the key pathophysiological mechanisms of the disease and therefore validating targets for novel therapeutic interventions. Finally, validating biomarkers in milder versions of the disorder would allow earlier evaluation of efficacy of novel compounds which may reduce the risk associated with drug development.

1.10. The current thesis: Topic, hypotheses and predictions

The promise of a successfully developed biomarker in schizophrenia to revolutionize its diagnosis, treatment options and management has stimulated the work that forms this thesis. The focus of this thesis was on the development of biomarkers that objectify the cognitive impairment in the schizophrenia spectrum. Cognition was chosen because of the data implicating it as a core feature of schizophrenia and the lack of efficacy of currently available medication on this core set of symptoms. The aim was to establish tests that reliably detect the cognitive deficit in the schizophrenia spectrum and are sensitive the action of agents modulating key neurotransmitter systems. This builds on the extensive knowledge regarding the neuropharmacology of cognitive biomarkers in schizophrenia spectrum which is reviewed in detail in Paper 1. The ultimate goal of this biomarker validation in schizotypy was to allow the early testing of efficacy of novel cognitive enhancing agents. Another priority of the work constituting thesis was the exploration of the neurophysiological mechanisms that underlie cognition in the schizophrenia spectrum. The aim was to gain better understanding of the key pathophysiological abnormality in this disorder and to elaborate better and more precise biomarkers to detect it. Based on these goals the following hypotheses and their corresponding predictions were generated:

Hypothesis 1: Schizophrenia is the extreme of a spectrum of disorders that is characterized by cognitive deficits

Prediction 1.1: Schizotypy is associated with cognitive deficits similar to the ones found in schizophrenia

Prediction 1.2: Schizotypy will feature abnormalities in trait but not state dependent cognitive domains as it represents a less extreme deviation from the norm than schizophrenia

Hypothesis 2: Cognitive abnormality in the schizophrenia spectrum is a continuously distributed trait

Prediction 2.1: Cognitive performance decreases with the increase of schizotypal personality traits

Hypothesis 3: The deficits in executive function in the schizophrenia spectrum are modulated by dopamine

Prediction 3.1: Cognitive abnormalities in schizotypy will be affected by drugs altering dopamine

Hypothesis 4: Impairment in higher cognitive function in the schizophrenia spectrum is a manifestation of a general abnormality in information processing

Prediction 4.1: Information encoding in both schizotypes and schizophrenia patients will be associated with reductions in the amplitude of early visual ERPs

Prediction 4.2: Early perceptual deficits correlate with cognitive deficits

Hypothesis 5: The information processing deficit in schizophrenia spectrum reflects a pathological change in cortical connectivity

Prediction 5.1: Cortical connectivity will be abnormal in both schizotypes and schizophrenia patients resulting in abnormalities in the power and phase relationships of neural oscillations evoked by visual stimuli

Prediction 5.2: Both groups will have evidence of dysfunctional long-range cortical connectivity during tasks that require top-down modulation.

1.11. Studies undertaken to address the thesis hypotheses

As part of this PhD thesis 4 studies ("Schiz01", "Low Schizotypy", "Schizotypy EEG" and "Schizophrenia EEG" studies) were undertaken to address the 5 hypotheses.

In the first study ("Schiz01"), is a study designed by an academic-industrial consortium in which high and average schizotypy scorers were recruited across three sites of the UK (Manchester, London and Cardiff). The two participant groups were compared using several cognitive measures. The results of this study were used to address Hypothesis 1 and specifically the prediction that high schizotypy scorers will feature cognitive abnormalities similar to the deficits reported in schizophrenia patients (Prediction 1.1).

The cognitive performance of the volunteers in the Schiz01 study was also challenged by the acute administration of 3 psychotropic agents (risperidone, amisulpride and nicotine) in a placebo-controlled, randomized, double-blind design. The effects of these compounds on the cognitive performance of the average and high schizotypy scorers were interpreted in the context of Hypothesis 3 and specifically in light of the prediction that the cognitive abnormalities in high schizotypy can be altered by drugs affecting dopamine neurotransmission (Prediction 3.1). The results of this analysis are presented in Chapter 4.

The second study ("Low Schizotypy") involved the recruitment of a sample of low schizotypy scorers who completed the same neurocognitive battery as the participants in the Schiz01 study. The cognitive performance of this low schizotypy group was then compared to the placebo-arms of the average and high schizotypy groups in the Schiz01 study. This comparison was used to test Prediction 1.2 which stated that schizotypy will be associated with deficits in the trait (e.g. working memory, antisaccade tasks) but not state neurocognitive biomarkers of schizophrenia (e.g. Salience Attribution Task) that were part of the battery. Hypothesis 2 which states that cognitive abnormality in the schizophrenia spectrum is a continuously distributed trait, was also tested by comparing the cognitive performance of the low, average and

high schizotypy scorers. The prediction was that the degree of cognitive impairment will increase linearly with the severity of schizotypal symptoms (low schizotypy < average schizotypy < high schizotypy, Prediction 2.1). These data form Chapter 5.

The results from the first and second studies, as well as the extensive evidence documenting cognitive impairment in the schizophrenia spectrum led to the completion of two studies which aimed to clarify the pathophysiology of cognitive abnormalities in the schizophrenia spectrum ("Schizotypy EEG" and "Schizophrenia EEG" studies). It was hypothesized that the cognitive deficits in the schizophrenia spectrum are part of a general abnormality in neural information processing (Hypothesis 4). The specific prediction in respect to this hypothesis was such generalized deficit would manifest itself through early event-related potential (ERP) abnormalities in samples of schizotypal individuals and schizophrenia patients (Prediction 4.1). Testing the validity of Prediction 4.1 in respect to schizotypal individuals was the aim of the third study ("Schizotypy EEG") whereby low and high schizotypy scorers were compared them in terms of the characteristics of their early visual ERPs, an analysis featuring in Chapter 6. The fourth study ("Schizophrenia EEG") probed Prediction 4.1 in schizophrenia patients by administering the same study design as the one in the Schizotypy EEG study to patients and average scoring schizotypy scorers. These results are presented in Chapter 8.

The datasets of the third and fourth study were used to test the idea that the perceptual abnormalities are related to cognitive impairment in the schizophrenia spectrum (Prediction 4.2). This possibility was tested by correlating the ERP abnormalities with cognitive performance in the schizotypy ("Schizotypy EEG") and schizophrenia samples ("Schizophrenia EEG"). The results are presented in Chapters 6 and 8 respectively.

Hypothesis 5 extended Hypothesis 4 by making the specific assumption that the generalized information deficit in the schizophrenia spectrum is due to a deficit in neuronal connectivity. The datasets of the Schizotypy and Schizophrenia EEG Studies were again used to explore this hypothesis by testing the predictions that schizophrenia spectrum will be charcterized by both local (Prediction 5.1) and long-range dysconnectivity (Prediction 5.2) patterns during perception. The validity of

these predictions in schizotypy ("Schizotypy EEG") and schizophrenia populations ("Schizophrenia EEG") were reported in Chapters 7 and 8 respectively.

1.12. Contribution of the author to the experimental work and manuscipts featuring in the thesis

The Schiz01 study was designed by an academic-industrial consortium before the start of the PhD programme of the thesis author. Ivan Koychev's studentship involved part-time work at the Manchester site of the study as study physician (medical screening of volunteers, administration of study drugs) and research assistant (volunteer recruitment, data collection). The author also analyzed the presented study data along the statistical plan laid out in the design of the study but also completed original post-hoc analyses that feature in Chapter 4. Ivan Koychev wrote the first draft of the article, coordinated the ensuing input from the co-authors and finalized the version submitted to European Neuropsychopharmacology.

The Low Schizotypy study was designed by the author with the aim of clarifying the results from the Schiz01 study. The author recruited the low schizotypy sample and collected the study data from this sample of volunteers; he participated in the recruitment and data collection of the placebo-treated average and high schizotypy samples of the Manchester site of the Schiz01 study; he analyzed the presented study data, wrote the first draft of the article that is featured in this thesis and is currently coordinating the input from the co-authors.

For the Schizotypy and Schizophrenia EEG studies**,** Ivan Koychev designed the studies, managed ethical and research approvals, recruited the volunteers and patients, collected and analyzed the study data, wrote the first drafts of the articles featuring in Chapters 6, 7 and 8, coordinated the ensuing input from the co-authors and after submission of Chapters 6 and 7 to Neuropsychologia was responsible for amending the two articles in response to reviewers' comments.

CHAPTER 2

GENERAL METHODOLOGY

Abstract

Chapter 2 reviews the recruitment procedures for the four experiments that feature in this thesis. It also provides information on the neurocognitive, eye-tracking and electrophysiological methods that were used.

2.1. Vulnerability and SPQ scores

The healthy volunteer participants that feature in the experiments contributing to this thesis were recruited on the basis of their online scores of the Schizotypal Personality Questionnaire in its full (SPQ, (Raine 1991), full list of questions in Appendix 1) or short version (SPQ-B, (Raine et al. 1995), full list of questions in Appendix 2). The full SPQ is a 74-item "yes/no" self-reported questionnaire that probes the presence of schizotypal personality traits according to the DSM-IV criteria for Schizotypal Personality Disorder (SPD). It has high test re-test reliability and good internal consistency (Raine 1991). The scores can be decomposed into three dimensions (Cognitive-Perceptual, Negative Interpersonal and Disorganised) by summing the number of positive responses to items contributing to each factor. SPQ-B is a 14 item "yes/no" self-reported questionnaire that also has high test reliability and adequate internal consistency.

SPQ was used to recruit individuals with high level of schizotypal personality traits (high schizotypy) for the experiments reported in Chapters 4, 5, 6 and 7. In Chapters 6 and 7 a high schizotypy scorer was defined as an individual with a SPQ score of 43 or more. These SPQ cut-off scores were based on results from a previous study using SPQ in 760 students from the Manchester University (Barkus et al. 2008) and the Manual for the SPQ (http://www-rcf.usc.edu/raine/spqrel.html). The high schizotypy cut-off was subsequently revised to a score of 41 or more in Chapters 4 and 5 in view of the SPQ scores of a sample of 14,000 individuals reported in Chapter 4.

The experiments reported in Chapters 4, 5 and 8 included a control group of average scoring individuals. For Chapters 4 and 5 these were defined as SPQ scorers in the range of 21-36 as reported by Raine et al. (Raine 1991). This range was subsequently redefined in Chapter 8 to 11-36 in light of the mean and standard deviation of SPQ scores obtained in the UK-based sample reported in Chapter 4.

The Chapter 5, 6 and 7 studies included a control group consisting of participants scoring low on the full SPQ (scores 0-9). The rationale for this decision was based on the lack of agreement on the optimal SPQ scores of control groups in schizotypy

studies. The aim was to address this by comparing the cognitive performance of low, average and high SPQ scorers and the results are reported in Chapter 5. The initial plan was to merge the samples reported in Chapters 6, 7 and 8 and report electrophysiological (EEG) differences between low, average, high schizotypy scorers and schizophrenia patients in an ensuing paper. However, due to facility availability different EEG amplifiers and experiment rooms were used for the two studies (low schizotypy vs. high schizotypy and average schizotypy vs. schizophrenia patients), which severely limited their comparability.

2.2. Participants: Other inclusion and exclusion criteria

The healthy volunteers recruited for the currently reported studies were from both sexes and in the age group 18-45 for Chapters 4, 5, 6 and 7, while in Chapter 8 the age range was revised to 18-55. The participants were also subjected to exclusion criteria aimed at limiting the effects of psychiatric or neurological symptoms, nicotine or caffeine abuse and medication intake. Therefore exclusion criteria were: i) history or presence of mental health disorders (using the Mini-International Neuropsychiatric Interview); ii) history or presence of epilepsy or other major neurological condition; iii) consumption of more than 5 cigarettes per day; iv) consumption of more than 8 standard caffeinated drinks or intake of caffeine in the two hours prior to the appointment; v) prescribed medication (apart from the contraceptive pill). Also, the visual nature of the paradigms used in the current thesis required the inclusion of participants with normal or corrected-to-normal vision only.

In the Chapter 4 experiment, participants were excluded if they had history of a medical disorder that might have affected the pharmacokinetics and pharmacodynamics of the study drugs. For the same reason participants were excluded if they had Body Mass Index (BMI) outside of the 18-30 range or had taken part in another drug trial in the 84 days prior to the experiment. In order to ensure comparability of the samples reported in Chapter 5, these three criteria were maintained when recruiting the additional low schizotypy control group. For the Chapter 4 study only, participants were excluded if they had a positive result on pregnancy or drugs of abuse urine dipstick tests or a positive alcohol breath test. For

the same study, in order to ensure minimal risk of hypotension-related adverse events participants outside of the normal blood pressure (diastolic BP of 60-90 mmHg, systolic BP of 100-140) were also excluded.

The following exclusion criteria were retained for the patient sample reported in Chapter 8: history or presence of neurological conditions, uncorrected visual impairment, and excessive caffeine use (drinking more than 8 standard caffeinated drinks). Prescribed medication, history of mental health disorders and heavy smoking were not exclusion criteria due to the nature of the sample. The potentially confounding effect of the first two factors was accounted for by covarying the electrophysiology results with daily antipsychotic dose, severity of psychiatric symptoms and duration of disease.

2.3. Questionnaires

All healthy volunteers completed the SPQ questionnaire at their first appointment at the research facility. The participants in Chapters 4 and 5 also completed the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE) questionnaire (Mason et al. 1995). The OLIFE is a 104 item questionnaire that provides an estimate of the level of schizotypal personality traits along four dimensions (Unusual Experiences, Cognitive Disorganisation, Introvertive Anhedonia and Impulsive Nonconformity; see Appendix 3 for a full list of the OLIFE questions). A commonly used approach in schizotypy research is to correlate the scores in each dimension to a cognitive performance related variable. This was done in the Chapter 5 data analysis in an attempt to replicate a previously reported correlation between Introvertive Anhedonia scores and performance on one of the neuropsychological tasks (Salience Attribution Test, (Roiser et al. 2009)).

2.4. Neuropsychological tests

2.4.1. National Adult Reading Test (NART)

All participants completed the National Adult Reading Test (Nelson et al. 1991), which is a reading-based estimate of IQ. It provides information regarding the premorbid IQ and is therefore well suited to account for differences in cognitive performance that are due to education rather than disease process. The NART was used to check whether the groups used in the individual studies were comparable in terms of their IQ. The procedure of this test requires that participants pronounce irregularly spelt words from a standardized written list (See Appendix 4 for the list of words and their correct pronunciation). The scores are then calculated on the basis of the number of correctly pronounced words.

2.4.2. N-back task

The N-back task is one of the most commonly used tests to probe working memory (Gevins et al. 1993). Abnormal performance on this task has classically been linked to prefrontal cortex dysfunction (Owen et al. 2005). In Chapters 4 and 5, N-back was used to probe the sensitivity of working memory paradigms to the schizotypy phenotype and the effects of drugs potentially affecting cognition.

In this task, participants were required to monitor a stream of visually presented stimuli that appeared on a computer screen and were required to respond whenever the stimulus on-screen was the same as the one shown N trials previously. N is an integer that could have been either 1, 2 or 3 and was specified at the beginning of each trial (Figure 2.1). In order to test whether participants were paying attention to the task, there were also trials in which they needed to respond whenever a specific letter was onscreen (“X”). See Appendix 5 for a full description of the N-back task reported in Chapters 4 and 5.

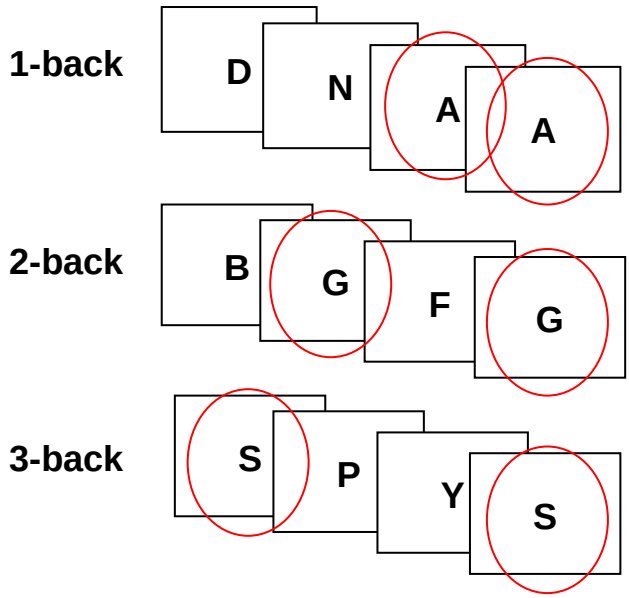

Figure 2.1. N-back task. Participants indicated by pressing a mouse button whenever the letter on screen was the same as the letter presented 1, 2 or 3 screens before (1-, 2- and 3-back respectively).

2.4.3. Spatial Working Memory (SWM) task

This computerized task was reported in Chapters 4 and 5 as a measure of spatial working memory. It corresponds to the Maryland LNS spatial working memory task from the MATRICS cognitive battery (Nuechterlein et al. 2008). Similarly to the N-back task, abnormal results are also classically interpreted as an indication of prefrontal cortex dysfunction (Lee et al. 2005).

In the SWM task, volunteers were presented with a number of treasure chests on a computer screen. The participants had to search for coins in the treasure chests using the mouse with only one treasure chest containing a coin at any one time (Figure 2.2). Once a coin had been found, it would move to another chest but never to a chest where it had already been within the current trial. The task had 3 levels of difficulty (trials with 4, 6 and 8 chests). See Appendix 5 for a full description of the SWM task reported in Chapters 4 and 5.

See also Chapter 3 for a discussion of the relevance of working memory paradigms (such as the N-back and SWM tasks) as biomarkers of schizophrenia.

Figure 2.2. Spatial Working Memory (SWM) task. Participants searched treasure chests for coins with only one treasure chest containing a coin at any one time. Within the trial coins were never found twice in the same chest. Discovered coins mounted up on the right of the screen as shown on the figure to guide the participant on the number of remaining coins.

2.4.4. Verbal Fluency (VF) task

This pen-and-paper task was used to test verbal fluency in Chapters 4 and 5. Abnormal performance on variations of this task has also been linked to abnormal prefrontal cortex activation (Curtis et al. 1998).

This thesis used a version of the VF task in which participants had to name as many words either beginning with a letter (F, A and S) or belonging to a category (animals and vegetables). There was also a condition in which two categories (fruit and furniture) were given and the participants had to alternate between them. See Appendix 5 for a full description of the VF task reported in Chapters 4 and 5.

2.4.5. Salience Attribution Test (SAT)

The SAT was reported in Chapter 5 as a measure of aberrant salience attribution. This abnormality has been shown to correlate with psychotic symptoms in schizophrenia patients as wells as with the Introvertive Anhedonia OLIFE subscale score in healthy volunteers (Roiser et al. 2009). Functional MRI studies report reduced ventral striatal hemodynamic responses during reward cue conditions (Juckel et al. 2006; Schlagenhauf et al. 2008) which has promoted suggestions that aberrant salience attribution may be an indicator of dysfunction in that brain region.

In the SAT coloured images of household objects or animals were presented prior to responding for possible rewards (money). One stimulus dimension (e.g. red vs. blue) very reliably predicted the availability or non-availability of money while the other (e.g. animals vs. household objects) was not a reliable predictor. If faster responding/greater reward rating occurred to one of the irrelevant features over the other (e.g. animals faster over household objects), this indicated aberrant salience. See Appendix 6 for full description of the SAT and Chapter 3 for a discussion of its relevance as a biomarker of schizophrenia.

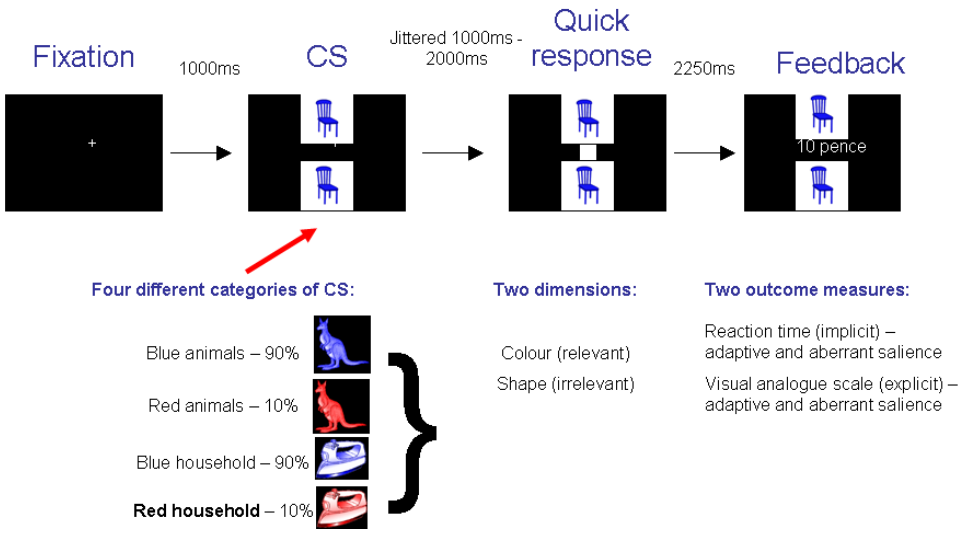

Figure 2.3. Salience Attribution Test (SAT). The participants had to respond as quickly as possible to the presentation of a square in order to win possible reward. The stimulus was preceded by images that predicted the probability for reward. One of the dimensions of the stimulus was a good predictor (e.g. red vs. blue color) while another salient dimension was irrelevant (e.g. animals vs. household objects). The figure is reproduced from Jonathan Roiser's work e.g. (Roiser et al. 2009) with the permission of the author.

2.4.6. Working memory event-related potentials (WM ERP) task

The experiments featuring in Chapters 6, 7 and 8 employed a working memory task to elicit event-related electroencephalographic or EEG activity (event-related potentials and oscillations). A very similar version of the task had been used previously by Haenschel et al. in a sample of schizophrenia patients (Haenschel et al. 2007; Haenschel et al. 2009). They reported aberrant modulation of the EEG activity by WM load in patients relative to controls. These results indicate that the EEG correlates of perceptual dysfunctions in schizophrenia might be the result of dysfunctional coordination between higher-order brain structures, such as the prefrontal cortex, and the sensory cortex.

In the task featuring in the current thesis, the participants were required to remember images that were sequentially presented in series of one, two or three (Figure 2.4).

After a fixed delay period a target probe appeared on the screen and the participants had to indicate whether it was part of the initial sample set by pressing a button. Full description of the WM ERP task can be found in the method sections of Chapters 6, 7 and 8.

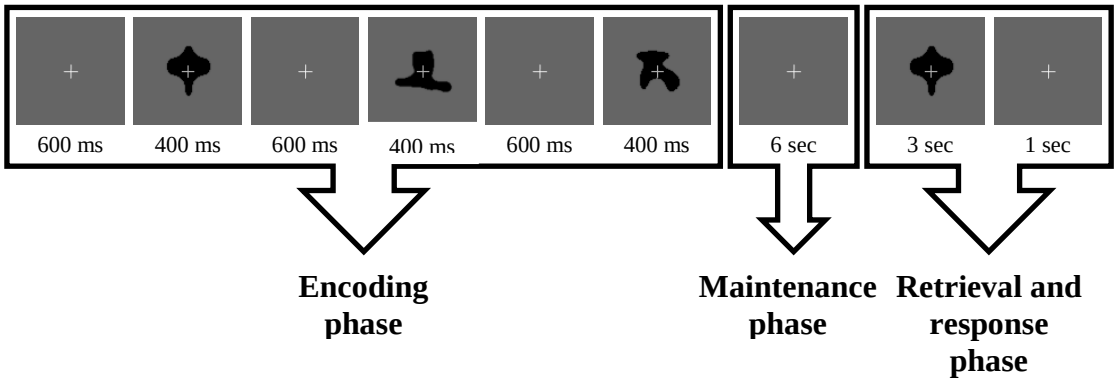

Figure 2.4. Working memory event-related potential task. During encoding one, two or three images were presented for 400 ms seconds each separated by an inter-stimulus interval of 600 ms. A delay period of 6 seconds ensued (maintenance phase). A target image then appeared and remained onscreen for 3 seconds and the participants were required to indicate by pressing a button whether it was shown during the encoding phase or not (retrieval phase). An inter-stimulus interval of 1 second separated the trials.

2.5. Eye-movement analysis

Two tasks probing the eye-tracking performance in low, average and high schizotypy were reported in Chapter 5. The inclusion of eye-tracking paradigms in the experiments was based on findings of various oculomotor deficits in schizophrenia (See sections 3.3.7 and 3.3.8. in Chapter 3).

The first task examined the quality of saccadic eye movements (rapid eye movements that allow the fixation of a new object that has appeared in the visual field) and had a prosaccade and an antisaccade condition. In the prosaccade condition a novel visual target appeared in the periphery and the participants had to direct their gaze at it. In the antisaccade condition the participants had to inhibit the prosaccade response to a new stimulus and instead look at its mirror image location on the opposite side of the

screen. Schizophrenia patients are typically unable to suppress the automatic prosaccade in the antisaccade task which has been attributed to suboptimal inhibition ability underpinned by a prefrontal cortex dysfunction (Hutton et al. 2006).

The second task required participants to follow a slowly moving target with their eyes only (Smooth Pursuit Eye Movement, SPEM). The first reports of aberrant smooth pursuit eye movements in schizophrenia patients date from 1908 (Diefendorf et al. 1908), a finding that has been consistently replicated ever since (Hutton et al. 1998; Hutton et al. 1998). Evidence from structural and functional imaging studies indicate that the structures underlying the abnormality in schizophrenia are the frontal cortex (Ettinger et al. 2004) and the striatum (Raemaekers et al. 2002).

See Appendix 6 for full details on the eye-movement procedures and Chapter 3 for a discussion of the biomarker status of eye-tracking in schizophrenia.

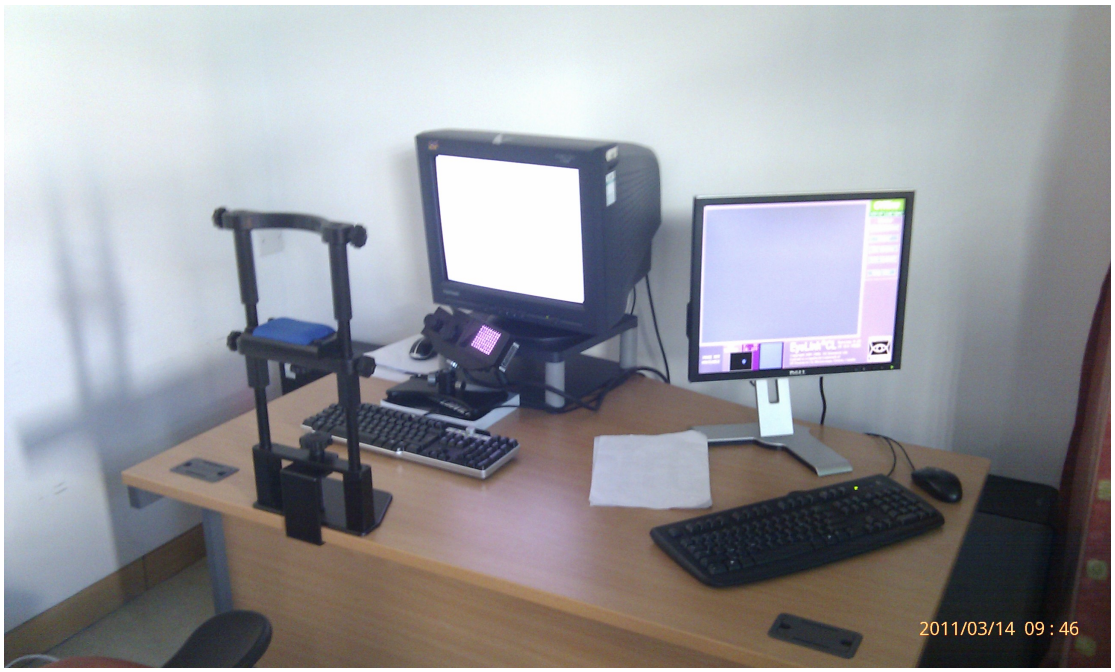

Figure 2.5. Eye-tracking set-up. The participant was seated with their chin supported on a chin rest and looking directly into a presentation monitor (left-hand side monitor). The data from the infrared eye-tracker was recorded by a researcher on a separate computer (right-hand side monitor).

2.6. Event-related electroencephalographic activity

Event-related potentials and oscillations were used to examine the processing of visual information in schizophrenia spectrum disorders in the experiments featuring in Chapters 6, 7 and 8. The next two sections deal with a general introduction to these electroencephalographic techniques, while full details on the procedures employed in this thesis can be found in the methods sections of Chapters 6, 7 and 8.

2.7 Event-Related Potentials (ERPs)

2.7.1. Background of ERPs

The electroencephalogram (EEG) is a recording of neural electrical activity obtained by amplifying the signal from electrodes placed in contact with the scalp. EEG was reported for the first time in a set of experiments by Hans Berger in 1929 (Berger 1929). Over the ensuing decades, it has been used in a variety of clinical and scientific contexts. The main drawback of raw EEG is that it represents a conglomeration of simultaneously occurring neural activities making the isolation of individual phenomena of interest problematic. Responses to sensory stimuli can however be extracted from the background EEG activity by simple averaging of data following the onset of each stimulus. This method is based on the idea that spontaneous EEG activity has no fixed temporal relationship with the time point in which the stimulus is delivered; in contrast neural responses to sensory stimuli are time-locked to their onset. Averaging the data immediately following uniform events therefore leads to augmentation of the sensory response and reduces the contribution of unrelated neural activity. These responses are called event-related potentials (ERPs), highlighting the fact that they represent electrical responses to controlled events.

2.7.2. Neural basis of ERPs

Two main types of electrical activity are generated by neurons and could thus be the neural basis of ERPs: action potentials and postsynaptic potentials. The former are voltage spikes that travel from the beginning of the axon to its terminals. At the

terminal they cause release of neurotransmitters into the synaptic cleft resulting in excitation of the post-synaptic neuron. The latter are voltages that arise when neurotransmitters bind to post-synaptic receptors. Action potentials have negligible contribution to the generation of the ERP signal, as they last only about a millisecond, occur at slightly different times even in neurons that fire in a coordinated fashion and are not fixed but rather travel rapidly down axons. In contrast, post-synaptic potentials last up to hundreds of milliseconds and occur instantaneously at fixed locations (cell body) which allows their summation. The simultaneous occurrence of postsynaptic activity in millions of spatially aligned neurons produces a signal which may be measurable at the scalp. These requirements are most likely to be met by pyramidal cells lying perpendicular to the scalp. It is thus assumed that the ERP peaks are produced almost exclusively by the post-synaptic signal of coherently activated pyramidal neurons (Luck 2005).

2.7.3. Advantages and disadvantages of the ERP technique

The graded waxing and waning of postsynaptic potentials is volume conducted to the scalp where it is picked up by the EEG electrodes. With this type of conduction the delay between the brain activity and its reflection in EEG signal is below the millisecond level. This renders the ERP technique superior to other neuroimaging methods in terms of its temporal resolution: it allows tracking of activity on millisecond basis. It is however poorer than other methods in regards to its spatial resolution (the ability to indicate where activities originate from). This is due mostly to the substantial blurring of signal resulting from the weak conductive capacity of the scalp (Luck 2005).

2.7.4. ERP analysis

Event-related potential data are analyzed by determining the latency and amplitude of peaks of interest in a single electrode or a group of electrodes and using these values in statistical comparisons. Latencies can be measured by visually identifying the peak of interest and determining the latency of its highest point. This method however may introduce a subjective element, especially given that peaks often reach their maximum

at different electrodes in different participants. A more robust approach is to determine the ERP latency of maximum activity using Global Field Potentials (GFP). This is a method that plots the overall ERP scalp activity which reduces the impact of individual topographical differences.

The main outcome measure of most ERP studies is the amplitude of ERP components. The most common approach in measuring peak amplitude is to determine a time window for each component of interest and to determine the maximum amplitude in this window. This method is called peak amplitude measure. Another method is to define the mean amplitude for the time window of interest (mean amplitude measure) (Luck 2005). The latter is the preferred approach due to several reasons. Firstly, searching for peaks in large time windows often detects the rising or falling edge of an irrelevant overlapping component. Using shorter time windows and using a non-automated approach to peak identification can help reduce the impact of this but introduces subjectivity of the data analysis, as each peak has to be individually selected by the researcher. Secondly, peak amplitude is susceptible to distortion by high-frequency noise. This is due to the possibility of noise deflection being registered as an ERP component, leading to artificially higher peak amplitudes in noisy recordings. Lastly, when there is substantial inter-trial variability in the peak latency, the peak amplitude of the averaged component will be lower than the individual ERPs. In contrast to peak amplitude, mean amplitude measurement allows shorter windows of interest and does not become biased by noise levels or latency jitter.

2.7.5. Visual Evoked Potentials (VEPs)

The current thesis dealt with the electrophysiology of early visual information processing in schizophrenia and consequently focused on several well characterized visual ERPs. Three major visual evoked potentials (VEPs) peak within the first 200 ms post stimulus: the so-called C1, P1 and N1 (Figure 2.6). C1 is the first VEP peaking at approximately 80-100 ms and is largest at the midline occipital electrodes. Source analysis studies have suggested that it originates from the primary visual cortex (V1). C1 is positive in response to images presented in the lower visual field

and negative for stimuli appearing in the upper visual field (Di Russo et al. 2003). C1 has traditionally been attributed to bottom-up processes, but recent data suggest that it is more sensitive to internal states than previously thought (Kelly et al. 2008; Rauss et al. 2009). C1 is followed by P1, which has a typical bilateral occipital distribution (Figure 2.7). It peaks around 100-130 ms but its latency varies significantly depending on the contrast of the stimulus. Its cortical generators have been suggested to be the middle occipital gyrus (dorsal visual stream) and the fusiform gyrus (ventral visual stream) (Di Russo et al. 2002). P1 is the earliest visual component that is under top-down influence, as its amplitude is sensitive to the direction of spatial attention (Di Russo et al. 2003; Lalor et al. 2007). A cornerstone human lesion study showed that prefrontal cortex plays a key part in this top-down modulation (Barcelo et al. 2000). P1 is followed by N1, a negative potential peaking typically between 150 and 200 ms (Figure 2.6). It also has a bilateral occipital distribution and has been linked to activity primarily in the ventral visual stream (parietal cortex and lateral occipital cortex) (Di Russo et al. 2002). N1 amplitude is also modulated by spatial attention (Heinze et al. 1990). Functionally, C1 is thought to represent activation of the primary visual cortex; P1 reflects early pattern detection processes; N1 represents discriminative processing (Luck 2005).

This thesis focused on the characteristics of P1 and N1 potentials in schizophrenia spectrum disorders, as their amplitude and latency are a sensitive measure of the quality of early information processing. In addition, the fact that both of them are subject to top-down modulation renders them useful in testing the efficiency of long-range connectivity in schizophrenia.

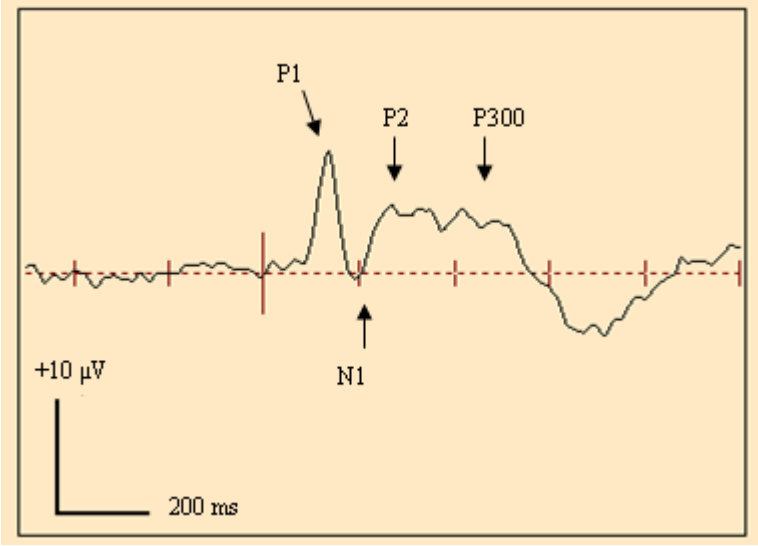

Figure 2.6. An example of occipitally recorded VEP. Arrows show all major visual peaks except for C1. Large vertical tick at stimulus onset, vertical ticks at every 200 ms thereafter.

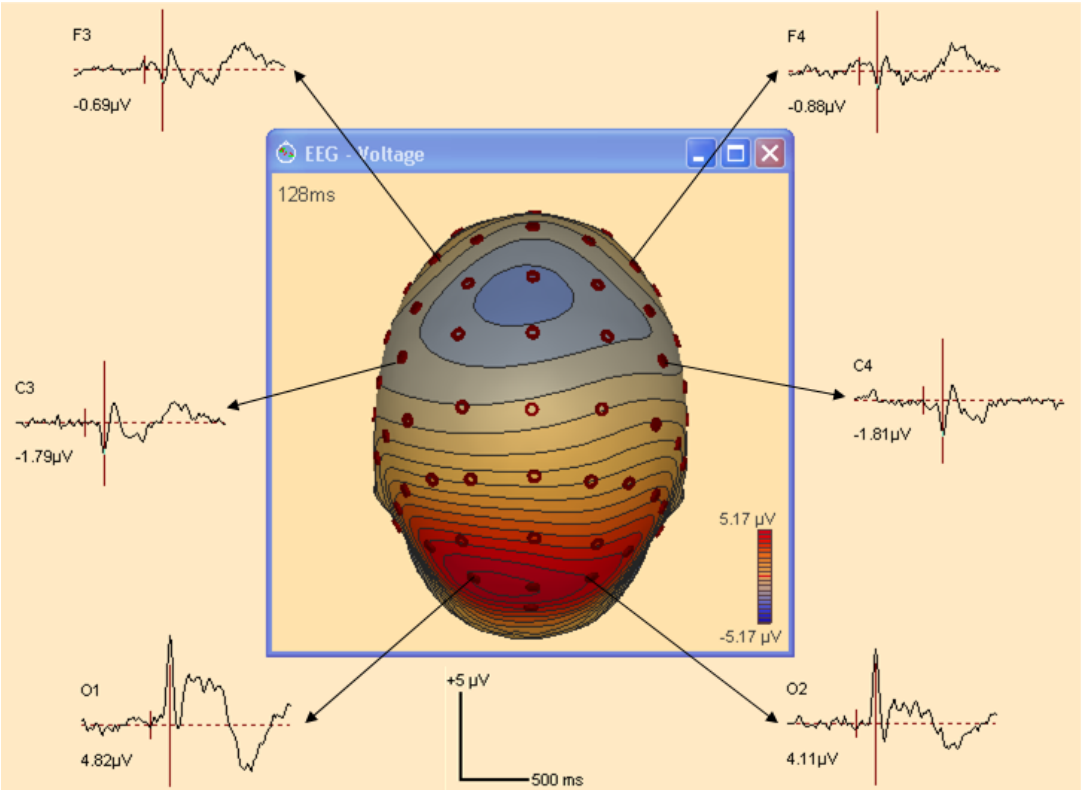

Figure 2.7. Topographical distribution of the P1 potential. Data presented for pairs of frontal (F3, F4), central (C3, C4) and occipital (O1, O2) electrodes.

2.8. Electroencephalographic analysis of neural oscillations

While the examination of ERPs has undoubtedly contributed to our understanding of the nature and timings of neuronal events, the rhythmic oscillatory EEG activity that ERPs arise from has in the past two decades become the focus of neurophysiology interest. This was due to increased access to computational power and proliferation of analysis techniques but perhaps most importantly of all to the discovery that neurons engage in synchronized oscillatory activity. It has been proposed that these neuronal oscillations are a fundamental mechanism that allows coordinated brain activity.

Studies in animals and humans have shown that during cognitive acts neurons align the rhythm (phase) of their action potentials to establish precisely synchronized neural assemblies (Singer 1999; Fries 2009). The resulting coordinated discharges have much greater impact than competing unsynchronized activity and the transmitted data gains crucial advantage in information processing. The process of phase synchronization allows the integration of local, as well as large scale networks. The temporal correlation between the emergence of synchronized oscillations and various cognitive acts, such as perception, working memory and consciousness, supports the functional relevance of this mechanism (Varela et al. 2001).

2.8.1. Types of oscillations

Oscillations of various frequencies are detectable using EEG in humans. They were arbitrarily subdivided in the 5 major frequency band by the International Federation of Societies for Electroencephalography and Clinical Neurophysiology in 1974: delta (0.4 – 4 hertz), theta (4-8 hertz), alpha (8-12 hertz), beta (12-30 hertz) and gamma (>30 hertz). There is some evidence to suggest that this distinction is functionally relevant. Higher frequency oscillations have been proposed to establish synchronization within local neuronal networks while lower frequencies underlie long-distance communication (Buzsaki 2006; Uhlhaas et al. 2008). The exact functional significance of the different frequency bands in relation to perception and working memory are discussed in the appropriate chapters.

2.8.2. Principles of the Time-Frequency (TF) analysis

The principal approach in analysing event-related EEG oscillations entails decomposition of EEG signal into its magnitude and phase information (the so-called "spectral decomposition") and relating the changes in these variables over time with regards to task events (broadly defined as "time-frequency analysis"). Time-frequency analysis is based on a model that sees EEG data as a convolution of sine waves at different frequencies that occur at the same time and have different phase angles with respect to the onset of the stimulus. The frequency of a sine wave is defined as the number of full cycles or oscillations that occur in one second (expressed in hertz). The magnitude of an oscillation refers to the maximum height of the sine wave's peaks relative to baseline. The phase provides information regarding where specific time points are located on the sine wave (expressed in degrees and ranging from -180^{o} to 180^{o}). Spectral decomposition of EEG signal estimates a complex number for each time point that allows the extraction of 2 characteristics of the sine wave at a given frequency: its magnitude and its phase. This is accomplished using a technique called "convolution" – a windowed transformation (most commonly a Morlet wave transform) centered on an EEG segment that multiplicates the raw data. Moving the window one time point at a time produces a complex number for each time point in the EEG data. This process is done separately for each individual trial and at the end of the process the complex number values for each time point are collected together. Squaring and averaging of these complex numbers provides the mean signal power of a given frequency at a particular time point. Dividing the complex number by its magnitude provides a new set of complex numbers which retain phase but not magnitude information regarding a given frequency at a given time point. Averaging these magnitude-independent phase variables over trials provides information regarding the inter-trial consistency of oscillations at a given frequency and time-point (phase-locking factor (PLF) or inter-trial coherence (ITC)).

2.8.3 Outcome variables of the TF analysis

Time-frequency analysis outputs several variables that describe different characteristics of the EEG signal on a single electrode level. Signal power is the first one, reflecting changes in magnitude of neuronal oscillations at a given time point relative to the pre-event baseline. Two types of signal power are distinguished on the basis of their relationship to phase information: evoked and induced power. Evoked power refers to changes in EEG data that are phase-locked to the stimulus onset across trials (Figure 2.8A). Such phase-synchronized oscillations are extracted by first averaging data across trials in the time domain. Only oscillations that have been in the same phase in relation to stimulus onset across trials survive this process and contribute to the formation of ERPs. In contrast, oscillations that were in different phases across trials in relation to stimulus onset cancel each other out during this averaging step. Evoked power is therefore extracted by performing a spectral decomposition on data that is already averaged over trials. Such phase-locked activity typically occurs in the first 250 ms and has been linked to perceptual (Tallon-Baudry et al. 1996; Fries et al. 2001) and top-down cognitive processes (Tiitinen et al. 1993; Debener et al. 2003). In contrast, induced power takes into account the non-phase locked oscillations that are excluded from evoked power calculation. It is obtained by spectral decomposition on single trial level which removes the effect of phase-information. Therefore induced power is also known as “asynchronous power” or “phase-invariant power”. Induced oscillations have been hypothesized to sustain various complex cognitive acts, such as working memory (Howard et al. 2003).

The second variable is the phase-locking factor (Figure 2.8B). As mentioned previously, this measure is independent from signal magnitude and provides data regarding the phase angle consistency of oscillations in regards to the stimulus onset. It ranges from zero to one, 0 indicating a completely random distribution of phase angles and one reflecting identical phase angles across trials. PLF has been hypothesized to represent the degree of neuronal response variability (Roach et al. 2008) and reductions in its value have been linked to increased “cortical noise” (Winterer et al. 2000; Winterer et al. 2004).

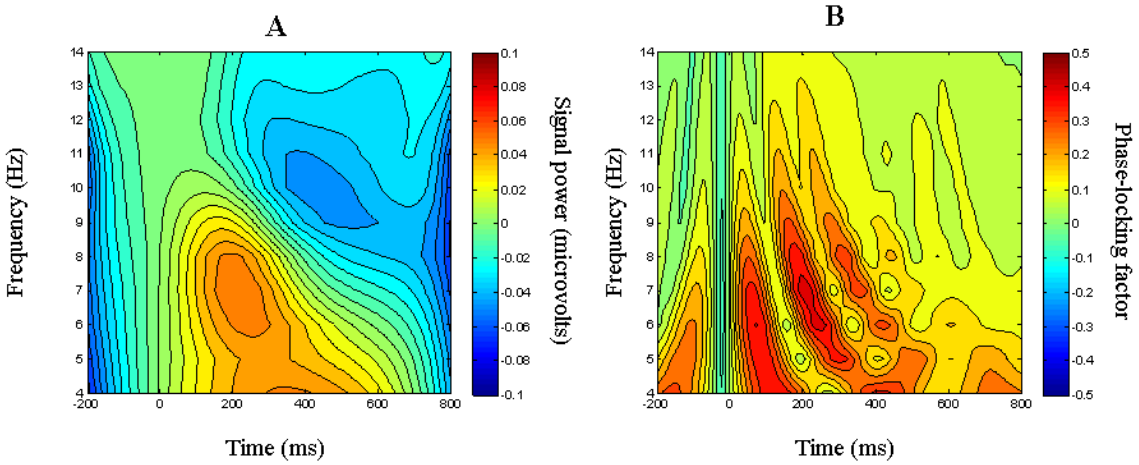

Figure 2.8. Example of evoked oscillations time-frequency plots. The plots represent the signal power (A) and phase-locking factor (B) of evoked oscillations in response to a visual stimulus in the 4-14 Hz frequency range for the -200 to 800 ms time period relative to the stimulus onset. The data is for 4 pairs of occipital electrodes (PO4/PO3; PO8/PO7; O1/O2; Oz/POz).

2.8.4. Analyses of neural synchrony

The time-frequency information can also be used to explore the degree of synchronized activity between pairs of electrodes. For this purpose, magnitude-normalised data (the same as the one used to calculate PLF on the single electrode level) is extracted for each time point at a given frequency for both electrodes for each individual trial. The difference in phase angles between the two electrodes is then calculated for each time point and for every trial. The single-trial differences in phase are then averaged across trials. The resulting variable is called phase coherence and ranges between zero and one. Zero indicates a completely random phase angle distribution across trials and one indicates that the two electrodes had completely synchronized phase angles. High phase coherence is interpreted as an indication of coordinated activity between the neuronal populations contributing to the signal recorded by the two electrodes.

Another way of inferring neuronal synchronization over long distances is by correlating activity of two electrode groups. This type of analysis requires the calculation of either power or PLF for two groups of electrodes at a given frequency

range and time period poststimulus (Figure 2.9). The averaged values for the two electrode groups are then correlated using Spearman's or Pearson's analysis. The disadvantage of this method is that unlike phase coherence it does not account for activity on a single trial level, but rather probes for overall correlation in activity. Its low computational requirements however make it a useful method for detecting general patterns of neuronal synchrony trends that could be probed further using phase coherence.

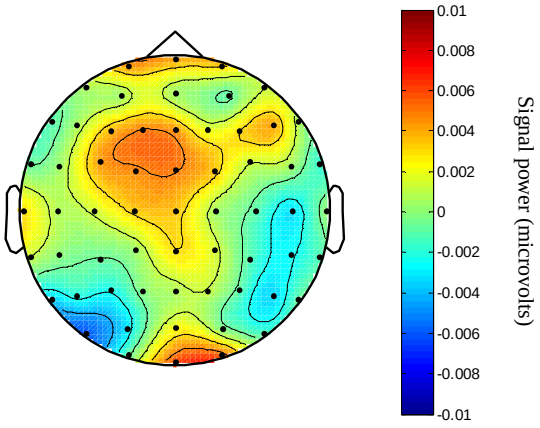

Figure 2.9. Topographical distribution of evoked oscillations during perception. The plot represents the signal power (expressed in microvolts) of evoked oscillatory response to a visual stimulus in the 14-28 Hz range for the 50-200 ms time post-stimulus period. View from above; frontal electrodes facing upwards and occipital electrodes facing downwards. The peak in signal power shows a central occipital and a fronto-central distribution. In this analysis, the central occipital and fronto-central sets of electrodes are correlated which could be interpreted as evidence for synchrony between the two topographical regions.

The focus of this thesis was perceptual information processing in schizophrenia which necessitated the use of evoked power and PLF measures. Correlations of power and PLF of electrode groups were considered adequate methods for detecting general patterns of long-range neuronal synchronization (see Chapters 7 and 8).

CHAPTER 3

Evaluation of state and trait biomarkers in healthy volunteers for new drug treatments in schizophrenia*

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Abstract

All drugs used in schizophrenia act on dopamine receptors. They have little effect on enduring negative symptoms or cognitive impairment and this is a major unmet need in the treatment of schizophrenia. Efforts to address this have led to the emergence of a number of novel candidate drug targets and potential compounds from preclinical research. Their clinical success rate however has been poor, highlighting the need to identify the likely efficacy of drugs early in their development. One way of achieving more efficient and objective assessment of the efficacy of novel compounds in schizophrenia is through the use of biomarkers for pathogenetically relevant processes. Validating such biomarkers in surrogate populations for illness could allow testing for drug efficacy as early as Phase 1 of drug development. In this article we review the relevance of several cognitive and physiological abnormalities as biomarkers in schizophrenia: their ability to detect state (dependent on symptom severity) and trait (present in full remission) abnormalities in patients as well as and the effect of available psychotropic drugs. We also evaluate these measures in three surrogates for illness: i) members of the general public with high trait schizotypy; ii) unaffected relatives of patients; iii) healthy volunteers in state of cortical glutamate disinhibition induced by low-dose ketamine. Several biomarkers are moderately abnormal in these groups when compared to schizophrenia patients and in some instances there has been exploratory work to determine their sensitivity to drug action. In perspective, the detection of efficacy of cognitive enhancing drugs in surrogate groups could be predictive of benefit for the cognitive and behavioural deficits of schizophrenia.

3.1. Background and rationale for biomarkers in drug development for schizophrenia

3.1.1. Introduction

The introduction of the first antipsychotic, chlorpromazine, in 1952 and the subsequent generation of typical and atypical D2 antagonists saw a dramatic improvement in the prognosis of schizophrenia and enabled the de-institutionalisation of patients to care in the community. However, many patients continue to experience symptoms in addition to the burden imposed by central nervous system (CNS) and metabolic side effects. Most patients change their treatment within the first 18 months (Lieberman et al. 2005). Furthermore, the efficacy of current treatments is largely confined to reduced psychotic or positive symptoms with limited efficacy in negative or deficit symptoms, resulting in poor levels of social and occupational functioning (Heinrichs 2005). Finding new pharmacological approaches to tackle these deficits remains a major unmet need in the treatment of schizophrenia (Nuechterlein et al. 2008). In addition little progress has been made on a truly disease-modifying therapy that has the potential of preventing schizophrenia.

The recognized limitations of schizophrenia therapy led to a rapid expansion of potential drug targets through technological advances such as genome sequencing, combinatorial chemistry and high-throughput screening (Hurko 2009). Novel drug development has mostly focused on compounds affecting single neurotransmitter systems that have been hypothesized to be pathogenetically relevant to schizophrenia (Roth et al. 2004). The main lines of development in relationship to the cognitive symptom domain have concerned the glutamate (e.g. glycine, metabotropic, AMPA receptor agonists; glycine transporter antagonists), acetylcholine (muscarinic and α_7-nicotinic receptor agonists), dopamine (e.g. D1 and D3 receptor agonists; D4 receptor antagonists; Catechol-O-methyltranferase inhibitors) and serotonin (e.g. 5-HT_{2A} and 5-HT_6 receptor antagonists; 5-HT_{1A} and 5-HT_4 receptor agonists) systems (Gray et al. 2007). The advances in compound generation however have not translated in increased clinical success rate. Instead, it has decreased sharply over the past two decades, as most novel compounds fail at the initial tests of efficacy in human disease,

phase 2 and 3 clinical trials (Hurko 2010). A recent review showed that practically all the agents that are currently in Phase 3 clinical trials have the same mechanism as the already available agents (D2 antagonism) (Gray et al. 2007).

3.1.2. Obstacles to novel drug development in schizophrenia

The currently observed high attrition rate for novel compounds has exposed several critical obstacles to drug development for psychiatric illnesses that may be particularly relevant to the development of an antipsychotic with potent cognitive enhancing action.

Firstly, novel agents are classically screened on the basis of their molecular actions and efficacy in animal behavioural models. However, only 3-5% of the compounds that were effective in preclinical screens were launched on the market (Hurko 2010). This suggests that while animal models probably capture a certain aspect of the main disease process, they are still far from being its reliable and precise replication (Marcotte et al. 2001).

Secondly, once a drug is introduced to a clinical population, its efficacy is assessed using traditional clinical end-points, such as clinical rating scales. Their sole dependence on the patients' reports and clinician's observations introduces a subjective element that reduces their sensitivity and precision (Jansson et al. 2007). In addition, these endpoints account poorly for the cross-ethnic differences in psychopathology (Brekke et al. 1997) which makes international comparisons difficult. This has been further complicated by placebo effects, which are especially elevated in clinical trials in psychiatry (Kemp et al. 2010; Kinon et al. 2011). All these factors obscure the true drug effects and inflate the sample sizes required to detect clinical efficacy in clinical trials.

The final and perhaps most important obstacle to novel drug development in schizophrenia is a conceptual one. In contrast to many physical diseases, the aetiology of schizophrenia remains unknown which makes the choice of appropriate targets for drug development especially risky. Several neurotransmitter systems have been

implicated in the pathogenesis of psychosis but as mentioned previously few drugs targeting non-dopaminergic transmitters show evidence of efficacy (Miyamoto et al. 2005). Given the probable complex components in schizophrenia, attributing the disease to a disturbance in a single neurochemical system is likely to prove too simplistic (Roth et al. 2004).

3.1.3. Biomarkers: Increasing the probability of technical success

The need to improve the probability of technical success of drug development has driven the identification and validation of biomarkers. A biomarker is defined by the USA FDA Food and Drugs Administration (FDA) as "A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention" (www.**fda**.gov). Biomarkers have the potential of augmenting the chances of successful drug development by the means of target validation, provision of surrogate end-points and patient segmentation (Breier 2005).

3.1.3.1. Target validation

Biomarkers relevant to target validation probe either disease-specific or drug activity processes. Disease biomarkers are used to explore the biological mechanisms involved in the disease pathophysiology. This information can then be used to improve the diagnosis of the condition, to mark its progression and to develop pathophysiologically relevant animal models. For instance, the finding of decreased TD4 cells in HIV gave not only an insight into the pathophysiology of the condition, but also provided a practical measure to track its outcome. Drug activity biomarkers provide information on whether the drug interacts with its respective target (Breier 2005).

3.1.3.2. Clinical surrogates

Biomarkers that consistently predict traditional clinical end-points could replace them and become "clinical surrogates". Clinical surrogates, being inherently more precise,

reliable and replicable than traditional end-points, could allow the detection of efficacy in smaller clinical trials. Also, classical clinical end-points, such as survival and quality of life, inevitably require long-term follow-up. If however a clinical surrogate predicts long-term treatment outcomes, it could reduce the duration of studies testing long-term benefit. Examples of successful clinical surrogates include blood cholesterol (predictor of cardiovascular mortality) and solid tumour size (predictor of mortality from a neoplastic cause). The MATRICS initiative has been developing a cognitive battery with the goal of providing of clinical surrogates for trials of cognitive enhancing drugs (Buchanan et al. 2007).

3.1.3.3. Patient segmentation

Some biomarkers also have the potential to stratify patients according to their likely treatment response or sensitivity to side-effects. Utilizing such biomarkers could help reduce the sample sizes of clinical trials by allowing selection more homogeneous patient population in phase 2 and 3 clinical trial which in turn reduces the variability of treatment response and decreases the likelihood of study discontinuation due to side effects.

3.1.4. Biomarkers: Uncovering the likely failures

Biomarkers could improve the chances of technical success of a drug by refining its targets, allowing its specific and precise assessment and selecting patient groups that are most likely to benefit. However, in the current situation of unclear pathophysiology of the main disease process, the vast majority of novel schizophrenia compounds are destined to fail. Therefore, a mechanism is needed to determine the likely failures as early as possible in their development and redirect resources to more promising compounds. This approach has been coined “quick win, quick kill” and aims to identify the likely failures fail as early as Phase I registration trial (Breier 2005). These proof of concept studies function by selecting only a subgroup of patients that is more likely to respond or by recruiting groups of individuals that have only limited symptom profile, i.e. surrogate populations

(Hurko 2009). Proof of concept studies precede the costly Phase 2 clinical trials which use more rigid diagnostic criteria, heterogeneous populations and traditional clinical end-points.

Biomarkers are a key component of such proof of concept studies, as they can provide the precise assessment of efficacy that these clinical trials of small sample size and short duration require. The Phase 1 proof of concept biomarkers do not necessarily need to go through the same rigorous validation as clinical surrogates because they help guide internal decision and resource allocation rather than argue the case for a registration of a compound. Instead, their usefulness is determined by their sensitivity to the disease process (both in patients and in surrogate populations) and to the action of drugs that a prospective compound is aiming to emulate.

3.1.5. Biomarkers in surrogate populations

The appeal of proof of concept biomarker studies in surrogate populations lies in their practicality, as they involve populations that are easier to recruit than homogeneous patient groups and lack the major confounding factors of patient samples. In respect to cognition in schizophrenia such potentially confounding factors are prior or concomitant drug treatment, chronicity, lack of cooperation, lower educational and premorbid IQ levels. In addition, these samples provide the option of testing potentially disease-modifying therapies, as they feature the vulnerability pattern, but not the fully developed disease.

Surrogate populations are defined as groups that feature a component of the main disease process but do not have the fully developed condition. Many medical disorders can be seen extremes of normally distributed functions such as blood-pressure in hypertension and glucose regulation in diabetes. In psychiatry, anxiety and depressive neuroses have long been viewed as extremes of normal variation in fearfulness and mood. That psychoses may represent extremes of normally distributed cognitive functions such as reward processing (aberrant salience hypothesis), perception (hallucinations extended from vivid mental imagery) and frontal lobe executive function, is gaining momentum. The continuum view of physical and

psychiatric disorders is encouraged by the absence of major gene effects, suggesting that many genes of small effect contribute to risk. This increases the likelihood that many individuals in the general population will have some of these genes and therefore may express some of the phenotype associated with the full disease.

The authors have been interested in the strategy to improve the sensitivity of biomarkers in surrogate populations. We believe that by studying biomarkers in individuals who lie further along the continuum of liability to experience psychosis will therefore improve the sensitivity of biomarkers to detect drug action relevant to the treatment of schizophrenia. We believe elevated psychosis liability through familial tendencies (unaffected relatives), predisposition to symptoms (schizotypal personality), or through drug-induced schizophrenia-like states will provide individuals who possess characteristics which are found in patients with schizophrenia and therefore provide a useful groups for biomarker testing. They are discussed in turn in the following sections.

3.1.6. Biomarkers in relatives: Endophenotypes and vulnerability

One healthy group who might show greater sensitivity to novel schizophrenia treatments are the unaffected first-degree relatives of schizophrenia patients since they will carry more susceptibility genes than found in the general population. However these genes are probably in insufficient numbers or are combined favourably which prevents the development of psychosis. Several neurocognitive characteristics that are shared between relatives and patients have been reported (Allen et al. 2009) and some are described in later sections. These changes imply the presence of shared susceptibility genes and lie closer to genetic mechanisms of disease than the overt clinical phenotype. Therefore, these biomarkers are a subgroup of the disease-specific biomarkers that relate to genetic vulnerability only. With the inclusion of a number of other criteria they have been termed endophenotypes (Gottesman et al. 2003).
In the psychosis literature they are primarily cognition or information processing related. Successful identification of endophenotypes could reveal neural pathways that underlie the schizophrenia phenotype. However, selecting volunteers for drug-efficacy biomarker studies on the basis of familial liability will require both openness

and tact to avoid understandable fears of being treated like their ill relatives and identified with disorder. Drugs that prove effective on biomarkers in relatives would have the potential to affect mechanisms of vulnerability and therefore prevent onset of disorder in those with at-risk mental states. There is some tentative evidence that relatives of patients with schizophrenia who express psychosis liability characteristics benefit functionally from treatment with a low dose atypical antipsychotic (e.g. (Tsuang et al. 1999)).

3.1.7. Biomarkers in schizotypy: Correlates of psychopathology

In keeping with the continuum view of schizophrenia, systematic surveys suggest that brief schizophrenia-like experiences and beliefs are surprisingly common in the general population and are also more prevalent among first-degree relatives of patients (Van Os et al. 1997). Such phenomena may be sufficiently intense and long-standing to interfere with everyday functioning and so warrant the diagnosis of schizotypal personality disorder. However, much evidence suggests that schizotypal personality traits are continuously distributed in the general population and that schizotypal traits may be quite prevalent in people with sufficient functioning to operate reasonably successfully in both social and occupational domains. In a later section we discuss evidence that healthy volunteers with high scores on schizotypal personality questionnaires show patterns of neurocognitive performance similar to these seen in schizophrenia. Selecting schizotypal populations may enhance the sensitivity of drug efficacy biomarker studies in the healthy population. Indeed, schizotypal symptoms themselves may be sensitive to new antipsychotic drugs and benefit from such interventions.

3.1.8. Biomarkers in drug-induced states: Dopamine

Administration of dopamine-releasing agents such as amphetamine and methylphenidate has been used extensively to model the symptoms of schizophrenia. These agents induce an acute schizophrenia-like syndrome in heavy users (Connell 1958), exacerbate positive symptoms in patients (although improvements in spontaneity and activation have also been reported), and induce symptoms when

given experimentally to volunteers. However, high doses are required to induce paranoid ideation and hallucinations and acute doses do not reproduce the cognitive and negative symptoms of schizophrenia. These findings, along with the data showing improvement of positive symptoms with dopamine antagonism gave rise to theory that schizophrenia is due to excessive dopaminergic neurotransmission. That enhanced dopamine release occurs in schizophrenia has now been firmly established by positron emission tomography (PET) measuring dopamine displacement of D2 radioligand binding (Laruelle et al. 1996; Abi-Dargham et al. 2000). Reports of increased uptake of fluoroDOPA suggest presynaptic dopamine neurones are more active in both acute and prodromal patients (McGowan et al. 2004; Howes et al. 2009). However, only subcortical striatal dopamine function has been quantifiable with these techniques and indirect evidence suggests that frontal cortical dopamine release may be reduced in schizophrenia. Indeed an important theory suggests that the primary abnormality in schizophrenia may be decreased frontal dopamine function with secondary increases in subcortical dopamine (Weinberger et al. 1988; Davis et al. 1991); the former mediating positive symptoms and the latter impaired cognition and negative symptoms.

How increased striatal dopamine release translates into positive symptoms is not clear. Dopamine clearly has an important role in perceived reward and learning in which its release by unexpected rewards (reward prediction error) triggers new learning. This has been visualised in humans for example in a study in which reward prediction error was associated with activity in dopamine areas that was attenuated by the dopamine antagonist haloperidol and facilitated by the dopamine precursor L-DOPA (Pessiglione et al. 2006). Excessive dopamine release in schizophrenia is postulated to result in aberrant reward learning and the formation of positive symptoms (Kapur 2003). Biomarkers based on reward prediction error are discussed in section 3.3.2. of this chapter.

Dopamine modulates frontal executive function and working memory (Goldman-Rakic 1994). However, the relationship may not be linear. Animal and human literature suggests that enhancing dopamine function from a low baseline improves executive functions whereas increases beyond an optimal level result in decreases in executive function therefore suggesting an inverted U-shape relationship. A further

complication is that D1 and D2 receptors may exert opposite influences on frontal executive function. The empirical evidence suggests acute amphetamine challenge improves rather than disrupts cognition in patients with schizophrenia (Pietrzak et al. 2010). The improvement may be explained by a reversal of deficient stimulation of D1 receptors in schizophrenia that predominate in frontal cortex. As a result of this development, the experimental application of acute amphetamine challenge has recently shifted towards improving performance in states of sub-optimal cognition and this is reviewed in later sections of this chapter.

It should also be noted that differences exist between the effects of acutely and chronically administered amphetamine. Repeated administration of amphetamine in experimental animals can result in increased hyperactivity responses and other effects of amphetamine. This is known as amphetamine sensitization and has been proposed a model for schizophrenia. Furthermore, sensitised animals also show evidence of cognitive deficits. Limited evidence suggests that amphetamine sensitisation can be demonstrated in healthy volunteers and further exploration of cognitive biomarkers in this paradigm would seem worthwhile. It might be possible, for example, to find drugs that prevent sensitisation without blocking the effect of amphetamine and these might be useful preventative treatments in high risk groups (Featherstone et al. 2007).

3.1.9. Biomarkers in drug-induced states: Glutamate, GABA and acetylcholine

Administration of the dissociative anaesthetic agent ketamine in sub-anaesthetic doses to healthy volunteers induces suspiciousness, thought disorder, some of the negative symptoms of schizophrenia and impairs performance on working memory (Pomarol-Clotet et al., 2006, Krystal et al., 1999a, Deakin et al., 2008). Ketamine blocks the ion channel associated with the N-methyl D-aspartate (NMDA) glutamate receptor. The psychotomimetic effects of NMDA channel blockers gave rise to the glutamate deficiency theory of schizophrenia. However, this is now better termed the NMDA deficiency hypothesis because drugs such as ketamine produce a paradoxical disinhibition of cortical glutamate release that acts on non-NMDA receptors. Many of the subjective and behavioural effects of ketamine can be blocked by agents that

decrease glutamate release (Deakin et al 2008). Thus increased glutamate release may be responsible for psychosis-like symptoms after ketamine as may the symptoms of schizophrenia itself (Deakin et al, 1989; 1997). Whether there is a primary impairment of NMDA function in schizophrenia is not clear, although this has been described in post-mortem hippocampus and in a single in-vivo SPET radioligand binding study (Law et al. 2001; Pilowsky et al. 2006).

The NMDA deficiency theory of schizophrenia has recently become pleasingly unified with GABA deficiency theories by evidence that a subclass of GABA interneurones that synchronise the firing of pyramidal neurones is driven primarily by NMDA receptors (Belforte et al. 2010). These so-called fast-spiking interneurones are thought to correspond to these containing parvalbumin which have repeatedly been reported to be deficient in post-mortem brain in schizophrenia (Lewis et al. 2006). Thus ketamine and related drugs may mimic NMDA hypofunction, impaired GABA neurotransmission and disinhibited glutamate release hypothesised to occur in schizophrenia. In-vivo methods of quantifying GABA and glutamate function are badly needed to test these theories.

The cholinergic system has also been implicated in drug-induced psychotics. The administration of anticholinergic agents, such as scopolamine or atropine is known to have the potential of causing ‘antimuscarinic psychosis’, a state that shares some of the behavioural features of endogenous schizophrenia (Perry et al. 1978; Perry et al. 1995; Minzenberg et al. 2004). Procyclidine, another antimuscarinic agent, was shown to block the antipsychotic effects of flupentixol in patients (Johnstone et al. 1983). Together with data showing alterations of the muscarinic and nicotinic receptors in schizophrenia (Terry 2008), this evidence has suggested that the acetylcholine system may be important in the pathogenesis of schizophrenia. Cognition is a likely target of a cholinergic disturbance (Minzenberg et al. 2004), as this neurotransmitter system is known to play an important modulatory role in memory, learning and synaptic plasticity (Sarter et al. 1997). In demonstration of this, the use of cholinesterase inhibitors such as donezepil in Alzheimer’s disease has been linked to slowing of the progression of cognitive deficits in this condition (Birks 2006). Unlike ketamine however, Procyclidine and other antimuscarinic agents are

limited in their use as pharmacological models of schizophrenia due to their unfavourable side effects profile.

3.2. Purpose of the review

The second part of the manuscript reviews the validity of several neurocognitive biomarkers from the major areas of interest in the literature with some more novel potential biomarkers developed by the authors. The emphasis is on potential biomarkers of drug efficacy in healthy volunteers that could be used in large-scale multi-centre studies. We focus on neurocognition because it is free of preconceptions about the neurochemical actions necessary for efficacy of a new drug and the need for treatments that improve cognition and negative symptoms. Functional brain imaging using positron emission tomography PET and functional magnetic resonance imaging (fMRI) is informative at identifying the involvement of neural systems in cognitive functioning. Neuroimaging is therefore showing promise as a modality for detecting drug-efficacy but there are many technical issues and it is beyond the scope of this article to provide a meaningful review of imaging biomarkers.

We will assess representative neurocognitive biomarkers according to their:

- Reliability (consistent effects reported by different laboratories or over time)
- Criterion validity (abnormal in criterion groups: patients, unaffected relatives, high schizotypes and after amphetamine or ketamine in healthy volunteers)
- Predictive validity (sensitive to the action of compounds effective in schizophrenia or cognition)
- Construct validity (relates to a known neurobiological system implicated in the disorder)

The importance of establishing the reliability of cognitive biomarkers in schizophrenia has been recognized by the MATRICS (Harvey et al. 2010) and CNTRICS (Carter et al. 2007) initiatives. These studies focus solely on schizophrenia patient samples and the results are useful in terms of establishing and standardizing cognitive clinical end points. However, as discussed previously, the various

confounds in this group (chronic disease and treatment, polypharmacy, institutionalization, florid positive symptoms, reduced cooperation) limit the conclusions that can be drawn regarding the pathophysiology of the subtle cognitive deficits and the disease. MATRICS recommends that participants have not more than moderate scores on formal thought disorder, hallucinations and delusions, negative and depressive symptoms, have minimal extrapyramidal symptoms, have been maintained on the same dose for 2-4 weeks and take only one antipsychotic (http://www.matrics.ucla.edu/matrics-recommendations-frame.htm). This limits the number of appropriate participants and still does not fully account for all confounds. In contrast, each of the healthy volunteer criterion groups that we will review provides a different viewpoint of the pathophysiology (genetic, psychopathological and molecular) with little or no impact of these confounding factors. We suggest that this approach is contributing to our understanding of the mechanisms behind cognitive abnormalities in schizophrenia and accelerate the evaluation of novel drug treatments.

3.3. Validity of cognitive and physiological biomarkers of cognitive processes related to schizophrenia.

3.3.1. Working memory: N-back and spatial working memory

Background

Working memory (WM) refers to a process for holding and managing information 'online' over short periods of time, allowing its manipulation and usage in reasoning, comprehension and decision-making. The distinction between short-term memory and working memory is subtle and not always consistent (Reichenberg et al. 2007). Working memory generally implies that the information is both stored and manipulated. It has been proposed that separate systems for the maintenance of verbal and visuo-spatial information exist (Baddeley 1986). In accordance the working memory tasks used in schizophrenia research as a rule involve either of the two modalities (Lee et al. 2005).

Paradigm description

In the N-back task, a series of digits are presented and participants are required to respond if the current digit is the same as one presented N trials previously where N varies between 0 and 3 in different trial blocks. This requires that the current rule is held in mind and that the relevant digit is updated from trial to trial. However the task also draws on other cognitive processes such as response inhibition, strategy formation and checking. Spatial working memory involves remembering locations of objects. Computerised tasks such as the Cambridge Automated Test Battery (CANTAB (Cohen et al. 1992)) often require a visual search of locations to collect a target object. These, now empty, locations need to be avoided to efficiently collect remaining targets. Thus a constant updating of memory of searched locations is required. Again processes such as strategy formation and behavioural inhibition are required.

Construct validity

Classic single cell recoding experiments in primates by Goldman-Rakic showed that cells in dorsolateral prefrontal cortex represent the spatial location of a cue over short

delays until the information is used to obtain a reward (Goldman-Rakic 1994). Functional imaging studies in humans confirm that working memory paradigms engage a dorsal network including dorsolateral prefrontal cortex and that these responses are abnormal in schizophrenia (Callicott et al., 2003). The dorsolateral PFC dysfunction is associated with disorganized symptoms (Perlstein et al. 2001), while the performance on the working memory tasks itself correlates with the negative symptoms (Carter et al. 1996).

Criterion validity

- Patients, relatives and high schizotypes

Meta-analyses have indicated that schizophrenia patients are significantly impaired on both verbal and visuo-spatial WM tasks (Lee et al. 2005). WM deficits are stable across time and fluctuations in clinical status (Hill et al. 2004) and are present before the initiation of treatment (Barch et al. 2001). First-degree relatives also appear to be affected, with effect sizes ranging from small to moderate (Snitz et al. 2006). WM memory deficits have also been reported in schizotypal individuals with (Johnson et al. 2003) and without (Park et al. 1997) family history of schizophrenia. Although working memory is strongly correlated with IQ, deficits that survive correction for reduced IQ have been reported in patients and high-risk subjects (O'Connor et al. 2009; Zanelli et al. 2010).

- Glutamate antagonist challenges

There is much interest in the role of impaired GABA function, possibly driven by deficient NMDA glutamate neurotransmission, in the impairment of WM in schizophrenia. In healthy volunteers, ketamine impaired WM performance in some but not all studies, especially when the task required manipulation of information; affinities with the WM deficits of schizophrenia have been noted (Fletcher and Honey, 2006, Morgan and Curran, 2006).

Predictive validity

- Dopamine antagonists

Studies in patients treated both acutely and chronically with typical antipsychotics have found no beneficial effect on cognitive function (Meltzer et al. 1999) but see

also (Keefe et al. 2007). The benefit of atypical antipsychotic therapy on working memory is most likely to be marginal (Heinrichs 2005) despite some studies reporting modest improvement (Houthoofd et al., 2008, Meltzer and McGurk, 1999, Purdon, 1999)(Houthoofd et al. 2008).

- Dopamine agonists

In healthy volunteers, compounds that increase dopamine activity have generally been shown to improve WM. Amphetamine has been shown to improve WM, especially in those individuals with low baseline performance (Mattay et al., 1996, Mattay et al., 2000). Similar effects have been reported with methylphenidate (Elliott et al., 1997, Mehta et al., 2000), but see (Turner et al. 2003). The selective D2 agonist, bromocriptine, also improved performance on spatial WM tasks (Kimberg et al. 1997; Luciana et al. 1998), but see (Kimberg et al. 2001). The mixed results of D2 agonism could be interpreted in the framework that sees D1 receptor agonism as the key factor in cognition enhancement. In demonstration of this, the disruption of working memory induced in healthy volunteers by a D2 antagonist challenge was alleviated by pergolide, a mixed D1/D2 agonist, but not the D2 agonist bromocriptine (Muller et al. 1998).

Importantly, data have emerged on the efficacy of dopamine agonists in improving working memory in schizotypal personality disorder (SPD). Firstly, acute amphetamine benefited working memory in SPD but not other personality disorders (Kirrane et al. 2000). Again, the poorer baseline performers improved the most. The enhancement of cognition in SPD under dopamine agonism also holds true for chronic treatment, as pergolide improved working memory after 4 weeks treatment in patients (McClure et al. 2010).

- Other agents

Cholinergic drugs modulate WM performance. Both muscarinic and nicotinic receptor antagonists impair WM performance in healthy volunteers (Green et al., 2005, Thompson et al., 2000). In one study abstinence from smoking in patients was associated with impaired WM performance but not in non-schizophrenic smokers and this was reversed with smoking reinstatement (Sacco et al., 2005).. Freedman et al

reported beneficial effects of a novel nicotinic agonist on some measures of WM in non-smoking patients along with improved negative symptoms (Freedman et al. 2008). Cholinesterase inhibitors on the other hand improve WM in healthy volunteers (Furey et al. 2000; Furey et al. 2000). Studies exploring the potential of compounds stimulating the cholinergic system as an adjuvant therapy in patients largely report improved executive function (Ribeiz et al. 2010).

3.3.2. Reward learning: Salience Attribution Test (SAT)

Background

Schulz and colleagues demonstrated that the presentation of unexpected (i.e. unpredicted) food rewards activates dopamine neurones in experimental animals. This is thought to act as a 'prediction error' or teaching signal (Schultz et al. 1997). Any initially neutral cue (stimulus) that predictably precedes a reward will itself acquire the ability to activate dopamine neurones. In this way predictive cues become imbued with 'motivational salience' (Berridge and Robinson 1998) and are able to capture attention and guide goal-direct behaviour. It has been hypothesized that in psychosis dysregulated dopamine release provides an inappropriate prediction error signal during the processing of irrelevant stimuli. This is thought to result in the inappropriate assignment of salience to external stimuli and internal representations such as thoughts or memories (Kapur 2003). According to the aberrant salience hypothesis, delusions and hallucinations form as cognitive misattributions of the origin and significance of the unusual and repeated experience of many inappropriately salient stimuli.

Task description

Studies exploring salience attribution use cognitive psychology paradigms in which stimuli are either coupled with reward or not. The degree of correct and aberrant learning is inferred from behavioural measures, including choices, reaction times or participant awareness judgements (Roiser et al. 2009). For example in the Salience Attribution Test (SAT), coloured images of household objects or animals are presented prior to responding for possible rewards (money). One stimulus dimension (e.g. red vs. blue – relevant dimension) very reliably predicts the availability or non-

availability of money while the other (e.g. animals vs. household objects – irrelevant dimension) has no bearing on the outcome. The rewarded stimulus feature (e.g. blue) promotes faster responding for reward relative to the unrewarded one (e.g. red), providing a measure of implicit adaptive (i.e. appropriate) salience; participants are also able to report this association overtly using visual analogue scales (explicit adaptive salience). Faster responding/greater reward rating occurring to one of the irrelevant features over the other (e.g. animals faster over household objects) indicates aberrant salience.

Such a distinction between adaptive and aberrant salience is important to directly test the aberrant salience hypothesis, since demonstrating an absence of normal reward processing is not necessarily directly indicative of the presence of context-inappropriate associations, the central tenet of this model. The first study to investigate behaviour on the SAT in patients with schizophrenia reported elevated explicit aberrant salience in patients with delusions, but not in those without (Roiser et al. 2009), consistent with the aberrant salience hypothesis (Kapur 2003).

Construct validity

In apparent variance with the salience attribution hypothesis, functional imaging studies report reduced ventral striatal hemodynamic responses during reward cue conditions (Juckel et al. 2006; Schlagenhauf et al. 2008) in patients with schizophrenia; this effect also correlated with negative symptoms. The proposed explanation for this paradoxical finding is as follows: in the context of many stimuli of heightened significance generally, reward-related cues may not differentially activate the ventral striatum, and thus fail to motivate behaviour (Ziauddeen et al.; Roiser et al. 2009). Furthermore, explicit aberrant salience in the SAT was associated not only with delusions but also with negative symptoms (Roiser et al. 2009). Interestingly, in healthy volunteers, the degree of aberrant explicit salience correlated with hemodynamic responses in the prefrontal cortex, hypothesised to contribute to negative symptoms (Juckel et al. 2006). Such findings highlight the importance of the distinction between negative symptoms, including anhedonia, that are secondary to the psychotic state, and enduring negative symptoms in the absence of psychosis (primary negative symptoms) that have a separate pathogenesis that is not responsive to antipsychotic drugs. The construct validity of the aberrant salience measurements

provided by the SAT has also been investigated using principal components analysis in healthy volunteers (Schmidt et al. 2009). This study found that aberrant salience was not related to potentially confounding measures including working memory, selective attention, latent inhibition or reward learning.

Criterion validity

- Patients, relatives and high schizotypes

Studies using reward-based paradigms have reported consistent abnormalities in schizophrenia patients (Waltz et al. 2007; Murray et al. 2008; Murray et al. 2008), especially in those with delusions (Roiser et al. 2009), as mentioned previously. Also, aberrant salience has recently been linked to high levels of schizotypy (Roiser et al. 2009; Schmidt et al. 2009; Housden et al. 2010). There are currently no data regarding unaffected relatives of patients with schizophrenia, but evidence from psychophysical experiments suggests that abnormalities in reward processing increase linearly with genetic risk (Glatt et al. 2006).

Predictive validity

- Dopamine antagonists

Normalisation of aberrant salience with successful antipsychotic treatment has been reported in patients using the SAT (Roiser et al. 2009). As predicted by the aberrant salience hypothesis, patients taking antipsychotics also scored lower on adaptive salience than controls (Kapur 2003). Additionally, the antipsychotic drugs haloperidol (Pessiglione et al. 2006) and olanzapine (Abler et al. 2007) have been reported to attenuate reward-related responses in ventral striatum in healthy volunteers. However, Juckel and colleagues reported a relative sparing of striatal reward-related responses in patients administered atypical but not typical antipsychotic drugs (Juckel et al. 2006).

- Dopamine agonists

The role of dopamine in aberrant salience attribution is supported by a study utilizing amphetamine challenge in healthy volunteers, which reported a loss of specificity of hemodynamic responses to rewards relative to punishments in the ventral striatum (Knutson et al. 2004). The effect of dopamine agonists on SAT performance has not yet been investigated.

3.3.3. Biconditional Learning (BCL)

Background

Cohen & Servan-Schreiber have attempted to account for a broad range of cognitive deficits observed in schizophrenia by appealing to a unitary mechanism (Cohen et al. 1992). They described the cognitive dysfunction seen in schizophrenia as a failure to produce the appropriate response as a consequence of an impaired ability to represent, maintain or apply task-setting information; a process that is thought to rely on intact function of the prefrontal cortex. Consequently the deficits in cognitive performance should be particularly evident when task-setting cues dictate when different responses are required to the same stimuli.

Paradigm description

Conditional discrimination paradigms may be used to assess the way in which task-setting cues can control performance. In these tasks, participants are required to learn associations between arbitrary pairs of stimuli, or between arbitrary stimuli and responses (e.g. (Petrides 1985)). These associations are learned by trial-and-error and based on feedback, either from the experimenter in human studies or food reinforcement in animal studies. In a conditional discrimination task the performance of a particular response may be appropriate in the presence of a specific cue but is inappropriate at other times. For example, participants may learn that in the presence of A, response X (but not Y) is required, whereas in the presence of B, Y (but not X) is required. In biconditional discrimination tasks, correct responses are dictated by the particular combination of cues, usually represented by AX+, BX-, AY-, BY+, where A, B, X, Y represent cues, and + and – respectively represent the presence and absence of appropriate outcomes.

Construct validity

In animal studies lesions to prefrontal cortex interfere with BCL (Haddon et al. 2006). Imaging studies in humans suggest prefrontal cortex is engaged in conditional discrimination learning (Mok et al. 2009).

Criterion validity

- Patients, relatives and high schizotypes

A pilot study using an allergy prediction task (e.g. (Aitken et al. 2000)), in patients with schizophrenia revealed a deficit in the solution of a biconditional discrimination (Walters et al. Unpublished findings). Similar results have been found in a sample of high schizotypes(Haddon et al. in press).

- Glutamate antagonist challenge

There are no translational drug studies in humans using a BCL task but in experimental animals the NMDA antagonist phencyclidine disrupted performance on conditional and biconditional discrimination (Dunn M. et al. 2005; Dunn et al. 2006; Dunn et al. 2006).

Predictive validity

- Dopamine antagonists

The NMDA-induced impairments on BCL in animals can be selectively reversed by the action of atypical, but not typical, antipsychotics (Dunn et al. 2007), and this action is likely to depend of prefrontal mechanisms (Dunn et al. 2007).

- Dopamine agonists

Animal data suggests that acute administration of amphetamine disrupts performance in a similar way to NMDA antagonists (Dunn and Killcross, 2006b). No data on the effects in humans are currently available.

3.3.4. Perception: Signal Detection Task (SDT)

Background

The cognitive mechanisms which underpin auditory hallucinations may be an extension of normal cognitive processes (Bentall 1990).The use of healthy volunteer proxies for hallucinatory phenomena such as inner and imagined speech have been used in functional imaging studies (Simons et al.; Shergill et al. 2000). However the use of a behavioural task which permits the identification of the cognitive mechanisms underpinning a propensity towards hallucinations would be most time and cost efficient as a biomarker for this symptoms. The signal detection task (Barkus et al. 2007) aims to objectively determine proneness to auditory hallucinations without using suggestion (Young et al. 1987; Cahill 1996).

Paradigm description

Participants are asked to indicate whether they hear a voice during brief periods of white noise. There is a voice in sixty percent of the trials. A third of the voice presentations are clearly audible while the remainder are at auditory threshold. The clearly audible voices give participants an indication of what to expect and those presented at auditory threshold allows for some perceptions to be ambiguous. From these data four pieces of information are provided (e.g.(Green et al. 1966; McNichol 1972)): hits (a voice is present and participants report hearing it), misses (a voice is present but participants do not report hearing it), correct rejections (a voice is not present and the participants do not report hearing it) and false alarms (a voice is not present but the participant reports hearing it) - the putative measure of hallucinatory proneness. Measures of sensitivity, specificity and response bias can be calculated using signal detection theory.

Construct validity

In a small fMRI study Barkus et al. reported that false perceptions (when compared to hearing a voice which was presented) activated closely similar areas to those associated with hallucinations in patients with psychosis (e.g.(Simons et al. 2009)) including the inferior and superior temporal gyri and the cingulate (Barkus et al. 2007). Also, a specific association between positive response bias and hallucinatory

proneness items rather than items relating to visual or thought intrusions into cognition was reported (Varese et al. 2010).

Criterion validity

- Patients, relatives and high schizotypes

A tendency to report false alarms has been reported patients with psychosis who report hallucinations (Bentall et al. 1985; Bentall et al. 1991). A similar pattern has been observed in healthy volunteers in association with high scores on questionnaire ratings of hallucinatory proneness or positive schizotypy (Bentall et al. 1985; Rankin et al. 1995; Barkus et al. 2007). Most of these studies report that this tendency exists in the absence of any difference in the ability to detect signal, although this is not a consistent finding (e.g. (Boecker et al. 2000)). Additionally performance on the SDT also seems to be mediated by age and positive schizotypy in a manner consistent with psychosis risk i.e. younger participants scoring higher on positive schizotypy reporting more false perceptions than older participants and younger participants scoring low on positive schizotypy (Barkus et al. Submitted).

Drug-validation studies would be of considerable interest but have yet to be carried out. Given the focus of this task on auditory hallucinations samples in these studies should be recruited on the basis of a propensity towards these symptoms.

3.3.5. Cortical electrophysiology: Early sensory Event-Related Potentials (ERPs)

Background

A number of studies suggest that schizophrenia is associated with impaired visual sensory perception: deficits have been demonstrated in motion, contrast sensitivity and spatial discrimination (Javitt 2009). ERPs recorded by electroencephalography have the temporal resolution necessary to identify the neural basis of impaired perception and are potential biomarkers of early sensory processing. Two promising measures of early sensory processing have been developed in the auditory and visual modalities (the mismatch-negativity (MMN) and P1 potentials, respectively). The MMN potential is a negative ERP wave peaking over the temporal cortical lobes at 150-200 ms post-stimulus in response to auditory stimuli that deviate from an established pattern (Naatanen et al. 1978). The visual P1 potential is generated by any

perceived visual stimulus. It peaks between 100 and 150 ms and has a bilateral occipital distribution (Di Russo et al. 2003).

Paradigm description

MMN tasks involve participants listening to repetitive sound patterns which are infrequently interrupted by stimuli that deviate in terms of intensity or duration (Michie 2001). The process is attention-independent and the participants are usually instructed to ignore the sounds while watching a film or reading a book. The visual P1 wave is typically evoked by watching a black and white checkerboard pattern repetitively flashed on a screen. The participants are instructed to ignore these stimuli but are visually engaged by an attentional task (e.g. pressing a button whenever an animal appears on the screen) e.g. (Yeap et al. 2006). In both cases the outcome measure is the peak amplitude or the mean amplitude of a window centred on the peak of interest.

Construct validity

Functional imaging studies have provided evidence for reduced activation during perception in both visual and auditory cortex of schizophrenia patients. In the case of MMN, a combined MEG/fMRI study demonstrated reduced activity within the secondary auditory cortex (planum temporale), an area proposed to be crucial for integration of the auditory stimuli (Kircher et al. 2004). A combined EEG/fMRI study of early visual potentials found reduced activation of the V1 and V2 visual areas (Martinez et al. 2008). Moreover, the P1 potential is predictive of performance on cognitive tasks that require visual encoding (Haenschel et al., 2007, Butler et al., 2009). This has been interpreted as evidence that inefficient encoding contributes to higher-order cognitive deficits. Similarly, the MMN abnormalities in schizophrenia predict social and occupational impairment (Light et al. 2005).

Criterion validity

- Patients, relatives and high schizotypes

MMN is reliably reduced both in patients (Umbricht et al. 2005) and at-risk individuals including unaffected relatives (Michie et al. 2000), schizotypal individuals (Niznikiewicz et al. 2009) and children at-risk for schizophrenia (Bar-Haim et al. 2003). In the visual domain, the P1 potential has been consistently shown to be of

reduced amplitude in patients (Doniger et al. 2002; Foxe et al. 2005; Schechter et al. 2005; Yeap et al. 2006), unaffected relatives (Yeap et al. 2006) and recently in high schizotypes (Koychev et al. 2010).

- Glutamate challenges

Ketamine challenge in healthy volunteers led to diminished MMN amplitude (Oranje et al. 2000; Umbricht et al. 2000; Kreitschmann-Andermahr et al. 2001) observed no effect on MMN. No studies of ketamine on visual P1 amplitude in healthy volunteers have been published but such effects have been reported in experimental animals (Heggelund et al. 1990; Kwon et al. 1991).

Predictive validity

- Dopamine antagonists

Treatment with typical or newer antipsychotic drugs has no effect on the MMN abnormality (Schall et al. 1999; Korostenskaja et al. 2005). Also, unmedicated and recent onset patients have a pattern of MMN and P1 abnormalities similar to these of chronically medicated patients (Javitt et al. 2000; Umbricht et al. 2006; Yeap et al. 2008). Finally, a recent analysis showed that there is no relationship between antipsychotic dosage or duration of treatment and the severity of the P1 potential abnormality (Yeap et al. 2008).

- Dopamine agonists

There have been no studies on the effects of acute dopamine agonist challenge in auditory MMN or P1 ERPs.

- Other agents

Benzodiazepine treatment in schizophrenia patients does not alter the MMN deficits (Kasai et al., 2002).

3.3.6. Cortical electrophysiology: Oscillation and coherence biomarkers

Background

Recent theories attribute the core dysfunction in schizophrenia to impaired connectivity between and within brain regions (Friston, 2005, Andreasen, 1999). Neural oscillations has been identified as the fundamental mechanism that enables coordinated brain activity and as such represents a natural target for schizophrenia research (Fries 2009). Single-cell and local field potential recordings have shown that neurons tend to synchronize their activity by aligning their action potentials in the same oscillatory rhythm. Oscillatory activity has been divided into low (delta 1-3 Hz; theta 4-7 Hz; alpha 8-12 Hz) and high frequency bands (beta 13-30 Hz and gamma 30-200 Hz), a distinction which has been proposed to have functional relevance (Buzsaki 2006) . However, there is considerable overlap and the classical cut-offs between bands is somewhat arbitrary (for reviews see (Uhlhaas et al. 2008; Uhlhaas et al. 2010)). The oscillations can be characterized in terms of their power and the degree to which their phases coincide between trials (phase-locking factor) or electrodes (coherence). Also, two types of oscillations are analyzed: time-locked (evoked) and non time-locked (induced). Evoked oscillations are hypothesized to represent perceptual binding, while induced underlie cognitive processes (Buzsaki 2006).

Task description

Neural oscillations are studied using event-related designs in EEG. Any task that evokes a repeated uniform cognitive response can be used to probe connectivity in schizophrenia. Working memory, perceptual binding and pattern deviance tasks have been employed in both visual and auditory domains.

Construct validity

A number of experiments have demonstrated a close link between synchronized oscillatory activity and the preparation, initiation and maintenance of cognitive and behavioural acts (Varela et al. 2001). Studies in patients have found that reduced evoked oscillations in the beta and gamma range predict working memory impairment

on a matching to sample task (Haenschel et al. 2009). Similarly, the disruptions of the non time-locked (induced) gamma oscillations have been linked to impaired performance on several cognitive tasks, suggesting that the neural processes underlying both induced and evoked oscillatory activity are critical to higher order cognitive processes (Cho et al. 2006; Basar-Eroglu et al. 2007).

Criterion validity

- Patients, relatives and high schizotypes

Abnormalities of the gamma, beta and alpha oscillations are well documented in schizophrenia patients (Uhlhaas et al. 2008). Evoked gamma bursts time-locked to auditory and visual stimulation show reduced power and degree of synchronization in patients (Uhlhaas et al. 2006; Spencer et al. 2008; Haenschel et al. 2009) and unaffected relatives (Tsai et al. 2004). In a recently completed analysis we found evidence of power and phase abnormalities in a sample of schizotypal individuals (See Chapter 7). The pathogenesis of the observed oscillatory abnormalities has been attributed to dysfunction within local GABA inhibitory networks that set the rhythm within neuronal networks, deficits in the glutamatergic system which mediates long-distance synchronization and/or demyelination that affects the cortico-cortical and cortico-subcortical connectivity (Uhlhaas et al. 2008).

Criterion validity

- Glutamate antagonist challenges

A study using ketamine in a gating auditory paradigm found augmented gamma and reduced theta response in healthy volunteers (Hong et al. 2009).

Predictive validity

- Dopamine antagonists

Data on modulation of oscillatory activity by antipsychotic drugs are limited with one group reporting reduced gamma activity in patients treated with atypical antipsychotics (Mayner et al. 2008). However, no correlation was found between chlorpromazine equivalents and amplitude of evoked and induced oscillations in

patient samples (Haenschel et al. 2009). Also, gamma band abnormalities have been reported in unmedicated patients (Gallinat et al. 2004).

- Dopamine antagonists and other agents

There are currently no data on the effect of dopamine agonists or other psychoactive compounds on neural oscillations in humans.

3.3.7. Oculomotor control: Saccadic eye movements

Background

The study of eye movements has received much interest in the validation of potential biomarkers due to findings of various oculomotor deficits in schizophrenia. The saccadic eye movements (rapid eye movements that allow the fixation of a new object that has appeared in the visual field) are some of the most widely studied measures in the context of schizophrenia.

Paradigm description

In the prosaccade task a novel visual target appears in the periphery and the participants have to direct their gaze at it. In the antisaccade task the participants have to inhibit the prosaccadic response to a new stimulus and instead look at its mirror image location on the opposite side of the screen. The performance measures of the task are the number of error prosaccades, the latency and the spatial accuracy of the mirror antisaccade.

Construct validity

Imaging studies have demonstrated that the antisaccade is a complex task activating a dorsal fronto-parietal cortical network as well as subcortical project targets; specifically, dorsolateral and ventrolateral prefrontal cortex, frontal and supplementary eye fields, the intraparietal sulcus, striatum, and thalamus (Munoz et al. 2004). Evidence from structural and functional imaging studies indicate that the structures underlying the abnormality in schizophrenia are the frontal cortex (Ettinger et al. 2004) and the striatum (Raemaekers et al. 2002). Performance on the task has been demonstrated to have high temporal stability (Ettinger et al. 2003). Also, the

antisaccade error rate correlate with the measures of executive function in schizophrenia patients (Hutton et al. 2004).

Criterion validity

- Patients, relatives and high schizotypes

Schizophrenia patients have been shown to have normal performance on the prosaccade task (Hutton et al. 2006; Haraldsson et al. 2008), although some reports suggest decreased latencies of the responses (Reilly et al., 2008a). In the antisaccade task however, they are consistently impaired, making significantly more errors, having slower antisaccade latencies, and showing deficits in calculating the spatial location of the mirror image (Fukushima et al. 1988; Hutton et al. 2006). Unaffected biological relatives and schizotypal individuals also show impaired antisaccade performance (Calkins et al. 2004).

- Glutamate antagonist challenges

Ketamine studies in healthy humans have found a decrease in prosaccade velocity and an increase in saccade latency but only non-significant impairments in antisaccade performance (Radant et al., 1998, Weiler et al., 2000). In contrast, a study in primates found that ketamine infusion impairs antisaccade performance (Condy et al. 2005). The discrepancy between studies may reflect the different dosages of ketamine that were used.

Predictive validity

- Dopamine antagonists

Antipsychotic treatment of schizophrenia patients with both first and second generation antipsychotics led to a significant decrease in peak saccade velocity in several studies, but without major effects on antisaccade error rate or latency (Muller et al. 1999; Straube et al. 1999). However, switching from first generation neuroleptics to risperidone was related to improved antisaccade performance (Burke et al. 2002). Another longitudinal study showed that risperidone was associated with improvements in antisaccade latency whereas haloperidol was not (Harris et al. 2006). Studies of healthy volunteers have shown dose-dependent decrease in prosaccade peak velocity and either no effects or negative effects on antisaccades (Reilly et al.

2008). These negative effects could be due to the sedating effect of neuroleptics, as benzodiazepines have similar effects in healthy volunteers (de Visser et al. 2003). In fact, a reduction of prosaccade velocity is a highly replicated biomarker of a compound's sedative effects (de Visser et al. 2003).

- Dopamine agonists

Methylphenidate and amphetamine have been reported to improve antisaccade performance (Klein et al. 2002; O'Driscoll et al. 2005; Wonodi et al. 2006). Importantly, beneficial effects of repeated amphetamine administration in the study by Wonodi et al. were seen only in individuals with high levels of schizotypy.

- Other agents

Antisaccade performance is also sensitive to the effects of nicotine (Newhouse et al. 2004; Levin et al. 2006). In healthy smokers, nicotine reduces the rate of reflexive errors (Rycroft et al. 2006) and the latency of antisaccades (Ettinger et al. 2009). Healthy non-smokers also show reduced antisaccade latency with nicotine (Rycroft et al., 2007, Ettinger et al., 2009). A recent fMRI study suggests that the improvements in antisaccade performance with nicotine may be due to enhanced neural efficiency in the frontal cortex (Ettinger et al. 2009). Importantly, nicotine also improves antisaccade performance in schizophrenia (Depatie et al., 2002, Larrison-Faucher et al., 2004). Conversely, procyclidine, a cholinergic antagonist, leads to antisaccade impairments in schizophrenia (Ettinger et al. 2003).

3.3.8. Oculomotor control: Smooth pursuit eye movements (SPEM)

Background

The first reports of the inability of people with schizophrenia to eye-track accurately a swinging pendulum date from 1908 (Diefendorf et al. 1908). About 100 years later, deficits in the smooth pursuit eye movements (slow eye movements that allow the stabilisation of a slowly moving target on the retina) are some of the most robust findings in schizophrenia research.

Paradigm description

In the SPEM paradigm, participants have to follow a small visual target moving at a constant velocity without moving their head. The outcome measures include the ratio between the speed of the moving target and the eye movements and the rate of catch-up saccades that that bring the image back onto the fovea.

Construct validity

The existing data indicates SPEM are executed by a circuit linking the visual, mediotemporal (MT), medial superior temporal (MST), prefrontal and motor regions of the cortex (Newsome et al. 1988). The deficit in schizophrenia spectrum individuals has been attributed largely to dysfunction in frontal (O'Driscoll et al. 1999) and motion sensitive (Lencer et al., 2003) regions. Similar to the antisaccade task, smooth pursuit performance has good temporal stability (Ettinger et al. 2003).

Criterion validity

- Patients, relatives and high schizotypes

Schizophrenia patients are less able to follow the target accurately than healthy controls (i.e. they show reduced pursuit gain and make more catch-up and intrusive saccades) (Campion et al. 1992; Ross et al. 2002; Trillenberg et al. 2004). Studies in relatives have found similar deficits in gain (Ross et al. 2002; Ettinger et al. 2004) and intrusive saccades (Rosenberg et al. 1997; Ross et al. 2002). Schizotypal individuals have also been demonstrated to have smooth pursuit abnormalities (O'Driscoll et al. 1998; Smyrnis et al. 2007).

- Glutamate antagonist challenges

Ketamine challenge studies have found a range of abnormalities, namely a dose-dependent nystagmus (Radant et al. 1998), increase in the number of anticipatory saccades (Avila et al. 2002) and deficit in measures that test retinal (but not extraretinal) target processing (Weiler et al. 2000).

Predictive validity

- Dopamine antagonists

Initiation of antipsychotic treatment has been reported to be associated with a decrease of pursuit gain, indicating a sensorimotor impairment (Lencer et al., 2008). Chronic treatment appears to have similar effect, as long-term medicated patients perform worse than chronic non-medicated and treated first-episode patients (Sweeney et al. 1999; Hutton et al. 2001), but see (Thaker et al. 1999).A study administering low doses of haloperidol, amphetamine and placebo in a healthy volunteer sample reported an increase in saccadic intrusions during smooth pursuit with the haloperidol that were not present in the other groups (Malaspina et al. 1994). Similar to the antisaccade data, the observed effects could at least partly be attributed to the sedating action of antipsychotics, as benzodiazepines have been shown to decrease SPEM velocity in healthy volunteers (Reilly et al. 2008). Also, evidence from healthy volunteer and schizophrenia studies indicates that nicotine improves SPEM performance (Domino et al. 1997) and the anticholinergic compound procyclidine worsens SPEM performance in schizophrenia (Ettinger et al. 2003).

- Dopamine agonism

In the only currently available study of the effects of acute amphetamine on SPEM, no significant effect of the challenge was reported (Malaspina et al. 1994).

3.4. Discussion

We have reviewed several cognitive and physiological biomarkers for schizophrenia for their potential as biomarkers for drug discovery in healthy volunteers. Several conclusions can be drawn on the basis of this literature.

3.4.1. Reliability

The MATRICS initiative stands out in terms of demonstrating reliability - that the same results in terms of group differences and correlations with outcome are seen in different centres and across time (Nuechterlein et al. 2008). This has been driven by the need to find drugs that improve the cognitive deficits of schizophrenia and to convince licensing authorities and Industry of the validity of MATRICS tests as markers of efficacy. There have been no other systematic studies of reliability of the other biomarkers reviewed.

3.4.2. Surrogate populations

Many of the biomarkers show differences between controls and criterion groups - patients, unaffected relatives and schizotypal individuals. The lack of institutionalization, chronic disease and medication in the healthy volunteer groups confirms the idea that the abnormalities observed in schizophrenia are not due to the confounding factors of illness course and treatment. Instead, it indicates that cognitive dysfunction is a core feature of schizophrenia that is present across the disease spectrum (Heinrichs 2005). Familial abnormalities suggest the measures are endophenotypic trait biomarkers. This is not weakened if the biomarkers are also abnormal in schizotypal individuals since they may also carry risk genes (e.g. (Fanous et al. 2004)). Equally, however, unaffected family members may have schizotypal features – this is rarely checked in the literature – so familiarity may involve an element of state-dependency (see (Diwadkar et al. 2006) for effects of familial risk and schizotypy interacting with age for working memory performance).

3.4.3. Ketamine as a pharmacological model of schizophrenia

The available data suggests acute ketamine administration has a general mildly disruptive effect on neurocognitive function in humans. The pattern of abnormalities has similarities to these observed in patients, relatives and high schizotypes (Krystal et al. 1999). It has been argue that the cognitive effects of ketamine and the symptoms it evokes may more closely mimic deficit symptoms and cognitive impairment in schizophrenia (Pomarol-Clotet et al., 2006) and this would be in keeping with lack of effect of haloperidol or clozapine on these phenomena. That ketamine also mimics some of the GABA/glutamate neurochemical abnormalities of schizophrenia suggests that ketamine-evoked biomarker changes in volunteers have significant construct validity.

3.4.4. Dopamine and cognition

Sensitivity to drug challenges aimed at improving cognition or clinical states was evident with several of the reviewed biomarkers. The most consistent finding is that dopaminergic treatments generally affect cognitive performance. An important characteristic is that enhancing dopamine function tends to selectively improve low baseline performance but worsen optimal performance. These findings fit in well with the idea that executive problems in schizophrenia spectrum disorders are due to suboptimal dopamine activity. Some authors have proposed a U-shaped curve to describe the relationship between dopamine and executive function, with hypo- and hyperdopaminergic states leading to cognitive abnormalities (Barch 2004). The proposed suboptimal dopamine function in the schizophrenia-spectrum has been attributed to the high activity version (val/val genotype) of the enzyme that metabolizes dopamine, catechol-O-methyl transferase (COMT). In support of this, tolcapone, an inhibitor of COMT, improved N-back performance in healthy volunteers at high loads (Mattay et al. 2000). Also, participants with the val/val genotype benefited preferentially by treatment with tolcapone in an episodic memory task. In a different study, low working memory performance in val/val participants was improved by a challenge with dextroamphetamine. The same agent led to deterioration at high working memory capacity in participants with the met/met

genotype (Fava et al. 1999). Abnormalities in other enzymes involved in clearing dopamine from the synaptic cleft have also been implicated, but evidence for direct involvement in schizophrenia spectrum pathophysiology is scarce (Apud et al. 2006). A second important feature of dopamine effects is that D1 agonists appear to be more effective than D2 agonists and this may reflect the greater concentration of D1 receptors in PFC than of D2. The implication of these findings is that frontal dopamine neurotransmission is a validated target for future drug development and a promising line of development.

Also, the improvement of some of the biomarkers by compounds affecting non-dopamine neurotransmitter systems in healthy volunteers (such as the benefit to eye-tracking performance by cholinergic agonists) demonstrates that cognitive processes are a focal point of neuromodulatory input and the possible drug targets are not limited to the currently explored dopaminergic and glutamatergic systems. Secondly, it shows that the biomarkers have good sensitivity to efficacy, regardless of the mechanism of action.

3.4.5. State and trait biomarkers

The reviewed literature showed a variable relationship between clinical state and biomarker performance; some showed a degree of state-dependency whereas others did not. The state dependent biomarkers included salience attribution, eye-tracking and perhaps working memory tasks where there is some evidence for varying degree of improvement with atypical antipsychotics. This effect could be due to their lower affinity for the D2 receptor which may permit endogenous dopamine activity (Kapur et al. 2001). This might be particularly important for prefrontal cortical function and the performance on tasks that depend on its integrity, such as working memory and eye-tracking, reflects this. In support of this, no improvement is found with typical antipsychotics, despite their efficacy in controlling positive symptoms. The practical implication of such biomarkers is that they could potentially be validated as clinical end-points to assess efficacy of agents that ameliorate both cognitive and clinical state.

Measures such as the MMN and P1 event-related potentials and evoked oscillations were generally not influenced by antipsychotic treatment or clinical state. This indicates that the underlying abnormality is probably state-independent and related to factors predisposing to schizophrenia. Findings of similar abnormalities in individuals at genetic or psychopathological risk for schizophrenia support this. Early visual ERPs and oscillatory synchrony and coherence can be informative about neural connectivity, dysfunction in which has been argued to be a core feature of schizophrenia. In other words the biomarkers relate to a neural process implicated in pathogenesis and so have some construct validity. Using such measures as biomarkers would be most useful in assessing novel agents that aim to modify the disease process through regulating connectivity. There is as yet little information about drug effects on early sensory EEG measures and this is an important priority for future research. It should be noted however that the state-independency most probably does not extend beyond early sensory ERP and oscillatory phenomena, as ERP components that mark later higher order cognitive information processing (e.g. P300) have been shown to normalize with antipsychotic treatment (Coburn et al. 1998).

The state/trait distinction is not cut and dried. For example, despite the modest data suggesting improvement of working memory and eye-tracking performance with atypical antipsychotic treatment, these deficits are still found in first-degree relatives. This indicates that they are at least to a certain extent independent from clinical state and are likely to persist in a milder form even when complete remission is achieved. Trait biomarkers have the potential to detect drugs that prevent onset of psychosis by acting on mechanisms of vulnerability that may be distinct from mechanisms of the symptomatic state.

Some studies suggest that biomarkers in the proposed target groups may have predictive utility for drug development. For example, McClure et al showed that pergolide improved visual-spatial working memory in a small sample of 25 people with Schizotypal Personality Disorder (diagnosed according to DSM-IV) when given for a short period of 4 weeks (McClure et al. 2010). This cognitive benefit was also associated with symptomatic improvement.

3.4.6. Future directions

One of the clear priorities of future research is the development of non-dopaminergic agents that are effective in treating the cognitive and psychotic features of schizophrenia. As argued previously the proposed biomarkers can assist in this endeavour by allowing early proof of concept studies in surrogate populations. However, as the spectrum of clinical efficacy of such compounds emerges they will help to validate biomarkers for drugs targeting different aspects of schizophrenia.

There is a clear need for more data on the reliability of the measures especially for the non-MATRICS biomarkers and for data about drug actions on the novel biomarkers (SDT, SAT) and the EEG measures. Further, standardised procedures need to be agreed on and established in each task. These are all key prerequisites in order for large, multi-site screening of novel compounds to take place.

Further validation of biomarkers can be achieved through prospective clinical trials in target groups such as unaffected relatives and high schizotypes. The example of the study by McClure et al. show that such design can give a more clinically relevant picture of the properties of the drug and the biomarker than the trials where acute drug administration takes place (McClure et al. 2010).

From the basic science point of view, more research is needed into the pathophysiological mechanism of the cognitive mechanisms that underlie the biomarkers. Dissecting the neurophysiological and molecular basis of the different components of complex functions such as working memory could reveal a number of prospective targets for drug development. Such informed approach to research and development will benefit from the possibility for quick validation of the resulting compound with the biomarker that they were derived from (in this case working memory).

Finally, imaging techniques such as fMRI and PET are an exciting field for cognitive biomarker research. More research however is needed in identifying reliable and

pathophysiologically relevant outcome measures that will be useful in the settings of a clinical trial.

CHAPTER 4

A validation of cognitive biomarkers for the early identification of cognitive enhancing agents in schizotypy: A three-centre double-blind placebo-controlled study*

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Contribution of the thesis author: The study was designed by an academic-industrial consortium before the start of the PhD programme of the thesis author. Ivan Koychev's studentship involved part-time work at the Manchester site of the study as study physician (medical screening of volunteers, administration of study drugs) and research assistant (volunteer recruitment, data collection). The author also analyzed the presented study data along the statistical plan laid out in the design of the study but also completed original post-hoc analyses that feature in Chapter 4. Ivan Koychev wrote the first draft of the article, coordinated the ensuing input from the co-authors and finalized the version submitted to European Neuropsychopharmacology.

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Abstract

A number of compounds aimed at improving cognition in schizophrenia have failed to demonstrate efficacy in Phase 2 and 3 clinical trials. Translational studies using biomarkers in surrogate populations, such as schizotypy, could be used to assess the efficacy of novel compounds. In this study, we aimed to validate the sensitivity and inter-site reliability of cognitive biomarkers (working memory (N-back), spatial working memory (SWM) and verbal fluency (VF) tasks) to detect the schizotypy phenotype and its reversal by psychotropic drugs. Healthy volunteers scoring high or average on a schizotypal personality measure (122 in each group) were randomized to receive a single dose of risperidone, amisulpride, nicotine or placebo in a double-blind randomized design. We found evidence for worse performance on N-back and VF tasks in the high schizotypy group, replicating previous research. This effect was counteracted by amisulpride on N-back: it improved the high schizotypy group but impaired the average schizotypy controls. A similar pattern was observed in the SWM and VF tasks. We interpret this finding in the light of the dopamine enhancing action of low dose amisulpride. In contrast, risperidone impaired both groups and nicotine had a beneficial effect for the low baseline performers only. These effects were consistent across sites. These data demonstrates the utility of biomarkers in detecting the effect of schizotypy and its reversal by drugs that enhance dopamine and cholinergic function. Studies using similar design could help the early assessment of potential of compounds designed to improve cognition in schizophrenia.

4.1. Introduction

Cognitive deficits are a core feature of schizophrenia (Green 2006) that predict functional outcome (Green et al. 2000; Hofer et al. 2005; Milev et al. 2005) and treatment adherence (Burton 2005). Currently available therapies offer marginal improvement at best (Heinrichs 2005) and development of novel agents aimed specifically at ameliorating cognitive deficits in schizophrenia is a recognized unmet need (Nuechterlein et al. 2008).

In the last two decades technological advances, notably genome sequencing, combinatorial chemistry and high-throughput screening, led to rapid expansion of potential drug targets for cognition. As a result, a number of theoretically sound compounds have emerged from animal models as safe and effective. However, the clinical success rate has been dwindling, as most novel compounds fail at the initial tests of efficacy in human disease, phase 2 clinical trials (Hurko 2010). This trend has exposed drawbacks of animal models of mental illness: despite capturing certain aspects of the condition, they do not predict efficacy. In addition, the noisiness of the traditional clinical end-points in psychiatry may have contributed to the rejection of otherwise promising compounds.

The use of biomarkers and surrogate end points to detect efficacy early in development has been proposed as a way of reducing the risk of failure in clinical development (Hurko 2009). The aim is to give a compound every chance to succeed, for example by selecting only a subgroup of patients that is more likely to respond or by recruiting groups of individuals that have limited symptom profile but lack the confounds associated with patient research (surrogate populations). These proof of concept studies precede the costly Phase 2 clinical trials which use more rigid diagnostic criteria, heterogeneous populations and traditional clinical end-points. Their principal goal is to single out the compounds that are unlikely to be effective in humans and thus inform internal decision making.

In the case of schizophrenia, such early assessment of drug efficacy could be accomplished using cognitive biomarkers validated in schizophrenia (for example the

ones developed by the MATRICS initiative (Nuechterlein et al. 2008; Keefe et al. 2010)) in surrogate populations such as high schizotypes. These individuals have personality traits corresponding to psychopathological manifestations of schizophrenia and also exhibit a profile of attenuated cognitive deficits (Raine 2006). This overlapping symptom profile, as well as evidence highlighting the common genetic and neurobiological basis of schizophrenia and schizotypy (Siever et al. 2002) support theories that see the two conditions as the two extreme ends of a spectrum of disorders (Meehl 1989; Tsuang et al. 2002; Lenzenweger 2006). Despite these similarities, schizotypal individuals are most commonly spared psychotic episodes, repeated hospitalizations and chronic antipsychotic treatment (Raine et al. 1995). Importantly for cognition research, IQ levels and education levels are largely normal (Raine 2006) and their cooperation with study procedures is not hampered by profound psychotic and negative symptoms. In contrast, a large proportion of schizophrenia patients have decreased IQ levels which predict negative symptoms and cognitive impairment (Leeson et al. 2009) thus possibly confounding the core cognitive deficit.

In this experiment, we aimed to validate the use of cognitive biomarkers for the detection of cognition enhancing drug action in schizotypy samples. We used an online schizotypy questionnaire (Schizotypal Personality Questionnaire, (Raine 1991)) to screen a large number of healthy volunteers and identify volunteers with elevated schizotypal traits. Our choice of recruitment method was based on: i) studies showing that SPQ scores are elevated in relatives of schizophrenia patients (Kremen et al. 1998; Yaralian et al. 2000; Vollema et al. 2002); ii) data demonstrating that the SPQ identifies reliably a sample with a high prevalence of schizotypal personality disorder (SPD) (Raine 1991; Kremen et al. 1998); iii) extensive literature on cognitive abnormalities in high SPQ scorers, for example two large studies have found that high scorers have eye movement abnormalities similar to the clinically diagnosed SPD and schizophrenia (Smyrnis et al. 2003; Smyrnis et al. 2007).

Three centers in the UK administered three cognitive tasks (two probing working memory and one testing verbal fluency) to volunteers with high and average SPQ scores and challenged their performance with three psychopharmacological agents in a double-blind randomized design. The agents were amisulpride (partial dopamine D2

antagonist), risperidone (full dopamine D2 antagonist), as well as a patch of nicotine (cholinergic agonist). We laid out the following criteria for successful validation:

1. The biomarkers detect cognitive deficits in the schizotypy group
2. The effect of schizotypy is reversed by antipsychotic and/or nicotine administration
3. The observed effects are reliable across several sites

4.2. Methods

4.2.1. Subjects and study criteria

Subjects were recruited from three sites in the United Kingdom: Manchester, London and Cardiff via an online questionnaire measuring schizotypy (Schizotypal Personality Questionnaire in its short (SPQ-B, (Raine et al. 1995)) and full version (SPQ, (Raine 1991))). Participants were screened via telephone interview to exclude relevant mental health and medical conditions. Volunteers that passed the telephone screening were invited for a screening appointment. At screening, participants provided written consent and completed the full version of the SPQ again. Volunteers with scores in the range of 21-36 formed the control average schizotypy group (AS) and those with scores of 41 or above formed the high schizotypy group (HS). Male and female participants, aged 18-45 years, fluent English speakers and physically healthy (BMI, blood pressure, ECG, blood biochemistry and ECG all within normal range) were included in the sample. The lack of relevant medical history was confirmed by letter from GP. The Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) was used to screen for psychiatric disorders. On both screening and randomization days participants had to test negative for alcohol (alcohol breath test), illicit drug use (urine dipstick) and pregnancy (urine dipstick). Other exclusion criteria were: known/suspected intolerance or allergy to the study drugs, smoking more than 5 cigarettes per day, consumption of more than 8 standard caffeinated drinks per day, history of migraines, significant visual or hearing impairment, participation in any other drug trial in the 84 days before the randomization visit, prescribed medication 14 days prior to or over the counter medicine 48 hours before the randomization. Additionally participants were asked not to consume caffeinated drinks on the randomization day.

13,275 people completed the full version of the online SPQ and a further 9,098 filled out the short version, SPQ-B (SPQ mean: 22.2, SD: 13.8; SPQB mean: 8.6, SD: 4.8). 945 individuals underwent telephone screening and 451 were excluded at this stage. Of the 494 people that attended a screening appointment, 250 were excluded. Data on

the reasons for exclusions at each stage are presented in Figure 4.1. The randomized sample consisted of 244 participants.

4.2.2. Randomization day procedures

High and average schizotypy individuals were separately randomized to one of four treatment arms: nicotine (7 mg nicotine patch and placebo capsule), amisulpride (placebo patch and 400 mg amisulpride capsule), risperidone (placebo patch and 2 mg risperidone capsule) or placebo arm (placebo patch and placebo capsule). The patch (nicotine or placebo) was applied first and the capsule (amisulpride, risperidone or placebo) was administered 3 hours later. The treatments were randomized by an independent pharmacy and both the research and the medical staff were blind to drug status.

A set of neuropsychological tests was completed 4.5 hours after application of the patch and 1.5 hours after administration of the drug capsule. The timing was chosen to allow the drugs to reach peak plasma concentrations by the time of cognitive testing. This paper presents the results of tests probing working memory (N-back and Spatial Working Memory, SWM) and verbal fluency (VF). The order of the tasks was randomized for each participant. Vital signs were assessed regularly to check for adverse reactions to the treatments.

244 participants attended the randomization visits at the three sites (97 in Manchester, 83 in London and 64 in Cardiff). There was no main effect of site on the SPQ scores of the final high and average schizotypy groups. The high and average schizotypy groups consisted of 122 participants each. 59 were randomized on placebo, 62 on amisulpride, 62 on nicotine and 61 on risperidone (Figure 4.1). The demographic data of randomized participants is presented in Table 4.1.

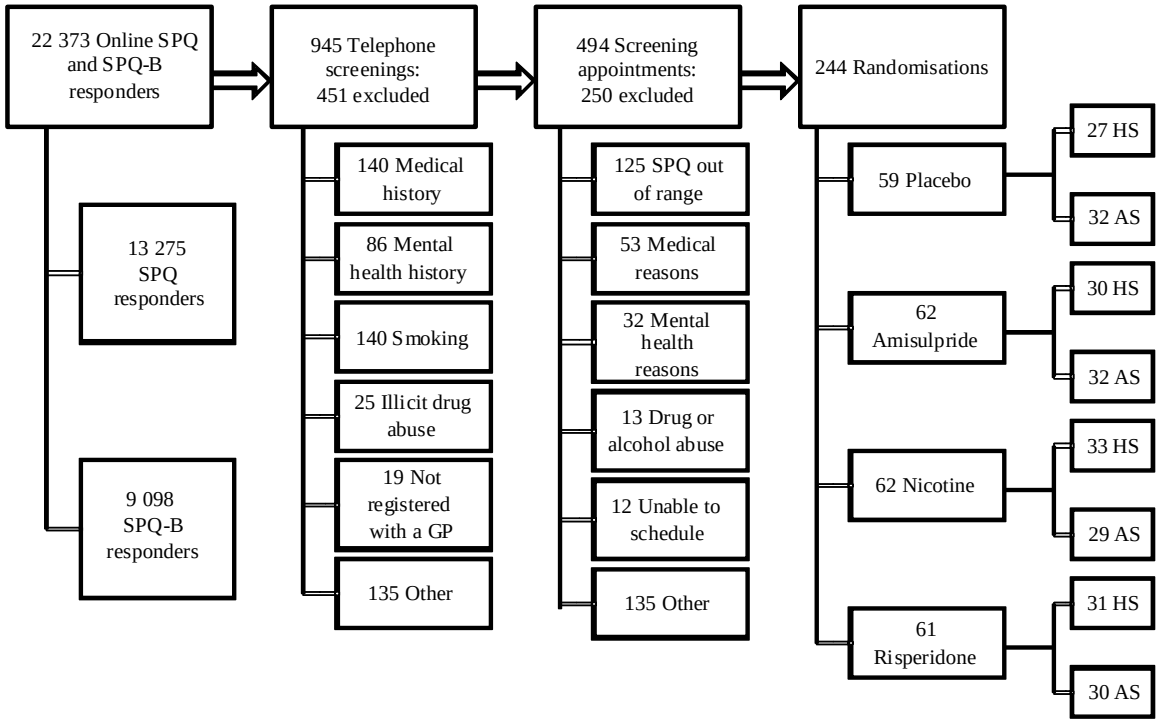

Figure 4.1. Flow-chart of participants screened, excluded and randomized as part of the study procedures. Abbreviations: HS – high schizotypes; AS – average schizotypes.

Table 4.1. Demographics of randomized study participants			
Demographics	Average schizotypy group (mean ± SD)	High schizotypy group (mean ± SD)	Significance
Age	23.5 ± 5.6	23.7 ± 5.3	p = .698
NART	113.6 ± 4.9	113.6 ± 5.2	p = .964
Years of education	15.5 ± 2.0	16.1 ± 2.2	p = .047
Sex	61	62 female	χ^2 = .898
SPQ total score	28.7 ± 4.5	50.0 ± 5.8	p < .001
Cognitive-perceptual SPQ subscale	10.6 ± 5.0	20.4 ± 4.7	p < .001
Interpersonal SPQ subscale	13.3 ± 5.0	22.4 ± 5.0	p < .001
Disorganized SPQ subscale	8.1 ± 3.4	13.5 ± 2.4	p < .001

4.2.3. Task description

Working memory (N-back) task

A series of alphabet letters were presented one at a time on a color monitor. Participants were instructed not to respond until they saw the same letter twice following one another. The task had three levels of difficulty according to the number of letters in between the two matching letters. In the 1-back condition the two letters followed each other immediately. In the 2-back condition the target letters were separated by one letter and in the three back two letters separated the target letters. Thus participants had to hold in mind one, two or three letters. Consequently, the 1-back condition exerted the lowest load on working memory and the 3-back condition the highest. There was also a baseline condition to control for attending to the task where participants simply needed to respond when they saw the letter 'X'. The participants completed 3 blocks of each condition presented in a pseudorandom order.

Spatial working memory (SWM) task

Treasure chests were presented on a computer screen. The participants were instructed to search for coins in the treasure chests. Only one of the chests contained a coin at any one time and once it had been found it moved to a treasure chest that it had not been present in during the trial. The participants completed trials with 4, 6 and 8 chests and 4 repetitions of each level of the task. A practice trial with only 3 treasure chests was completed to ensure the understanding of the task.

Verbal fluency (VF) task

Letter and category VF and word production were assessed during a succession of one minute periods. For the letter VF test participants were asked to verbally report as many words as they could beginning with the letters F, A and S (FAS condition). The experimenter wrote down the words produced. In the category VF test the categories used were vegetables and animals (category naming condition). Participants were then asked to switch between two categories (fruit and furniture) during the same one minute period (category swap condition).

Intelligence quotient (IQ)

IQ was determined using the National Adult Reading Test (Nelson et al. 1991), a reading-based estimate of premorbid intelligence. We collected this data to check that the groups have comparable IQ and as a potential covariate of performance. The participant was asked to pronounce irregularly spelt words from a standardized written list. The scores were determined on the basis of the number of correctly pronounced words.

4.2.4. Statistical analysis

Outcome variables

The dependent variables in the N-back task were percentage correct, errors of commission and the reaction times of correct and incorrect responses for each of the four conditions of the task (attention, 1-back, 2-back, 3-back). In the SWM task, 4 outcome measures were extracted for each of the three task levels: time to complete, mean number of choices, mean number of within and between search errors. For all conditions of the VF task the following measures were calculated: mean number of correct words, set and repetition errors.

Statistical analysis

Before analysis, the data was checked for outliers. For the N-back task, the criterion for outlier was performance at the attention and 3-back conditions that fell outside the 95% confidence interval. Participants that had below 20% accuracy on the 3-back condition were also excluded from the analysis. For the VF task, participants were classed as outliers if their number of either set or repetition errors on the FAS condition were outside the 95% confidence interval. For the SWM task, outliers were identified by visual inspection of boxplots and the extreme values tables produced from SPSS. The dependent variables were entered into a repeated-measures ANOVA (with the exception of set and repetition errors of the VF task which were entered into univariate ANOVAs) with between-subject factors of group, drug, sex and site. The within-subjects factor was condition of the task (level of difficulty for the N-back and SWM task; condition (FAS, category naming and category swap) for the VF task). Covariates added into the model were IQ, age and time since dosing. Covariates that

were found to be non-significant were removed from the model for each variable. In case of a main effect of level of difficulty, polynomial contrasts were run to determine the character of the relationship. Significant effects of drug were investigated by a post-hoc simple contrast of the study drugs versus placebo. The effect of schizotypy was examined both in the ANOVAs and in the placebo-treated groups. Schizotypy group by drug interactions were explored by three way interactions between schizotypy, drug and level of difficulty of the task. Significant interactions were reported with Huyhn-Feldt correction for sphericity and were followed by univariate ANOVAs on the identified level of difficulty in the two schizotypy groups separately. In case of significant main effect of drug in these analyses, post-hoc comparisons of the study drugs versus placebo were then used to explore the effect of each drug in the two schizotypy groups. Also, to test the hypothesis that amisulpride affected the two schizotypy groups differentially, we performed ANOVA analyses on the level of the task where the interaction between group, drug and task level occurred including the amisulpride and placebo treatment arms only. Since this is an exploratory study with multiple endpoints, no correction for multiple testing was made on any of the analyses.

4.3. Results

4.3.1. N-back

Subjects

For 2 participants there was no data on the N-back test available (1 AS on amisulpride and 1 HS on amisulpride). 2 participants (1 HS (risperidone) and 1 AS (nicotine)) were excluded based on the criteria for outliers. The final sample consisted of 240 participants, 120 high and 120 average schizotypes. The two schizotypy groups used in the N-back analysis did not differ in terms of age, IQ and sex. The HS group had significantly more years of education however (p= .042).

Main effects

Performance in both schizotypy groups decreased with increasing task difficulty ($F(3,573) = 6\ 383$, $p < .001$) in a linear fashion ($F(1,191) = 7.527$, $p < .01$). The main effect of schizotypy was significant in the errors of commission model with the HS group making more errors than the AS group ($F(1,46) = 6.628$, $p = .013$). The main effect of drug was significant for errors of commission ($F(3, 191) = 4.010$, $p < .01$), an effect that was due to risperidone worsening performance in comparison with placebo ($p = .06$). Risperidone also increased the latency of correct responses ($F(3, 189) = 7.804$, $p <.001$) and the latency of errors of commission ($F3, 190) = 8.428$, $p <.001$).

Interactions

A significant drug, schizotypy and WM load interaction was evident in the errors of commission model ($F(9, 573) = 2.489$, $p = .019$). The 3-back condition was confirmed as the level of this interaction by visual inspection of the histograms (Figure 4.2). Univariate ANOVA with a dependent variable of errors of commission at 3-back was performed separately for each schizotypy group to explore this effect. Simple contrasts in the HS group demonstrated that amisulpride and nicotine improved performance against placebo, the latter significantly ($p = .024$), the former at a trend for significance ($p = .055$). In the AS group risperidone and amisulpride both worsened performance, $p = .041$ and $p = .076$ respectively (Figure 4.2).

To confirm the differential effect of amisulpride on the two groups, we performed a post-hoc test, where only the placebo and amisulpride treated groups were retained in the univariate ANOVA. The outcome measure was errors of commission at the 3-back level. The interaction between group and drug was highly significant in this analysis ($F(1, 96) = 7.827$, $p < .01$).

Effects of covariates and site

IQ was a significant factor in the errors of commission ($F(1,191) = 5.717$, $p = .018$) but not the percentage correct model. IQ and time since dosing were significant covariates in regards to the latency of correct responses, ($F(1, 189) = 5.189$, $p = .024$ and $F(1, 189) = 8.645$, $p < .01$. respectively). There were no significant effects of site in the N-back analyses.

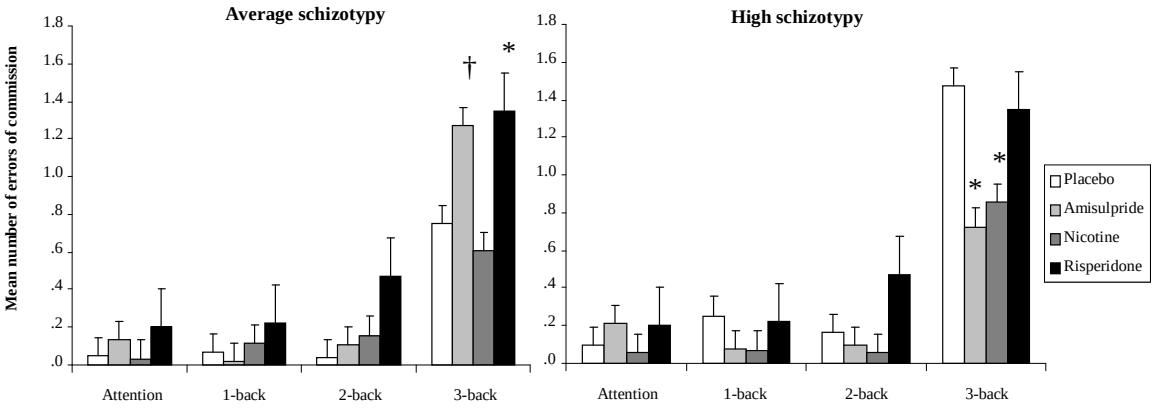

*Figure 4.2. Effect of study drugs on the mean number of errors of commission in the N-back task. Task load on the horizontal axis, mean number of errors of commission on the vertical axis. High schizotypy group on the left-hand side, average schizotypy on the right-hand side. Symbols: * = $p \leq .05$; † = $.05 < p < .10$.*

4.3.2. Spatial working memory

Subjects

For 7 subjects, no data on SWM was available (3 HS (1 on nicotine and 2 on risperidone) and 4 AS (2 on placebo, 1 on nicotine and 1 on risperidone). The final sample consisted of 237 subjects, 118 HS and 119 AS. The two schizotypy groups were well matched in terms of age, IQ and sex, but the HS group had significantly more years of education (p= .031).

Main effects

The performance on the task as measured by the number of between search errors decreased with difficulty ($F(2, 376) = 4.527$, $p = 0.011$) and the relationship was linear ($F(1, 186) = 5.4909$, $p = .020$). There were no main effects of schizotypy across drug conditions for any of the outcome variables (time to complete, number of choices per trial, within search errors or between search errors). There was no main effect of schizotypy in the placebo group either. There were no main effects of drug in any of the SWM models.

Interactions

The interaction between drug, schizotypy and task difficulty was significant in the between search errors model ($F(6,376) = 4.257$, $p < .01$). Inspection of the histograms (Figure 4.3) confirmed that this interaction was at level 3 of the task. To explore this effect we performed univariate ANOVAs within each schizotypy group. In the HS group, risperidone worsened the performance significantly in comparison with placebo ($p = .05$, Figure 4.3). No difference was found between the treatment arms in the AS group. To test the hypothesized differential effect of amisulpride, we repeated the same univariate ANOVA analyses in the groups treated with placebo and amisulpride only. The interaction between drug and schizotypy did not reach significance.

Effect of covariates and site

IQ was a significant factor in the between search errors model ($F(1,188) = 6.860$, $p = .010$). Age was a significant factor in the time to complete model ($F(1, 185) = 5.893$,

p = .016). The factor of site approached significance in the between search errors model (F(2, 188) = 2.712, p = .069). This was due to the participants in Cardiff performing the task better than the ones in Manchester (p = .078) and London (p= .025)

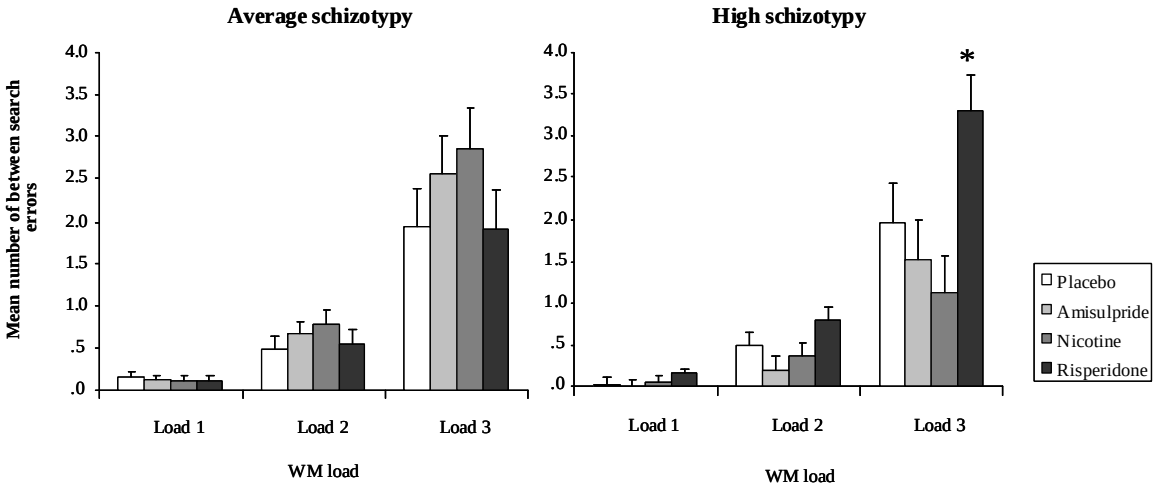

*Figure 4.3. Effect of study drugs on the mean between search errors on the SWM task. Task load on the horizontal axis, mean number of between search errors on the vertical axis. High schizotypy group on the left-hand side, average schizotypy on the right-hand side. Symbol: * = p ≤ .05.*

4.3.3. Verbal fluency task

Subjects

5 participants were excluded from the analysis due to being outliers on the number of errors on the FAS task (4 HS (3 on nicotine, 1 on amisulpride) and 1 AS (nicotine)). The final sample consisted of 117 HS and 120 AS participants. The two groups did not differ in terms of age and IQ. The HS group had higher number of years of full-time education at a trend for significance ($p = .082$).

Main effects

The main effect of schizotypy approached overall significance in respect to the correct words model, the high schizotypes performing worse than the controls ($F(1, 188) = 3.673$, $p = .057$).This trend was sustained in the placebo-treated groups where the effect was significant ($F(1,46) = 6.063$, $p = .018$). There was a trend for significance for the factor of drug in respect to the number of correct words ($F (3,188) = 2.371$, $p = .072$). Simple contrasts showed that the effect was due to risperidone decreasing the mean number of correct words produced in comparison with placebo, $p = .01$ (Figure 4.4).

Interactions

The correct words model revealed an interaction between drug, schizotypy and condition that approached significance ($F(6, 376) = 2.023$, $p =.062$). Visual inspection of the histograms presented in Figure 4.4 indicated that the level of the interaction is the category swap condition. A univariate ANOVA on this level was performed for the two schizotypy groups separately. In the controls, all study drugs led to worsening of performance ($p = .012$, $p = .038$ and $p < .01$ for amisulpride, nicotine and risperidone respectively). No such effects were observed in the HS group.

To test the hypothesized differential effect of amisulpride on the two schizotypy groups, we performed the univariate ANOVA in the category swap condition for the placebo and amisulpride treated groups only. This analysis revealed a significant drug and schizotypy interaction ($F(1, 95) = 4.574$, $p = .035$), indicating that while

amisulpride improved performance in the HS group, it had the opposite effect in the AS controls (Figure 4.4).

Effect of covariates and site

IQ was a significant covariate for the correct words model ($F(1,186) = 19.441$, $p < .001$). There were no significant effects of site in the VF models.

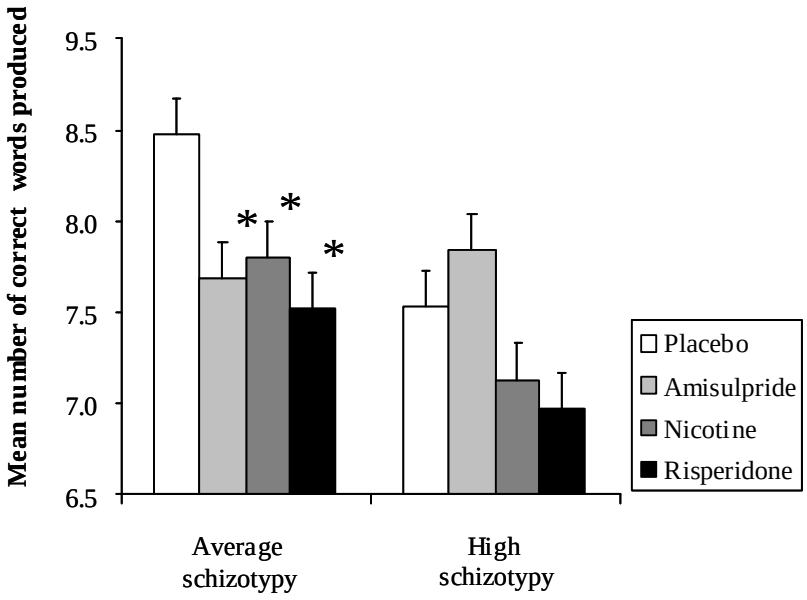

*Figure 4.4. Effect of study drugs on the mean number of correct words on the VF task. The two schizotypy groups on the horizontal axis, mean number of correct words on the vertical axis. Symbols: * = $p \leq .05$.*

4.4 Discussion

In this double-blind placebo-controlled study we aimed to validate the use of cognitive biomarkers to detect drug action in schizotypy. We laid out three validation criteria: the biomarkers should be sensitive to the schizotypy phenotype; this effect of schizotypy should be reversed by some or all of the drug challenges; the first two criteria should be consistent across different sites. In this section we will discuss the results of the study in respect to each of those in turn.

4.4.1. Criterion 1: Sensitivity of the biomarkers to the schizotypy phenotype

Two of the tasks satisfied this requirement. On the N-back task, the HS group performed worse than the controls in respect to the 3-back errors of commission measure, consistent with a subtle working memory deficit. This is in line with the results from a recently published study on a subgroup of the same sample where we again found evidence of behavioural and neurophysiological abnormalities during a working memory task (Chapter 6). Such working memory deficits are one of the most widely replicated findings in both schizotypy and schizophrenia and are considered a neurocognitive hallmark of the schizophrenia spectrum (Lee et al. 2005; Raine 2006). The performance in high schizotypes tends to be intermediate between that of healthy controls and schizophrenia patients (Trestman et al. 1995). On the VF task, the HS group produced significantly lower number of words on the category swap condition, but not on FAS or category naming conditions. This indicates that the detected abnormality may not due to verbal fluency impairment per se, but rather a central executive mechanism related to working memory (mental manipulation and inhibition of irrelevant cues). Hence, both biomarkers appear to be sensitive to the effect of schizotypy on executive function in its working memory and inhibitory domains.

The findings of deficits on the N-back but not the SWM task could be attributed to the key differences that exist between the two working memory tasks. In the former the presentation of each stimulus was very brief (1 second) while in the latter it was

unlimited. Previous research has indicated that schizophrenia patients require longer stimulus presentations to achieve stable working memory representations (Hartman et al. 2003; Fuller et al. 2005; Fuller et al. 2009). There is also evidence for abnormalities in the earliest stages of information processing driving higher-order cognitive impairment (Butler et al. 2007; Haenschel et al. 2007). In addition, cognitive performance in patients can sometimes be improved by increasing the duration of the encoding phase of the tasks (Tek et al. 2002; Lencz et al. 2003). In the previously mentioned study on a sub-sample of the HS, we found that they showed abnormal WM performance on a working memory task that allowed only brief encoding but intact performance in cognitive tasks with unlimited stimulus presentation (Chapter 6). This data indicates that early information processing is a key component in the pathogenesis of schizophrenia spectrum cognitive abnormalities. The practical implication is that these abnormalities will be more easily demonstrable using tasks that allow only brief stimulus encoding.

4.4.2. Criterion 2: Reversal of the effect of schizotypy by drug challenge

All drug challenges induced effects that were detectable using the proposed biomarkers, but amisulpride provided the clearest evidence for reversal of the schizotypy effect on cognition. In the HS group it reduced the number of errors of commission on the N-back task but worsened the performance in the AS group (Figure 2). In the SWM task the same effect was evident in respect to the between-search errors model, but this effect did not reach significance (Figure 3). In VF the AS produced significantly more words than the HS in the category switch task when placebo treated. AS participants treated with amisulpride produced significantly fewer correct words whereas performance improved non-significantly in the HS (Figure 4). A direct comparison between the amisulpride and placebo treated groups revealed that amisulpride had differential effect on the two schizotypy groups. These effects of amisulpride could be explained by data showing that when given in low doses (less than 10 mg/kg) it blocks the presynaptic dopamine receptors and enhances dopamine neurotransmission (Schoemaker et al. 1997). This is compatible with the results from a study that found improvement of working memory performance in schizotypal

personality disorder (SPD) after acute amphetamine administration (Kirrane et al. 2000). The benefit of dopamine enhancing agents in schizotypy is not limited to acute challenges, as a recently published study also found improvement in the cognitive function of SPD patients after 4-week treatment with pergolide, a combined D1 and D2 receptor agonist (McClure et al. 2010). Further, dopamine agonist challenges in humans and primates improve cognition, but only in those with low baseline performance (Barch 2004). These findings fit in well with the idea that the relationship between dopamine and executive function is best described by a U-shaped curve (Barch 2004). According to this theory, hypodopaminergic states of the prefrontal cortex (e.g. schizophrenia spectrum disorders) improve with enhancement of dopamine function, while people that have optimal dopamine function are worsened by these challenges.

In contrast to amisulpride, risperidone worsened spatial working memory in HS and verbal fluency performance of the AS group or did not otherwise benefit the performance. These findings are consistent with reports that administration of acute high potency D2 antagonists to healthy volunteers induces cognitive impairment (Luciana et al. 1998; Honey et al. 1999; Mehta et al. 1999). The observed effect of risperidone in our study could have also at least partly been due to its sedative effects (Miller 2004). In support of this interpretation, the latency of N-back responses was increased in the risperidone treatment arm. These sedative effects have been attributed to risperidone's H1-receptor affinity (Richelson et al. 2000).

Nicotine had mixed effects on cognition. However, it showed an overall tendency to improve the HS group but impair the AS one. In N-back it reduced the number of errors of commission in the HS group but had no effect on AS performance. In VF however, nicotine did not improve performance in the HS group but impaired the AS control group. This suggests that the two tasks engage different cognitive mechanisms. The beneficial effect of nicotine on N-back could reflect its well-known ability to improve attention (Newhouse et al. 2004). This may have interfered with the requirement for inhibition in the category swap condition of VF.

4.4.3. Criterion 3: Site-independence of criteria 1 and 2

There were no differences between the sites in respect to the main effect of schizotypy, drug or their interaction. The only interaction between schizotypy group and site that approached significance was found in between search errors model of the SWM. As this effect was not sustained in other measures of the SWM test or indeed one of the other two tasks, we consider this to be a random finding.

4.4.4. Limitations

Several limitations of this study exist. First and foremost, an inherent problem with validating biomarkers is the lack of drugs known to reliably improve cognition in schizophrenia. Consequently there is currently no criterion treatment against which biomarkers, surrogate populations and novel treatments can be validated.

Another consideration is that our choice of schizotypy groups could have lessened the main effect of schizotypy. Firstly, we used a self-reported schizotypy measure (Raine 1991; Raine et al. 1994) which may have missed certain domains of schizotypal psychopathology (such as circumstantial thinking and speech, constricted affect, odd behaviour and appearance). These may be evident in a clinical interview but often remain unrecognized by the schizotypal individuals (Compton et al. 2008). As a result, it may be that the HS group did not fully capture the extreme of the schizotypy spectrum. Another observation that supports this conclusion is that a large part of the total psychopathology score in the HS group (50.0 ± 5.8) was accounted for by the cognitive-perceptual subscale (20.4 ± 4.7). This may be significant in the light of theories that distinguish between neuro- and pseudo-schizotypy (Raine 2006). The former is argued to be genetically akin to schizophrenia and is characterized by interpersonal, disorganized and cognitive symptoms while the latter is related to psychosocial factors and features cognitive-perceptual psychopathology and intact cognition. It is therefore possible that a significant proportion of the HS sample was made up of pseudo-schizotypy individuals which lessened the overall degree of cognitive impairment in the group. Secondly, the HS group included only individuals who were non- or light-smokers (less than 5 cigarettes per day) and had no history or

presence of substance abuse. Given the link between schizotypy and increased incidence of substance abuse and smoking (Esterberg et al. 2007; Barkus et al. 2010) it could be argued that our high schizotypy sample may be particularly high functioning. On a similar note, the HS group had more years of education relative to the AS control group. Thirdly, we also excluded people with concurrent past or present Axis I disorders, including depression. Since depression is common in schizotypal personality the high schizotypy sample may not have been representative. However, we wished to avoid the effects of current or past symptoms of depression on performance. Finally, the use of an average scoring schizotypy control group rather than low scoring one could also have led to lessening of the effect of schizotypy. Despite these considerations regarding our choice of schizotypy groups, two of the tasks demonstrated the anticipated effect of schizotypy. We interpret this as further evidence for the validity of these cognitive biomarkers.

Since the statistically significant effects were not corrected for multiple comparisons and the control group was average rather than low scorers, further studies are required to validate these biomarkers in high schizotypy against a low scoring control sample.

4.4.5. Conclusion

In summary this double-blind three-centre study showed that biomarker measures of WM can reliably detect the schizotypy phenotype and are also sensitive to the action of psychopharmacological agents, such as amisulpride, risperidone and nicotine. The experiment's large sample size and the consistency of effects across sites strengthen the validity and reliability of these conclusions. The reversal of the schizotypy effect by amisulpride adds further weight to claims that suboptimal prefrontal cortex dopamine neurotransmission is at the core of the schizophrenia spectrum disorders. These results support the use of cognitive biomarkers and surrogate populations such as schizotypy in translational studies aimed at early assessment of efficacy of cognition enhancing agents in schizophrenia.

CHAPTER 5

Preparing for proof of concept studies of novel cognitive enhancing agents in schizotypy: Who is a control?

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Contribution of the thesis author: The study was designed by the author with the aim of clarifying the results from consortium-sponsored study reported in Chapter 4. Ivan Koychev recruited the low schizotypy sample and collected the study data from this sample of volunteers; he participated in the recruitment and data collection of the average and high schizotypy samples of the Manchester site of the Schiz01 study; he analyzed the presented study data, wrote the first draft of the article that is featured in this thesis and is currently coordinating the input from the co-authors.

Abstract

Increasing number of compounds aimed at improving cognition in schizophrenia fail to demonstrate efficacy at clinical stages of drug development. Translational studies using cognitive biomarkers in surrogate populations of schizophrenia could help identify the compounds destined to fail early in their development. Using measures to define high schizotypy psychometrically may be a particularly useful approach to identify populations featuring moderate schizophrenia spectrum-related cognitive impairment. However there is still no agreement regarding the optimal control group for cognitive studies in schizotypy, as both average and low scoring individuals have been used. In addition, more work is needed to define the boundaries of cognitive impairment in schizotypy. In this study we aimed to investigate these two questions by comparing the cognitive performance of low, average and high scoring schizotypes on a range of cognitive biomarker and eye-tracking tasks. We found a linear relationship between schizotypy and performance on two working memory tasks and the error rate on the antisaccade eye-tracking task. In contrast, average schizotypy was marginally superior to low schizotypy in respect to only one task that detected the schizotypy effect (verbal fluency). In addition, two other tasks (salience attribution and smooth pursuit eye movement tasks) did not distinguish between the three groups. These results suggest that maximum schizotypy effect in regards to working memory and inhibition-related cognitive performance can be obtained in low vs. high schizotypy design. This conclusion fits with the full dimensional model of schizotypy, which sees liability to schizophrenia and its associated cognitive impairment as a continuously distributed trait in the population. In addition, we demonstrated that some areas of cognitive impairment in schizophrenia (such as salience attribution) are probably related to state-specific processes (such as psychotic symptoms) and may not yield meaningful results in proof of concept studies in schizotypy.

5.1. Introduction

Cognition is a core symptom domain in schizophrenia that predicts functional outcome (Green et al. 2000; Hofer et al. 2005; Milev et al. 2005) and treatment adherence (Burton 2005). However, it is left largely unaffected by currently available medication (Heinrichs 2005) and the development of agents to affect the cognitive deficits in schizophrenia is a recognized unmet need (Nuechterlein et al. 2008).

A key reason for the lack of effective cognitive enhancing therapy in schizophrenia is the high attrition rate of novel agents, especially in phase 2 and 3 clinical trials (Hurko 2010). Compounds fail mostly because of lack of clinical efficacy, a trend that reveals critical missing links between the animal and clinical stages of drug development. One way of addressing this issue is to single out agents that are likely to fail in small Phase 1 clinical studies (Hurko 2009). The aim is to give a compound every chance to succeed, for example by selecting only a subgroup of patients that is more likely to respond or by recruiting groups of individuals that have only limited symptom profile but lack the confounds associated with patient research (surrogate populations). Such proof of concept studies precede the costly Phase 2 clinical trials and use biomarkers to assess efficacy instead of the traditional clinical end-points.

In the case of schizophrenia, such early assessment of cognitive enhancers could be accomplished using cognitive biomarkers in surrogate populations such as high schizotypes. These individuals have personality traits corresponding to the schizophrenia psychopathology and also exhibit a profile of attenuated cognitive deficits (Raine 2006). This overlapping symptom profile, as well as evidence highlighting the common genetic and neurobiological basis of schizophrenia and schizotypy (Siever et al. 2002) support theories that see the two conditions as the two extreme ends of a spectrum of disorders (Meehl 1989; Tsuang et al. 2002; Lenzenweger 2006). Despite these similarities, schizotypal individuals are most commonly spared psychotic episodes, repeated hospitalizations and chronic antipsychotic treatment (Raine et al. 1995). Importantly for cognition research, IQ levels and education levels are largely normal (Raine 2006) and their cooperation with study procedures is not hampered by psychotic and negative symptoms.

Defining schizotypy psychometrically is an effective way of identifying populations with schizophrenia-like cognitive impairment (Smyrnis et al. 2003; Smyrnis et al. 2007) and may be a useful approach in proof of concept studies. However it is still unclear whether individuals scoring in the average or low ranges on questionnaires measuring schizotypal personality traits (such as the Schizotypal Personality Questionnaire, SPQ (Raine 1991)) should form the comparator group used against high scorers. This controversy reflects the existence of two theoretical frameworks to describe the relationship between schizotypy and schizophrenia. The first framework proposes that only a small percentage of people have a key disturbance, the results of a dominant combination of schizophrenia risk genes, that is manifested by the development of schizophrenia or extreme schizotypal symptoms and neurocognitive deficits (Matthysse et al. 1986; Meehl 1989). According to this threshold model, there should not be any difference in the neurocognitive performance of healthy volunteers with anything but the most extreme schizotypal symptoms (i.e. average and low scoring schizotypes should have the same cognitive performance). The second theoretical framework postulates that the schizotypal personality traits are a continuum from health to schizophrenia ('full dimensional model'). These authors argue that there is no need to introduce arbitrary cut-off points above which schizotypy lies (Eyseneck et al. 1976; Claridge 1994). Instead, the vulnerability to schizophrenia is represented by correlated schizotypal and neurocognitive symptoms that have a continuous distribution in the population. According to this model, the most appropriate control group would be low scoring schizotypes, as they should have the most intact cognitive performance.

In addition to defining the optimum control group, more work is needed to identify the boundaries of cognitive impairment in schizotypy. It is probable that while some cognitive deficits are associated with the core schizophrenia spectrum deficit, other cognitive domain abnormalities are driven primarily by the psychotic process and are therefore not reliable measures of the schizotypy phenotype. For example, we found recently that high schizotypy scorers have impaired working memory performance relative to low schizotypy scorers in tasks that require swift information processing but have normal executive function in paradigms with longer encoding periods

(Chapter 6). This suggests that speed of information processing is a more reliable biomarker of the schizophrenia spectrum phenotype than executive function.

In this study we aimed to investigate these two questions by comparing the cognitive performance of low, average and high scoring schizotypes on a range of cognitive biomarker tasks. We included general cognitive tasks (tests of working memory and verbal fluency), as well as measures probing salience attribution and eye-tracking abilities. Our first hypothesis was that some but not all tasks will detect the schizotypy phenotype. Our second hypothesis was that the pattern of cognitive performance in the two control groups will favour the full dimensional model e.g. average schizotypes will have an intermediate performance between that of the low and high schizotypes.

5.2. Methods

5.2.1. Subjects, study criteria and design

Average and high scoring schizotypes were recruited from three sites in the United Kingdom (Manchester, London and Cardiff) via an online version of the Schizotypal Personality Questionnaire in its short (Raine et al. 1995) and full version (Raine 1991). Participants were screened using telephone interview to exclude mental health and medical history. The included participants were invited to a screening appointment at which consent was obtained and the full SPQ was completed again. Volunteers that had a score in the 21-36 range were assigned to the average schizotypy (AS) group and those scoring 41 or above formed the high schizotypy (HS) group. Other inclusion criteria at the screening visit were age between 18 and 45 years, fluency in the English language, no medical history and body mass index in the range of 18-30. Exclusion criteria were history or presence of mental health disorders (screened for using the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998)), daily consumption of more than 5 cigarettes or more than 8 standard caffeinated drinks, history of migraines, significant visual or hearing impairment,

The included participants were invited a day of testing. On the day participants were allowed to take part if the criteria for the study had not been violated and if there had been no prescribed medication in the 14 days prior before or over-the-counter medicine in the 2 days before. At the onset of the experiment, a nicotine (7 mg) or placebo patch was applied. Three hours later a capsule of either amisulpride (400 mg), risperidone (2 mg) or placebo was administered. Various neuropsychological tests were completed 1.5 hours after the capsule administration. In the current analysis, only participants that had received placebo patch and placebo capsule were included in the analysis (27 HS and 31 AS).

A group of low scoring schizotypes (LS) was recruited in Manchester only. The participants attended a single appointment where the schizotypy status was confirmed (SPQ score of 9 or less) and the same inclusion and exclusion criteria as the ones

described earlier were applied. The included LS participants completed the same battery of neuropsychological tests as the AS and HS but received no treatment. 35 participants were recruited of which 4 were excluded due to SPQ scores out of range and 1 due to medical history.

The demographics of the participants included in the study are presented in table 5.1.

Table 5.1. Demographics of the three study groups

Demographics	High schizotypy group: mean ±SD	Average schizotypy group: mean ±SD	Low schizotypy group: mean ±SD	Significance values
SPQ	50.1 ± 6.1	27.8 ± 4	3.8 ± 3.1	$p < .001$
Age	25.3 ± 5.0	23.8 ± 4.6	25.4 ± 5.8	$p = .239$
IQ	114.2 ± 6.2	114.2 ± 4.9	113.8 ± 6.0	$p = .958$
Years of education	16.3 ± 2.2	15.5 ± 1.7	17.4 ± 2.6	$p = .004$
Sex	13 f 14 m	16 f 15 m	15 f 15 m	$\chi^2 = .125$

5.2.2. Task description

Working memory (N-back) task

A series of alphabet letters were presented one at a time on a color monitor. Participants were instructed not to respond until they saw the same letter twice following one another. The task had three levels of difficulty according to the number of letters in between the two matching letters. In the 1-back condition the two letters followed each other immediately. In the 2-back condition the target letters were separated by one letter and in the three back two letters separated the target letters. Thus participants had to hold in mind one, two or three letters. Consequently, the 1-back condition exerted the lowest load on working memory and the 3-back condition the highest. There was also a baseline condition to control for attending to the task where participants simply needed to respond when they saw the letter ‘X’. The participants completed 3 blocks of each condition presented in a pseudorandom order.

Spatial working memory (SWM) task

Treasure chests were presented on a computer screen. The participants were instructed to search for coins in the treasure chests. Only one of the chests contained a coin at any one time and once it had been found it moved to a treasure chest that it had not been present in during the trial. The participants completed trials with 4, 6 and 8 chests and 4 repetitions of each level of the task. A practice trial with only 3 treasure chests was completed to ensure the understanding of the task.

Verbal fluency (VF) task

Letter and category VF and word production were assessed during a succession of one minute periods. For the letter VF test participants were asked to verbally report as many words as they could beginning with the letters F, A and S (FAS condition). The experimenter wrote down the words produced. In the category VF test the categories used were vegetables and animals (category naming condition). Participants were then asked to switch between two categories (fruit and furniture) during the same one minute period (category swap condition).

Salience Attribution Test (SAT)

On this task participants responded quickly to a probe (a black square) in order to win money (possible earnings for the whole task ranging between £5-20). Coloured images of household objects or animals were presented immediately before the probe. One stimulus dimension (e.g. red vs. blue – relevant dimension) very reliably predicted the availability or non-availability of money while the other (e.g. animals vs. household objects – irrelevant dimension) was not a reliable predictor. The rewarded stimulus feature (e.g. blue) generally comes to speed responding for reward relative to the unrewarded one (e.g. red), providing a measure of implicit adaptive (i.e. appropriate) salience; participants are usually also able to report this association overtly using visual analogue scales (explicit adaptive salience). If faster responding/greater reward rating occurs to one of the irrelevant features over the other (e.g. animals faster over household objects), this indicates aberrant salience.

Eye-tracking (ET) task

Eye-tracking is a technique that allows the recording of the pattern of eye movements in response to task conditions. In the prosaccade task a novel visual target appeared in the periphery and participants had to direct their gaze at it. In the antisaccade task participants had to inhibit the prosaccadic response to a new stimulus and instead look at its mirror image location on the opposite side of the screen. In the Smooth Pursuit Eye Movement (SPEM) paradigm, participants were required to follow a small visual target moving at a constant velocity without moving their head. The participants completed the SPEM task at three target speeds.

Intelligence quotient (IQ)

IQ was determined using the National Adult Reading Test (Nelson et al. 1991), a reading-based estimate of premorbid intelligence. We collected this data to check that the groups have comparable IQ and as a potential covariate of performance. The participant was asked to pronounce irregularly spelt words from a standardized written list. The scores were determined on the basis of the number of correctly pronounced words.

5.2.3. Statistical analysis

Outcome variables

The dependent variables in the N-back task were percentage correct, errors of commission and the reaction times of correct and incorrect responses for each of the four conditions of the task (attention, 1-back, 2-back, 3-back). In the SWM task, 4 outcome measures were extracted for each of the three task levels: time to complete, mean number of choices, mean number of within and between search errors. For all conditions of the VF task the following measures were calculated: mean number of correct words, set and repetition errors, mean number of correct transitions on the category swap condition. The dependent variables in the SAT were reaction time, adaptive and aberrant salience based on reaction time, omission errors and premature responses. In the prosaccade and antisaccade conditions of the ET task, the following variables were calculated: frequency of saccade errors, percentage of corrections after

error, as well as latency, gain and peak velocity of the correct saccades. For SPEM, the saccadic frequency during pursuit was calculated for each target speed.

General description of pre-planned statistical analysis

Before analysis, the data was checked for outliers. For N-back, the criterion for outlier was performance at both the attention and 3-back condition outside the 95% confidence interval. Participants that had below 20% accuracy on the 3-back condition were also excluded from the analysis. For the VF task, participants were classed as outliers if their number of either set or repetition errors on the FAS condition were outside the 95% confidence interval. For the SWM task, outliers were identified by visual inspection of boxplots and the extreme values tables produced from SPSS. The dependent variables were entered into a repeated-measures ANOVA (with the exception three VF variables (set errors, repetition errors and mean number of correct transitions) which were entered into univariate ANOVAs) with between-subject factors of group, sex and site. The within-subjects factor was level of difficulty or condition of the task. IQ, age and years of education were added as covariates to the model and were retained if statistically significant. In case of a main effect of level of difficulty, polynomial contrasts were run to determine the character of the relationship. In the case of a main effect of group of schizotypy, polynomial and LSD comparisons were performed to compare the three groups). In case of a group and level interaction, simple contrasts between the different task levels were performed to determine the level of the interaction.

For the SAT only, we performed correlations between the variables and the four subscales of the OLIFE questionnaire. This was based on a previously published data showing a correlation between aberrant salience and the Introvertive Anhedonia subscale.

5.2.4. Ethical Approval

The study has been approved by The University of Manchester Ethics committee (reference number 08176) and has been carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

5.3. Results

5.3.1. N-back task

Task difficulty

On the measure of percentage correct the main effect of level of difficulty was highly significant ($F(3, 222) = 55.058$, $p < .001$) due to worsening of performance with increasing task difficulty ($F(1, 74) = 119.789$, $p < .001$). The main effects of task difficult in the latency of correct responses and error of commission models were significant ($F(3, 222) = 101.507$, $p < .001$ and $F(3, 222) = 30.322$, $p < .001$ respectively), due to a linear increase in reaction times with higher task difficulty ($F(1, 74) = 224.494$, $p < .001$ and $F(1, 74) = 41.590$, $p < .001$).

Main effect of schizotypy

The main effect of schizotypy group was not significant in the percentage correct model, but its interaction with task difficulty approached significance ($F(6,222) = 1.936$, $p = .076$). The most difficult condition, 3-back, was identified as the level of the interaction through contrasting the different task conditions. The univariate ANOVA with a dependent variable of percentage correct at 3-back revealed a significant main effect of schizotypy ($F(2,74), = 3.165$, $p = .048$). The polynomial contrast confirmed that a linear relationship exists between this variable and the extent of schizotypy ($T = 2.41$, $p = .024$, Figure 5.1). In the contrasts between the groups, LS but not AS was significantly different from the HS ($T = 2.51$, $p = .014$ and $T = 1.034$, $p = .304$ respectively).

In the errors of commission model the main effect of schizotypy group was significant ($F(2,84) = 3.908$, $p = .001$). This was due to HS making more errors of commission than AS and LS ($T = 2.770$, $p = .007$ and $T = 2.387$, $p = .020$ respectively). Schizotypy group also interacted with level of difficulty ($F(6, 219) = 6.095$, $p < .001$). 3-back was indentified as the level of the interaction by contrasting the different conditions and we performed am univariate ANOVA with errors of commission at 3-back as a dependent variable. The polynomial contrast revealed that the relationship between

the number of errors of commission and schizotypy was linear (T = 3.720, p < .001, Figure 5.1). The main effect of schizotypy group was highly significant (F(2,88), = 3.628, p < .001), due to worse performance in HS relative to AS (T = 2.642, p =.010) and LS (T = 2.862, p =.005).

The factor of schizotypy group had no main effect on the latencies of correct responses and errors of commission. It also did not interact with task difficulty in these two models.

Covariates

The covariate of IQ approached significance in the errors of commission model (F(1, 73) = 3.040, p = .085).

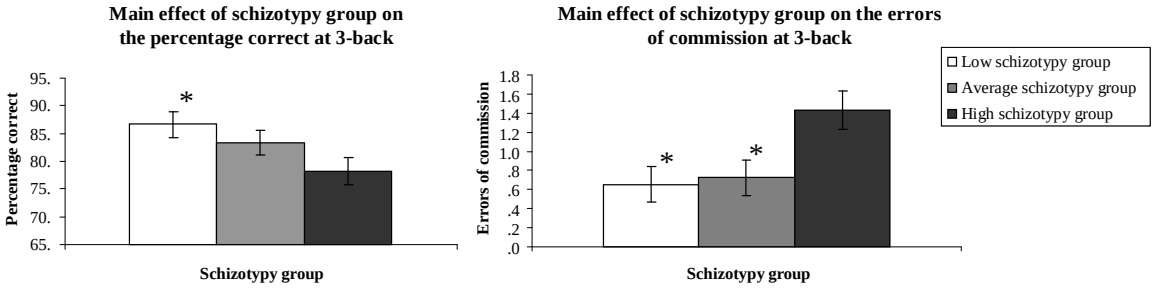

*Figure 5.1. Main effect of schizotypy group on the N-back task measures. Symbols: * = p ≤ .05 for comparison versus the high schizotypy group.*

5.3.2. Spatial working memory

Task difficulty

The main effect of task difficulty was significant in all four SWM models: $F(2, 140) = 446.625$, $p < .001$ for number of choices; $F(2, 140) = 10.804$, $p < .001$ for within search errors; $F(2, 140) = 41.592$, $p < .001$ for between search errors; $F(2, 140) = 753{,}563$, $p < .001$ for time needed for completion of each level. The polynomial contrasts revealed that the effect was due to linearly decreasing performance and increasing time needed to complete with increasing task difficulty.

Schizotypy effect

The main effect of schizotypy approached significance in the between search error model ($F2, 71) = 2.649$, $p = 0.78$). This effect was due to LS making lower number of between search errors at trend for significance relative to HS ($T = 1.847$, $p = .069$) and AS ($T = 1.925$, $p = .058$). Schizotypy group also interacted with task difficulty in respect to the total number of choices ($F(4, 140) = 2.933$, $p = .023$), and between search errors ($F(4, 142) = 4.068$, $p = .004$). Contrasting the different task indicated that the interaction occurred at level 3 (8 chests). A univariate ANOVA at level 3 with a within-subject factor of total number of choices revealed a significant main effect of schizotypy group ($F(2, 70) = 3.267$, $p = .044$, Figure 5.2). The relationship between schizotypy and total number of choices was linear ($T = 2.413$, $p = .018$) even though the there was no statistically significant difference between LS and the other two groups in LSD comparisons ($T = 1.063$, $p = .292$ and $T = 1.310$, $p = .195$ for comparisons vs. AS and HS respectively). The factor of schizotypy group also had a significant main effect on the univariate ANOVA at level 3 using a within-subject factor of between search errors ($F(2, 71) = 4.204$, $p = .019$, Figure 5.2). The relationship between schizotypy group and between search errors was linear ($T = 3.701$, $p<.001$) and this was reflected in better performance in LS relative to AS ($T = 2.400$, $p =.019$) and HS ($T = 2.458$, $p =.016$).

Covariates

There were no significant covariates in the SWM models.

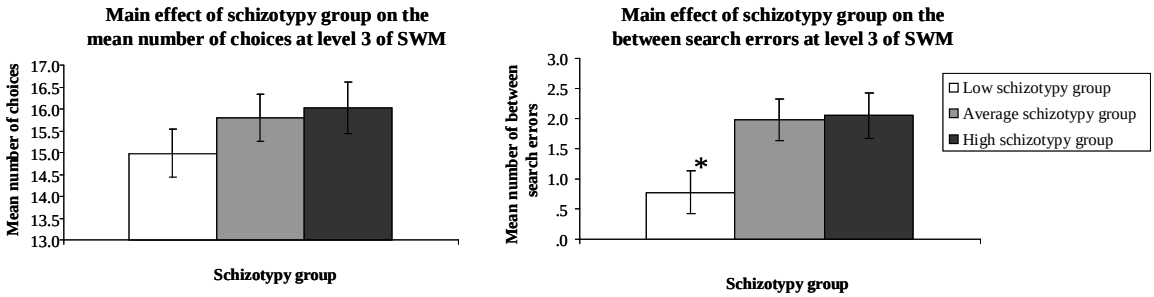

*Figure 5.2. Effect of schizotypy group on the SWM task. Symbol: * = $p \leq .05$ for comparisons versus the high and average schizotypy groups.*

5.3.3. Verbal fluency task

Schizotypy effect

The main effect of schizotypy group reached significance in the correct words model ($F(2, 74) = 3.216$, $p = .046$, Figure 5.3). This was due to HS having producing significantly lower number of correct words relative to both AS ($T = 2.524$, $p = .014$) and LS ($T = 2.055$, $p = .043$). The relationship between schizotypy and performance in this analysis was quadratic at trend for significance ($T = 1.815$, $p = .076$), indicating that AS had marginal superiority over LS. The main effect of schizotypy group was also significant in respect to the number of correct transitions on the category swap VF task ($F(2, 74) = 4.308$, $p = .017$, Figure 5.3). Pairwise comparisons demonstrated that HS had made significantly lower number of correct transitions compared to both AS ($T = 2.572$, $p = .012$) and LS ($T = 2.067$, $p = .042$). The relationship between schizotypy and transitions was confirmed to be quadratic by polynomial contrasts ($T = 2.12$, $p = 0.037$). The factor of schizotypy group had no main effect on the set and repetition error models.

Covariates

IQ was a highly significant covariate in the correct words model ($F(1,74) = 18.723$, $p < .001$) and the number of successful transitions model ($F(1,74) = 10.587$, $p = .002$).

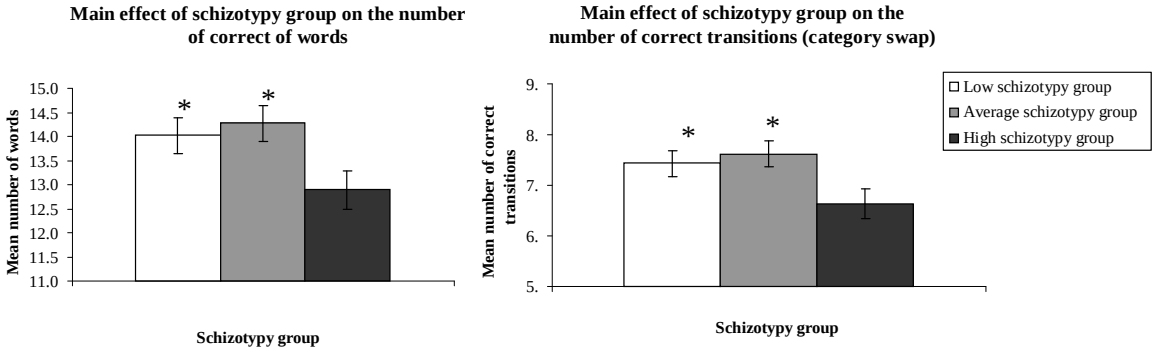

*Figure 5.3. Effect of schizotypy group on the VF task. Symbols: * = $p \leq .05$ for comparisons versus the high schizotypy group.*

5.3.4. Salience Attribution Test

Schizotypy effect

Schizotypy was not a significant factor in any of the seven SAT models (reaction time, implicit and explicit adaptive salience, implicit and explicit aberrant salience, number of omissions and premature responses).

Covariates

IQ was a significant factor in the reaction time ($F(1,82) = 4.291$, $p = .041$), adaptive explicit salience measure ($F(1,81) = 9.724$, $p = .003$) and number of omissions ($F(1,83) = 6.263$, $p = .014$) models. Age was a significant covariate in respect to reaction time ($F(1,82) = 7.823$, $p = .006$).

OLIFE questionnaire correlation

The four OLIFE subscales did not correlate significantly with any of the seven SAT variables.

5.3.5. Prosaccade and antisaccade eye-tracking task

Schizotypy effect: prosaccade task

In the prosaccade condition there was no main effect of schizotypy in any of the four prosaccade models (number of errors, latency, gain and velocity of the saccades).

Schizotypy effect: antisaccade task

In the antisaccade condition schizotypy was a significant factor in regards to the number of antisaccade errors model ($F(2, 73) = 8.219$, $p = .001$, Figure 5.4). The polynomial contrast showed that this relationship between schizotypy and antisaccade errors is linear ($p < .001$). The pairwise comparisons revealed that HS made significantly higher number of antisaccade errors compared to both AS ($T = 2.871$, $p = .005$) and LS ($T = 4.109$, $p < .001$). There was no main factor of schizotypy in the analysis of the percentage of corrective saccades after an error as well as in the latency, gain or velocity of the saccades models.

Covariates

The only significant covariate in these models was age in respect to the percentage of corrective saccades model in the antisaccade task ($F(1,84) = 5.291$, $p = .025$).

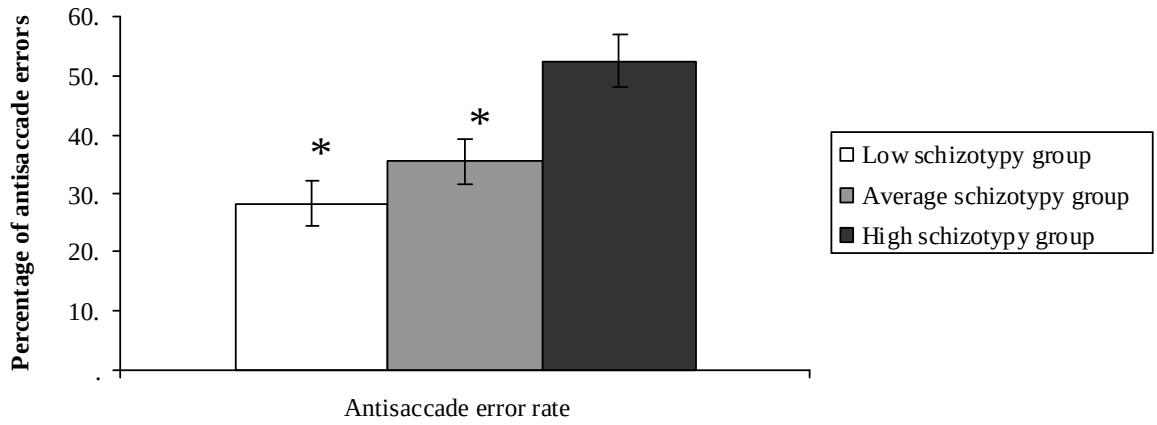

*Figure 5.4. Effect of schizotypy group on the antisaccade error rate. * = $p \leq .05$ for comparisons versus the high schizotypy group.*

5.3.6. Smooth pursuit eye movement task

Schizotypy effect

Schizotypy was not a significant factor, nor did it interact with the factor of task speed in respect to the saccadic frequency during smooth pursuit.

Covariates

There were no significant confounds in the saccadic frequency model.

5.4. Discussion

In this report we aimed to clarify the relationship between schizotypy and neurocognition by comparing the performance in three healthy volunteers groups defined by their scores on the Schizotypal Personality Questionnaire (low, average and high schizotypy scorers). We tested whether all the tasks from our battery detect the schizotypy effect and whether low or average scorers are the optimal controls for cognitive comparison versus high schizotypy scorers.

5.4.1 Tasks sensitivity to the schizotypy phenotype: working memory, antisaccade and verbal fluency

Outcome variables of four tasks detected the schizotypy phenotype (N-back, spatial working memory, verbal fluency and antisaccade eye-movement tests) while two other tests did not distinguish between the groups (salience attribution and smooth pursuit eye-movement tasks).

The effect of schizotypy on the two working memory tasks in the battery (N-back and SWM) is in line with previous research. Individuals with high levels of schizotypal personality traits tend to have intermediate working memory performance between (Siever et al. 2002; Raine 2006). It has been hypothesized that working memory impairment might be a critical component that forms several more complex cognitive deficits in the schizophrenia spectrum disorders (Roitman et al. 2000). In demonstration of this, performance on working memory tasks has been shown to be the single most important neurocognitive factor accounting for the differences between schizotypal individuals and controls (Mitropoulou et al. 2005; McClure et al. 2007). The evidence for working memory deficits being core abnormalities in the schizophrenia spectrum has prompted Raine at al. to propose that a dopamine-mediated prefrontal cortex disruption might be part of the schizotypy phenotype (Raine et al. 1992). This is compatible with data showing that worse working memory performance in schizotypal personality is associated with smaller volume of the ventro-lateral prefrontal cortex. The relation of this frontal deficit to dopamine has been demonstrated by studies showing the working memory performance in

schizotypal individuals can be improved by acute (Kirrane et al. 2000) and chronic (McClure et al. 2010) administration of agents enhancing dopamine neurotransmission. Similarly, the analysis of the larger dataset that this study is part of revealed that enhancement of dopamine function (through low-dose amisulpride challenge) improved the working memory performance of high but not average schizotypes (Chapter 4). These data support the notion that dopamine dysfunction is related to working memory impairment in schizotypy. Additionally, this deficit is responsive to drug challenges and is a promising target for proof of concept studies on novel cognition enhancing medication.

The fact that the abnormality was detected reliably only in the most difficult conditions of the task argues that the psychometrically defined schizotypy group is a high functioning population. On a similar note, in a study on a subsample of the same population we found that the working memory deficit in high schizotypy was demonstrable on a challenging working memory task that required quick stimulus encoding but not on a different one where encoding was longer (Chapter 6).Therefore differences in task difficulty may explain why some previous studies did not find executive function deficits in high SPQ scorers (Jahshan et al. 2007). Proof of concept studies featuring high functioning risk groups may thus benefit from employing more difficult cognitive tasks that the ones demonstrating deficit in schizophrenia.

5.4.2. Optimal schizotypy control group: Working memory tasks

The finding that working memory performance of the average schizotypy group is intermediate between that of low and high schizotypy group suggests are in line with the predictions derived from the Eysenck theoretical framework of schizotypy (Eyseneck et al. 1976). According to this ‘full dimensional’ model, as Claridge coins it, ‘traits that describe deviance – in this case schizophrenia – are represented in personality as healthy diversity’ (Claridge 1994). In contrast, the threshold model, predicted from the theory of Meehl sees deviant traits as confined to the disease domain (Claridge 1994). The latter model would expect all non-high scorers (low and average schizotypes) to have the same, superior to high schizotypy, working memory performance. Our results thus favour the full-dimensional over the threshold model

and indicate that working memory comparisons in schizotypy populations would benefit by selecting a low vs. high schizotypy design. This has been the preferred approach in some (Gooding et al. 1999) but not all (Tallent et al. 1999) studies in schizotypy.

A few studies have investigated the correlation between schizotypy scores and executive function in a healthy population. Some (Park et al. 1997; Gooding et al. 2006; Matheson et al. 2008) but not all (Jahshan et al. 2007; Noguchi et al. 2008) have found an inverse relationship between schizotypy scores and neurocognitive performance. One of the studies that did not find such a correlation also failed to detect impairment of executive function in the high scorers (Jahshan et al. 2007). It could be hypothesized therefore that the tasks in the negative studies were not sufficiently difficult to demonstrate the subtle schizotypy deficit.

5.4.3. Optimal schizotypy control group: Antisaccade task

The finding of increased antisaccade error rate but normal spatial accuracy and latency of pro- and antisaccades in the high schizotypy group also replicates previous findings (Siever et al. 1990; Siever et al. 1994; Clementz et al. 1995; Thaker et al. 1996; O'Driscoll et al. 1998). This shared abnormality between schizotypy individuals and schizophrenia patients has been shown to be due to underlying abnormality in the frontal cortex (Ettinger et al. 2004) and the striatum (Raemaekers et al. 2002). The antisaccade error rate also correlates with measures of executive function in schizophrenia patients (Hutton et al. 2004) while acute enhancement of dopamine neurotransmission has been reported to improve antisaccade performance (Klein et al. 2002; O'Driscoll et al. 2005; Wonodi et al. 2006). This indicates that antisaccade error performance may share some of the neural mechanisms that underpin working memory.

The relationship between schizotypy and antisaccade performance was linear, similar to the pattern obtained for the working memory tasks. This result also favours the full-dimensional model of schizotypy and the use of low schizotypes as controls in comparisons with high schizotypes. One study has so far investigated the relationship

between antisaccade error rate and SPQ scores (Smyrnis et al. 2003). Although the authors found that the error rate in the population had a similar distribution to the SPQ scores (skewed normal distribution), there was no correlation between the two variables. Instead, the authors found that only the extremely high scorers had increased antisaccade error rates, favouring the threshold approach to schizotypy. The discrepancy between these two sets of results could be due to problems with the validity of the SPQ scores in the Smyrnis et al. (2003) study given their translation in Greek for the first time, as acknowledged by the authors. Differences in the phrasing of the questions could have led to mixing of the low and average scoring groups, masking the linear relationship between schizotypy and antisaccade error rate. In addition, the authors reported that anxiety and depression scores were correlated with both the antisaccade error rate and schizotypy. It is therefore possible that the lack of correlation between SPQ scores and antisaccade error rate was due to the inclusion of anxiety and depressive disorders in the group. In our study, we excluded participants with such disorders which might have led to a more confound-free comparison of schizotypy and SPQ interaction.

5.4.4. Optimal schizotypy control group: Verbal fluency task

The findings from the verbal fluency task appear to favour the threshold approach: the average schizotypy comparison yielded higher effect size than the low schizotypy one. This could however also be due to the specific profile of verbal fluency in schizotypy: one study reported that positive schizotypy is associated with normal verbal fluency performance but increased usage of rare words (Duchene et al. 1998). The authors interpreted this as an indication that magical ideation is linked to the ability to form broad associative connections which foster or mask deficits in verbal fluency (Raine 2006). It is thus possible that the small advantage of the average schizotypy over the low schizotypy group could have been due to their high positive schizotypy scores. In comparison, our high schizotypy group however had high scores on the negative and disorganized scores which could explain their inferior verbal fluency performance.

5.4.5. No effect of schizotypy: Smooth pursuit eye movement task

We also found that the saccade rate and gain during smooth pursuit eye-movements failed to distinguish between the schizotypy groups. So far the reports using these SPEM measures in schizotypy have been mixed. One study reported no difference in pursuit gain and saccade rate (Siever et al. 1994), while another found reduced gain but normal saccade rate (Gooding et al. 2000). In addition, Smyrnis et al. found no relation of these variables with SPQ scores, but reported disrupted performance in the high scorers on the SPQ disorganization factor. These mixed results could be interpreted in the light of Thaker et al.'s studies on schizotypy individuals with and without family risk of schizophrenia (Thaker et al. 1996). They showed that the SPEM abnormality is found only in schizotypal individuals who have family history of schizophrenia and argued that the SPEM deficit is specifically associated with the familial risk for schizophrenia. Smyrnis et al. (2007) did not report the rate of schizophrenia family history in their sample but it is possible that the SPEM abnormality in the high disorganization scorers was due to higher genetic loading (Smyrnis et al. 2007). In our sample, only a small proportion reported being first-degree relatives of schizophrenia patients. We therefore consider our negative SPEM finding to support the view proposed by Thaker et al. that SPEM abnormality is primarily linked to the genetic risk of schizophrenia (Thaker et al. 1996).

5.4.6. No effect of schizotypy: Salience Attribution Test

The negative findings regarding the SAT indicate that psychometrically defined schizotypy is probably not associated with deficits in salience attribution. We also failed to replicate an earlier report linking the negative schizotypy symptom of introvertive anhedonia to aberrant salience (Roiser et al. 2009). This suggests that salience attribution measures might be more relevant as state-dependent biomarkers. In support of this, several studies have shown that the salience attribution abnormalities in schizophrenia patients are correlated with psychotic symptoms and the negative symptoms secondary to the psychotic state (Roiser et al. 2009; Ziauddeen et al. 2010). Additionally, treatment with atypical antipsychotics has been demonstrated to normalise salience attribution in patients (Juckel et al. 2006).

5.4.7. Limitations

The results of this explorative analysis should be treated with caution as several important limitations exist. First and foremost the average and high schizotypy groups were recruited as part of a larger placebo-controlled study which investigated the effects of acute administration of risperidone, amisulpride, nicotine on cognition. The two samples were required to attend two appointments (data recruited on the second, full-day appointment), were placebo-treated and were recruited from three sites in the UK. In contrast, the low schizotypy group attended a single 3 hour appointment in which the data was recorded, did not receive placebo medication and was recruited in Manchester only. We therefore cannot rule out the possibility that the superior performance in the low schizotypy group was due to these protocol differences. It is feasible that fatigue or placebo effects could have led to the reduced performance in AS relative to LS, a scenario that favours the threshold model of schizotypy.

Two lines of evidence suggest that fatigue or placebo effects might not have fully accounted for the superior low schizotypy effect. Firstly, there was no group difference in respect to the reaction times and latencies on the SWM, N-back and antisaccade tasks, measures that one would expect to be affected by placebo or fatigue effects. Secondly, the superior performance of the low schizotypy group was confined solely to measures where a difference between the placebo-treated average and high schizotypy was already evident. The lack of schizotypy effect on the other tasks argues against a generalized placebo or fatigue effects-driven cognitive superiority in the low schizotypy group.

The finding of higher years of full-time education in the low schizotypy group also seems unlikely to have influenced the results significantly due to the same arguments as the ones that concern the placebo-effect. In addition, this variable was an insignificant confound in all models. This echoes previous findings of lack of correlation between years of education and neurocognitive performance, such as in the large sample eye-tracking studies by Smyrnis et al. (Smyrnis et al. 2003; Smyrnis et al. 2007).

5.4.7. Conclusion

In summary, this study explored the neurocognitive correlates of low, average and high psychophysically defined schizotypy. The results on the working memory and antisaccade tasks showed the performance of average schizotypes was intermediate between that of low and high schizotypes. These results argue in favour of the full dimensional view of schizotypy and suggest that low schizotypy might be the most appropriate control group in proof of concept studies of cognitive enhancing agents in high schizotypy.

CHAPTER 6

Visual information processing deficits as biomarkers of vulnerability to schizophrenia: An event-related potential study in schizotypy*

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Abstract

We aimed to clarify the importance of early visual processing deficits for the formation of cognitive deficits in the schizophrenia spectrum. We carried out an event-related potential (ERP) study using a computerised delayed matching to sample working memory (WM) task on a sample of volunteers with high and low scores on the Schizotypal Personality Questionnaire (SPQ). The amplitudes of the visual ERPs to the encoding and retrieval stimuli in the task were measured using the BESA software. The hypothesis was that high schizotypes would have deficits in early visual processing (reduced P1 amplitude) and working memory similar to those observed in schizophrenia. The high schizotypy group identified fewer previously encoded target cues than the low schizotypy group in the WM task and their mean cue-evoked P1 amplitudes were significantly reduced, both in the encoding and the retrieval phases of the task. Accuracy on the WM task correlated with the P1 amplitude. None of the later components (N1, P2) were significantly different between the groups, nor were there differences in performance on the CANTAB tests. The results are compatible with the hypothesis that trait vulnerability to schizophrenia is associated with impaired early visual processing which may contribute to impaired cognitive memory performance. However, the high schizotypes are apparently able to compensate for the visual processing deficits and perform normally when stimuli are presented for longer as in the CANTAB tasks. This study adds to growing evidence that the schizophrenia spectrum is characterized by early sensory abnormalities.

6.1. Introduction

Visual processing abnormalities have been consistently reported in schizophrenia. Studies using psychophysical methods have found deficits in motion (Stuve et al. 1997; Chen et al. 1999; Brenner et al. 2003; Chen et al. 2003) and contrast sensitivity (Slaghuis 1998; Keri et al. 2002; Butler et al. 2005), perceptual organization (Silverstein et al. 1996; Silverstein et al. 2005), spatial discrimination (O'Donnell et al. 1996; Tek et al. 2002; Keri et al. 2004) and the ability to detect targets masked after short intervals (Butler et al. 1996; Cadenhead et al. 1998; Green et al. 1999; Schechter et al. 2003).

The perceptual findings are supported by the available neurophysiological evidence. Studies in patients using event-related potential (ERP) electroencephalographic (EEG) techniques have found a reduction in the amplitude of P1 (Foxe et al. 2001; Doniger et al. 2002; Schechter et al. 2005; Yeap et al. 2006; Haenschel et al. 2007; Yeap et al. 2008), a positive ERP component peaking at 100 ms post-stimulus. This component has a characteristic distribution over the lateral occipital scalp regions and reflects early activation of the visual cortex (Ellemberg et al. 2001; Di Russo et al. 2002; Di Russo et al. 2003). The P1 reduction has been linked to impairment in the magnocellular visual pathway (Foxe et al. 2001; Butler et al. 2007) and data from psychophysical studies support this association (Keri et al. 1998; Slaghuis 1998; Schwartz et al. 2001; Keri et al. 2002; Keri et al. 2005). The magnocellular pathway is the part of the visual pathway that rapidly transmits low-resolution information and projects primarily to the dorsal visual stream in the cortex. The function of this pathway has been proposed to be spatial orientation, motion detection and overall stimulus perception (Steinman et al. 1997; Vidyasagar 1999; Norman 2002). In contrast, the slower parvocellular (ventral) visual pathway (transmitting high definition, color information) appears to be functioning normally in schizophrenia, as electrophysiological studies have shown that if parvocellular-biased stimuli are used, no deficits in the early visual processing are evident (Butler et al. 2007; Lalor et al. 2008). Also, the evoked potential N1 that follows P1 is of normal characteristics, which has been attributed to intact early ventral/parvocellular input (Foxe et al. 2005). This pattern of preferential magnocellular abnormalities in schizophrenia might have

functional implications, as early stimulus recognition is dependent on the efficient interplay between the magno- and parvocellular pathways (Kveraga et al. 2007). The existing evidence supports this: an electrophysiological study showed reduced activity from the visual cortex once the information from the two streams is integrated (Doniger et al. 2002).

It has been suggested that these early sensory impairments contribute to higher order cognitive (Bruder et al. 1998; Brenner et al. 2002) and social (Sergi et al. 2003) impairments, which in turn affect outcome (Green et al. 2000). A recent study addressed this issue by testing working memory in adolescent schizophrenics versus control using ERPs. It showed that the P1 amplitude predicted WM performance in controls, but was reduced in patients (Haenschel et al. 2007). Another study in schizophrenia patients found that contrast sensitivity deficits correlated with reduced ability to recognize facial emotions (Butler et al. 2009), the abnormality being most pronounced with magnocellular-biased stimuli.

Despite the growing evidence for early sensory abnormalities driving higher order cognitive deficits, studies on schizophrenia patients suffer from several methodological weaknesses which may be particularly relevant when exploring subtle cognitive processes. Firstly, most of the studies exploring cognition in schizophrenia are conducted in chronically ill patients, where the effects of neuroleptics and continuous hospitalizations introduce significant confounds to the data interpretation (Raine et al. 1995). Negative symptoms, such as lack of motivation and apathy, might also reduce the engagement and compliance with the study procedures (Raine et al. 1995). Studies on first-episode patients provide a good alternative and two such studies have confirmed the presence of P1 visual deficits (Haenschel et al. 2007; Yeap et al. 2008). In this type of studies however, confounds are still possible, as florid psychotic symptoms could blur the subtle cognitive abnormalities. Lastly, schizophrenia is associated with restricted educational opportunity (Gambini et al. 1992) and IQ levels (Reichenberg et al. 2007). This can cause problems in matching a control group and in interpreting group differences.

A different approach to the pathophysiology of schizophrenia is offered by studies in subjects with schizotypal personality traits. This is based on the idea that

schizophrenia lies on the extreme of a spectrum of disorders with a common phenomenological, genetic and neurobiological basis (Kendler et al. 1993; Siever et al. 2002; Siever et al. 2004). In support of this, it has been shown that schizotypal personality individuals experience schizophrenia-like symptoms: cognitive-perceptual, deficit-like and disorganized psychopathology (Kendler et al. 1993; Raine et al. 1994; Raine et al. 1995; Bergman et al. 1996; Bergman et al. 2000). In demonstration of the common genetic basis of the two conditions, family studies have found that relatives of schizophrenia probands have higher incidence of schizotypal personality disorder (Siever et al. 1990; Kendler et al. 1993) and vice versa (Battaglia et al. 1995; Bergman et al. 2000). Lastly, subjects with schizotypal personality traits have been shown to have structural brain abnormalities (Buchsbaum et al. 1997; Silverman et al. 1998; Dickey et al. 1999) and neuropsychological deficits (Siever et al. 2002) similar to schizophrenia, albeit of lesser severity. Despite the similarities that subjects with schizotypal personality traits share with schizophrenia, they are nonetheless spared repeated hospitalizations, chronic antipsychotic therapy, severe neuropsyhological dysfunction and symptoms and most have normal educational and IQ levels. This makes them particularly suited for studies aiming to distinguish neurophysiological abnormalities associated with vulnerability to schizophrenia from those that are the consequence of its overt symptoms, treatment and course. Applying this approach to the P1 visual deficit appears particularly appropriate, as it has been demonstrated both in unaffected relatives (Yeap et al. 2006) and bipolar patients(Yeap et al. 2009), which suggests that it is more likely to reflect general vulnerability to psychosis. In further support of this no correlation has been found between the P1 reduction and disease chronicity or medication dose in patients (Yeap et al. 2008).

In this study we aimed to test whether the findings of early visual processing deficits reported in schizophrenia can be extended to healthy volunteers with elevated schizotypal personality traits (high schizotypy) using event-related potentials. As we also intended to explore the relevance of visual processing for the formation of higher-order cognitive deficits, we employed a delayed matching-to-sample task used in schizophrenia patients (Haenschel et al. 2007). We hypothesized that vulnerability to schizophrenia, as indexed by high scores on schizotypal questionnaires, will be characterized by a reduction of the P1 visual potential, but normal later ERP components (N1, P2). We also predicted that P1 amplitude will correlate with the

performance on the task. In addition we wished to determine whether the effect of impaired early visual processing deficits on WM generalized to effects on two other cognitive functions (central executive and spatial memory), as measured by two tasks from the CANTAB neuropsychological battery.

6.2. Materials and methods

6.2.1 Subjects

45 healthy volunteers were recruited via the University of Manchester research volunteering e-mail list, posters and flyers and selected according to their online responses on the short version of the Schizotypal Personality Questionnaire (SPQ-B, (Raine 1991)). All participants signed a consent form prior to any experiment procedures, completed the full version of the SPQ (74 questions) (Raine 1991) and were screened for current and past mental health disorders (using Mini-International Neuropsychiatric Interview), neurological conditions and significant visual impairment. The inclusion criteria was a score of 43 or more on the SPQ for the high schizotypy group and 9 or below for the control group respectively, as well as no history of psychiatric or neurological conditions, no prescribed medication and no significant visual impairment. The SPQ cut-off scores were based on results from a previous study using SPQ in 760 students from the Manchester University (Barkus et al. 2008) and the SPQ manual (http://www-rcf.usc.edu/~raine/spqrel.html). During the screening stage 5 participants were excluded (3 participants due to SPQ score out of range, 1 - history of depression and 1 - severe astigmatism). Once included, the subjects also underwent a semi-structured personality interview based on the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) instrument. All interviews were carried out by one medically trained researcher, Ivan Koychev, who had been trained in using the instrument.

After processing of the data, 1 participant was excluded due to unidentifiable P1 component (merging of the P1 and P2 components) and 1 due to abnormal distribution of the P1 component (midline instead of bilateral distribution of the P1 peak). The final groups used in the analysis were 18 high schizotypes and 20 controls. The two groups were well-matched for age and IQ. The demographic, SPQ and family mental health history data is presented in table 6.1. The results from the SCID-II interview in the high schizotypy group revealed that 12 participants met the criteria for a personality disorder (5 paranoid, 3 paranoid and schizotypal, 2 schizotypal, 1

schizoid and 1 depressive), 5 were subtreshold (2 paranoid, 2 schizotypal and 1 schizoid) and 1 did not meet any criteria for a personality disorder. No participants from the control group fulfilled the SCID-II criteria for personality disorders.

Table 6.1. Demographic and mental health family history data of schizotypal individuals and controls

	High schizotypes	Controls	P value
Age	23.1 ± 4.1	23.5 ± 3.4	.7
Sex			
Male	12	13	
Female	6	7	
Handedness			
Right	18	17	
Left	0	3	
IQ (NART)	114.3 ± 4.8	114.9 ± 4.8	.7
SPQ score			
SPQ total score	49.4 ± 5.3	3.1 ± 2.3	<.001
Cognitive-perceptual SPQ score	19.5 ± 5	.7 ± .9	
Negative SPQ score	19.5 ± 5	1.6 ± 1.6	
Disorganized SPQ	13.1 ± 2.6	1.0 ± 1.1	
Family history of schizophrenia			
First-degree	1	0	
Second-degree	4	3	
No history	13	17	

6.2.2 Stimuli and task – ERP experiment

A delayed discrimination task (minor modifications from a previously published study (Haenschel et al. 2007)) that probes the effect of working memory load on visual information processing was presented on a personal computer using E-Prime software (Psychology Software Tools, Inc., Pittsburgh, the USA) (Figure 6.1). Thirty-six non-natural objects were presented in the center of a black screen (0.6 x 0.6 visual angles). The participants were instructed to encode one, two or three subsequently presented images into WM. After the delay (maintenance) period a target probe appeared on the screen and the participants had to indicate whether it was part of the initial sample set by pressing a button. Each block consisted of 60 trials, 20 of each working memory load. The trials were intermixed pseudorandomly. All subjects completed 4 blocks.

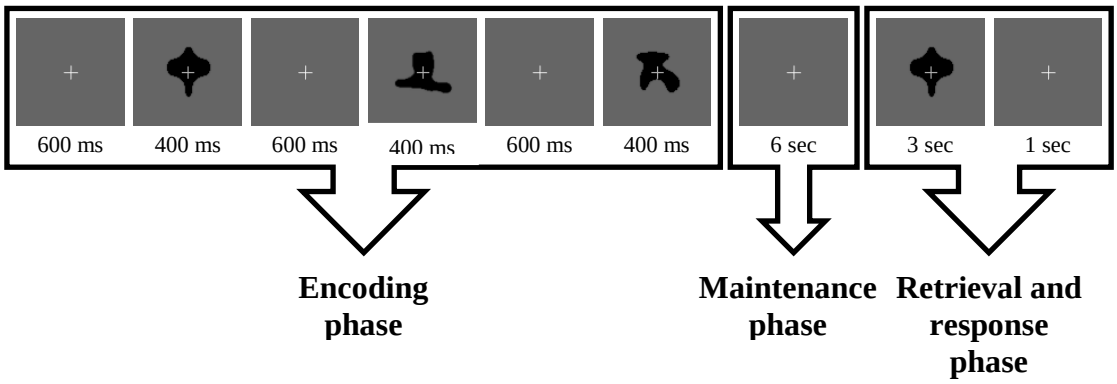

Figure 6.1. Working memory event-related potential task. During encoding one, two or three images were presented for 400 ms seconds each separated by an interstimulus interval of 600 ms. A delay period of 6 seconds ensued (maintenance phase). A target image then appeared and remained on the screen for 3 seconds and the participants were required to indicate by pressing a button whether it was shown during the encoding phase or not (retrieval phase). An interstimulus interval of 1 second separated the trials.

6.2.3. Stimuli and task – neuropsychological experiment

Two tasks from the CANTAB neuropsychological battery were used (Cambridge cognition, http://www.cantab.com/science/default.asp). The first one, Paired Associates Learning (PAL), focuses on the visual memory abilities. Boxes were displayed on the screen and opened in a randomized order. One or more of them contained a pattern. The patterns were then displayed in the middle of the screen, one at a time, and the participant was required to touch the box where the pattern was originally located. If the participant made an error, the patterns were re-presented to remind the participant of their locations. The difficulty level increased through the test. The second task (Intra-Extra Dimensional Set Shift (IEDSS)) probes the ability for rule acquisition and adaptation to rule reversal, functions attributed to the central executive. Two artificial dimensions were used in the test: color-filled shapes and white lines. Simple stimuli were made up of just one of these dimensions, whereas compound stimuli were made up of both, namely white lines overlying color-filled shapes. The subject started the task by seeing two simple color-filled shapes, and was required to learn which one is correct by touching it. Feedback taught the subject which stimulus was correct, and after six correct responses the stimuli and/or rules were changed. These shifts were initially intra-dimensional (e.g. color filled shapes remain the only relevant dimension), then later extra-dimensional (white lines become the only relevant dimension).

6.2.4. ERP data acquisition, processing and analysis

Continuous EEG recording was obtained using ActiveTwo BioSemi electrode system (BioSemi, Amsterdam, the Netherlands) from 72 electrodes digitized at 512 Hz with an open passband from DC to 150 Hz. In the BioSemi system, the classical ‘ground’ electrodes are replaced with two separate ones: Common Mode Sense (CMS) active electrode and Driven Right Leg (DRL) passive electrode. These 2 electrodes form a feedback loop, which drives the average potential of the subject (the Common Mode voltage) as close as possible to the ADC reference voltage in the AD-box (the ADC reference can be considered as the amplifier ‘zero’). A detailed description of the

BioSemi electrode referencing and grounding convention can be found at http://www.biosemi.com/faq/cms&drl.htm.

Data were analyzed using BESA version 5.2 (Brain Electric Source Analysis, Gräfelfing, Germany). For the purpose of the analysis an averaged reference was employed. Only trials where the participants responded correctly were included in the analysis. The epoch within each trial was defined as the period starting at 400 ms prestimulus and ending at 1000 ms poststimulus. For the encoding phase, the stimulus was defined as the last object to appear within the encoding series (object 1 in load 1, object 2 in load 2 and object 3 in load 3). For the retrieval phase, the stimulus was the target image. Baseline was defined as the period between -100 and 0 ms. An automatic predefined source model was used for artifact correction in the period from 400 ms prestimulus to 1000 ms poststimulus (Ille et al. 2002). The model included topographies for horizontal, vertical eye movements and blinks. These standard templates were used to apply weighted corrections to all channels in trials in which the signal amplitude in the horizontal or vertical channels oculomotor channels exceeded ±250 μV and ±150 μV respectively. The continuous data was then examined for outstanding blink artifacts and those were removed manually. The trials that survived artifact correction were averaged together with a high-pass filter of forward phase shift of 0.3 Hz (6 dB/octave) applied before the procedure. A low-pass filter of 0-phase shift of 30 Hz (24 dB/octave) was used on the data after averaging. The mean percentage acceptance rate and the standard deviation for the two groups is as follows: high schizotypes - encoding 87 ± 2 % and retrieval 89 ± 2%, controls - encoding 89 ± 2 % and retrieval 91 ± 2%.

Because the task was designed to probe the early visual components (P1, N1, P2), data from three pairs of occipital electrodes were used in the analysis (PO4/PO3, PO8/PO7, O2/O1). Utilizing the fact that the P1 and N1 visual potentials are well characterized (Di Russo et al. 2002), global field power was employed to identify P1 and N1 as the first two major consecutively occurring peaks of respectively positive and negative voltage in the 50-200 ms post-stimulus period. Their latencies were defined as the time points of maximum amplitude in the respective peaks. The P1 amplitude was defined as the mean amplitude of the 20 ms window around the P1 peak (local mean amplitude) (Luck 2005). The same approach was used for N1,

whereby mean amplitude was calculated for a 30 ms centered on the N1 peak. The mean amplitude for P2 was defined as the 60 ms period beginning 50 ms after the N1 peak.

6.2.5. Statistical analysis

ERP data

Repeated measures ANOVA with a within-subjects factor of working memory load and between-subjects factor of group was performed on the mean amplitudes and latencies of the components of interest. Repeated measures 3x2x3 ANOVAs using within-subject factors of working memory load (1, 2, 3), hemisphere (left and right) and electrode (PO4/PO3, PO8/PO7, O2/O1) and a between-subject factor of group was calculated for the mean amplitude of each component. We used polynomial contrasts to determine whether the increase in WM load resulted in a linear or quadratic increase in the component amplitude. To test for correlation between P1 amplitude and task performance, we averaged the values of the amplitude for the three electrode pairs (PO4/PO3, PO8/PO7, O2/O1) over the three WM loads for retrieval and encoding separately and ran Pearson's correlation between the resulting values and the overall accuracy on the WM task.

CANTAB data

For both PAL and IEDSS the total number of errors and trials were calculated. For PAL we also extracted the number of mean errors to success and the number of stages completed on the first try. In the IEDSS analysis of we calculated the number of errors before and after the dimensional shift. The two groups were then compared on each of these measures using t-tests.

6.2.6. Ethical approval

The study has been approved by The University of Manchester Ethics committee (reference number 08175) and has been carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

6.3. Results

6.3.1. Behavioural data

Figure 6.2 demonstrates the mean reaction time to the correct trials and mean percentage correct for the two schizotypy groups.

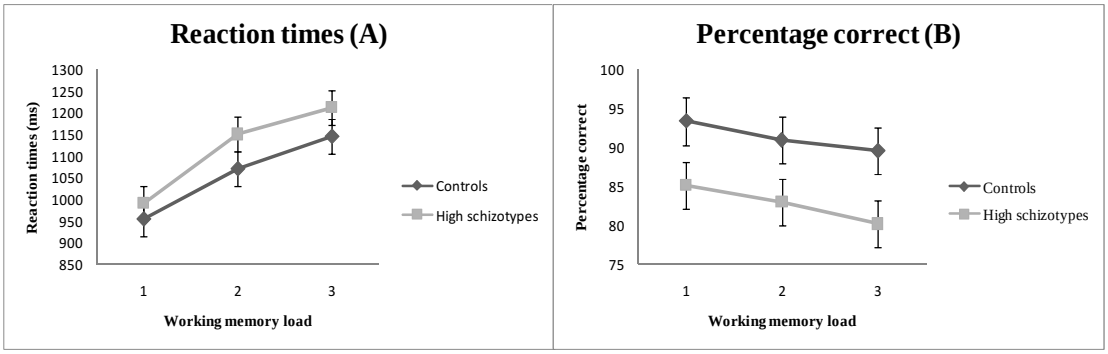

Figure 6.2. Reaction times (A) and percentage correct (B) for high schizotypes (light grey) and controls (dark grey). Reaction times in milliseconds on the vertical axis and working memory load on the horizontal axis (A). Percentage correct on the vertical axis and working memory load on the horizontal axis (B).

The two groups did not differ in terms of their reaction times. In both groups the reaction times increased with WM load ($F(2,72) = 108.327$, $p < .001$). The monotonic increase was confirmed by the linear contrast ($F(1,36)168.077$, $p < .001$). Analysis of the reaction times to the incorrect trials also revealed non-significant difference between the groups, but there was a significant increase in the reaction times to the incorrect trials when compared to the correct ones ($F(1,30) = 41.962$, $p < .001$).

Overall accuracy was significantly lower in the high schizotypy group compared to controls ($F(1,36) = 4.841$, $p = .034$). The accuracy in both groups decreased with WM load ($F(2,72) = 15.282$, $p < .001$). This relationship was found to be linear using a polynomial contrast ($F(1,36) = 34.387$, $p < .001$).

6.3.2. ERP data: Encoding

P1 component

The grand mean ERP to all encoding conditions for the two groups are presented in Figure 6.3. P1 during encoding peaked at a latency of 148 ± 2.3 ms and 148 ± 2.2 ms for the high schizotypy and control groups, respectively. There was no effect of group or WM load on latency.

P1 amplitude was significantly reduced in the high schizotypy group compared with the control group ($F(1,36) = 5.026$, $p = .034$, Figure 6.4A). The effect size of this factor was moderate, $r = .350$. The main effect of WM load was statistically significant ($F(2,72) = 3.907$, $p = .024$, Figures 6.4A and 6.5). The polynomial contrast revealed that the mode of increase was quadratic ($F(1,36) = 5.579$, $p = .024$), the P1 increasing in amplitude from load 1 to load 2 and then decreasing from load 2 to load 3 (Figure 6.4A). There was no interaction between the factors of group and WM load (Figure 6.5).

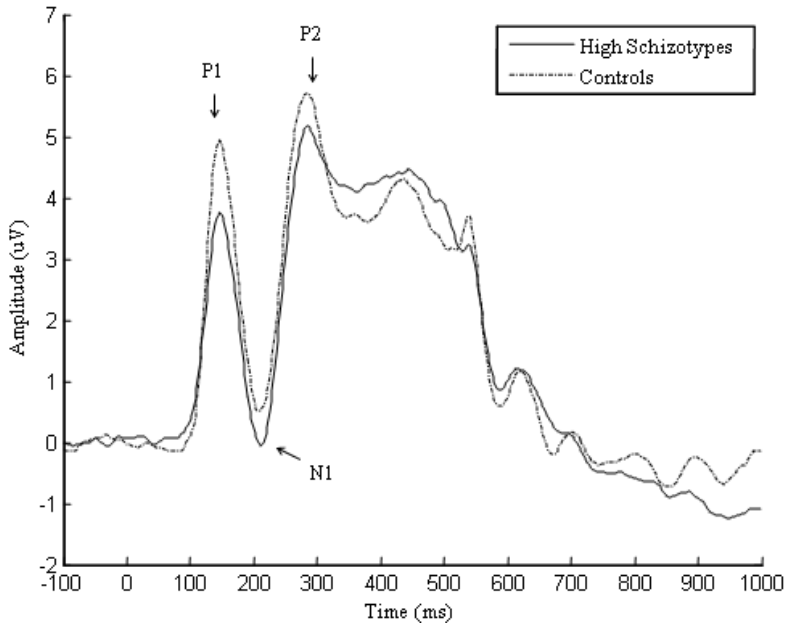

Figure 6.3. Grand averaged waveforms for the encoding conditions in high schizotypes (black solid line) and controls (black lines and dots). Plot is the average for electrodes PO7, PO8, PO3, PO4, O1 and O2. Amplitude in microvolts on the vertical axis and time in milliseconds on the horizontal axis.

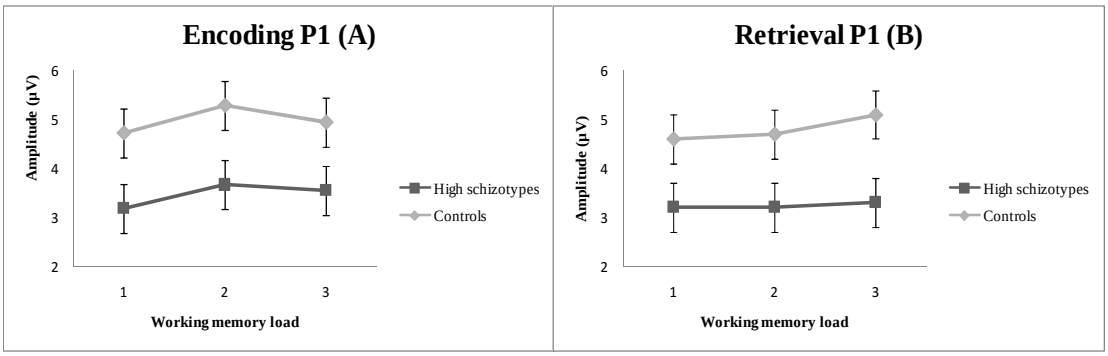

Figure 6.4. Averaged waveform for the encoding phase of working memory loads 1 (black solid line), 2 (black lines) and 3 (black dots) in high schizotypes (A) and control (B). Plot is the average for electrodes PO7, PO8, PO3, PO4, O1 and O2. Amplitude in microvolts on the vertical axis and time in milliseconds on the horizontal axis.

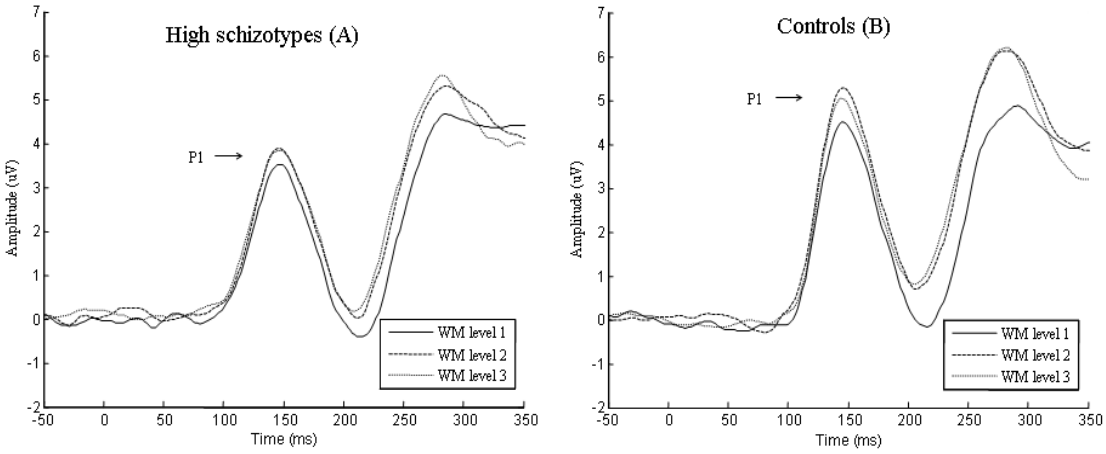

Figure 6.5. Grand averaged waveforms for the retrieval conditions in high schizotypes (black solid line) and controls (black lines and dots). Plot is the average for electrodes PO7, PO8, PO3, PO4, O1 and O2. Amplitude in microvolts on the vertical axis and time in milliseconds on the horizontal axis.

The topography of the P1 peak in response to encoding stimuli in both groups is presented in Figure 6.6.

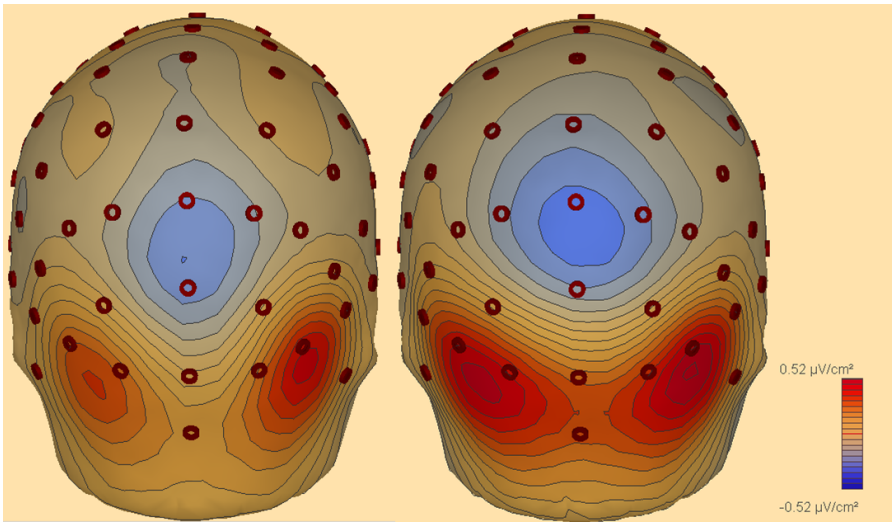

Figure 6.6. Topographical representation of the P1 peak in high schizotypy (left-hand side) and control (right-hand side) groups in current source density ($\mu V/cm^2$).

N1 component

The N1 component peaked at 208 ± 4 ms and 208 ± 3 ms for the high schizotypy and control groups, respectively. There was no significant latency difference between the schizotypy groups and WM loads. The two schizotypy groups did not differ also in terms of their N1 amplitudes. However there was a significant main effect of WM load ($F(2,72) = 10.435$, $p < .001$), the polynomial contrast revealing a linear increase of N1 amplitude with WM load ($F(1,36) = 14.279$, $p = .001$).

P2 component

The encoding stimuli evoked a P2 component with a mean latency of 281 ± 3 ms in the high schizotypes and 274 ± 3 ms in controls and this difference approached significance ($F(1,36) = 3.176$, $p = .083$). The main effect of WM load on latency was statistically significant ($F(2,72) = 3.915$, $p = .024$), the effect due to linear latency decrease with increasing WM load ($F(1,36) = 5.625$, $p = .023$). The factors of schizotypy and WM load did not interact. P2 component amplitude was not significantly different between schizotypy groups, but increased with load ($F(2,72) = 7.009$, $p = .002$) in a linear fashion ($F(1,36) = 59.613$, $p = .004$). There was no interaction between group and WM load in the P2 amplitude model. .

The amplitude and latencies of P1, N1 and P2 components in response to encoding stimuli are presented in table 6.2.

Table 6.2. Amplitudes and latencies during encoding

	Mean (95% CI; SE) Amplitude, µV			Mean (SE) Latency, ms		
Encoding	WM Load 1	WM Load 2	WM Load 3	WM Load 1	WM Load 2	WM Load 3
P1						
Controls	4.7 (3.7-5.8; .5)	5.3 (4.2-6.4; .5)	5.0 (4.0-5.8; .4)	149 (3)	149 (3)	147 (3)
High schizotypes	3.2 (2.1-4.2;.5)	3.7 (2.5-4.8; .5)	3.6 (2.6-4.5; .5)	148 (3)	147 (3)	148 (3)
N1						
Controls	-0.1 (-1.2-0.9; .5)	1.0 (0-2.0; 0.5)	1.3 (0.4-2.2; .4)	208 (3)	204 (3)	202 (4)
High schizotypes	-1.0 (-1.2-0.9; .5)	0.4 (-0.6-1.4; .5)	0.6 (-0.4-1.5; .5)	209 (4)	209 (3)	207 (4)
P2						
Controls	3.5 (2.6-4.5; .5)	4.5 (3.4-5.5; .5)	4.5 (3.5-5.6; .5)	276 (4)	272 (4)	274 (3)
High schizotypes	3.5 (2.5-4.5; .5)	4.0 (2.9-4.1; .5)	3.9 (2.9-5.0; .5)	286 (4)	280 (4)	277 (3)

6.3.3. ERP data: Retrieval

P1 component

The grand mean ERP to all retrieval conditions for the two schizotypy groups are presented in Figure 6.7. The latency of P1 in response to retrieval stimuli was 141 ± 2 ms for the high schizotypy group and 139 ± 2 ms for the controls. There were no significant main effects of group or WM load on P1 latency.

The P1 amplitude was significantly lower in the high schizotypy group compared with the controls ($F(1,36) = 5.140$, $p = .029$, Figure 6.4B), effect size of $r = .354$. There was no main effect of WM load (Figure 6.4B) nor did WM load interact with schizotypy group.

N1 component

The N1 component in the retrieval phase peaked at 205 ± 2 ms in the high schizotypy group and at 201 ± 2 ms in the controls. The main effects of schizotypy group and WM level did not reach statistical significance nor did they interact in respect to N1 amplitude and latency,

P2 component

The P2 component peaked at 285 ± 4 ms in the high schizotypes and at 275 ± 4 ms in the controls. In respect to latency, the difference between the schizotypy groups approached significance ($F (1,36) = 3.946$, $p = .055$), while the main effect of WM load was not significant. The main effects of schizotypy group and WM load were not significant in respect to P2 amplitude. Schizotypy and WM load did not interact in the retrieval P2 models.

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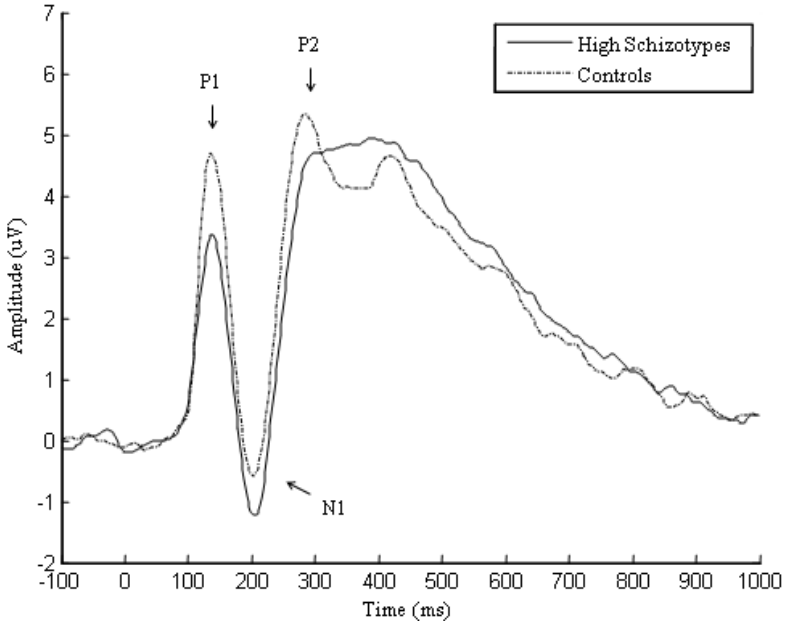

Figure 6.7. Amplitude of the P1 in response to the encoding (A) and retrieval (B) stimuli for high schizotypes (light grey) and controls (dark grey). Amplitude in microvolts on the vertical scales and working memory load on the horizontal scales.

The amplitude and latencies of P1, N1 and P2 components in response to retrieval stimuli are presented in table 6.3.

Table 6.3. Amplitudes and latencies during retrieval						
	Mean (90% CI; SE) Amplitude, µV			Mean (SE) Latency, ms		
Encoding	WM Load 1	WM Load 2	WM Load 3	WM Load 1	WM Load 2	WM Load 3
P1						
Controls	4.7 (3.6-5.7; .5)	4.7 (3.7-5.6; .5)	5.1 (4.0-6.1; .5)	141 (3)	137 (3)	138 (3)
High schizotypes	3.2 (2.1-4.3; .5)	3.2 (2.2-4.2; .5)	3.3 (2.2-4.4; .5)	141 (2)	142 (2)	141 (3)
N1						
Controls	0.2 (-1.0-1.2; .5)	0.0 (-1.1-1.2; .6)	0.4 (-.7-1.4; .5)	202 (3)	201 (3)	201 (3)
High schizotypes	0.0 (-1.2-1.1; .6)	- 0.1 (-1.3-1.1; .6)	- 0.4 (-1.4-.7;.5)	205 (3)	204 (3)	206 (4)
P2						
Controls	4.4 (3.2-5.4; .5)	4.2 (3.2-5.2; .5)	4.2 (3.1-5.3; .6)	273 (3)	275 (4)	277 (4)
High schizotypes	3.6 (2.4-4.7; .6)	3.7 (2.6-4.7; .5)	3.8 (2.7-5.0; .6)	287 (4)	282 (6)	286 (4)

6.3.4. Effect of genetic loading

Given the presence of family history of schizophrenia in the groups, it could have been argued that the difference in P1 amplitude was driven by a few familial cases. To resolve this we removed the first-degree relative from the high schizotypy group from the analysis. The significant difference was retained both in terms of the encoding and retrieval P1 amplitudes, $F(1,35) = 4.437$, $p = .042$ and $F(1,35) = 4.64$, $p = .038$, respectively. Similarly, after removing the second degree relatives from both groups (4 and 3 for the high schizotypy and control groups, respectively) the P1 difference between the two groups remained significant both for the encoding and retrieval conditions ($F(1,28) = 6.145$, $p = .019$ and $F(1,28) = 6.174$, $p = .019$, respectively).

6.3.5. Correlation between P1 amplitude and performance

Pearson's correlation coefficients were calculated to assess the relationship between P1 amplitude and accuracy on the WM paradigm. A significant positive correlation was found between the P1 amplitude of the response to encoding stimuli and accuracy on the task, $R = .307$, $p = .030$. The P1 amplitude during the retrieval phase was also positively correlated with performance, $R = .279$, $p = .045$.

6.3.6. Results cognitive battery

Paired Associate Learning

There was no main effect of schizotypy group in respect to any of the PAL outcome measures.

Intra- and Extra-Dimensional Set Shift

There was also no statistically significant difference between the two groups in the IEDSS models. The high schizotypy group made more errors than controls at the extra-dimensional set shift (4.9 ± 6.3 and 2.7 ± 0.9, respectively), but this effect did not reach statistical significance ($t(36) = 1.607$, $p = .117$).

6.4. Discussion

The present study on healthy volunteers scoring high and low on the SPQ (Raine 1991) adds to the growing body of evidence suggesting that the schizophrenia spectrum disorders are characterized by early sensory processing deficits. Specifically, we found that the high schizotypy group exhibited reduced P1 visual evoked responses, but intact later peaks (N1 and P2). We also found evidence of correlation between the size of the P1 amplitude and the performance on the delayed matching-to-sample task. In accordance with this the high schizotypy group made significantly more errors on this WM task, but interestingly no differences were evident between the groups when tested with two CANTAB paradigms. We will discuss each of these findings in turn in the following section.

6.4.1. Group difference in amplitude

The major finding of this study is that the P1 amplitude reduction that is consistently reported in schizophrenia is also evident in high schizotypy. The effect sizes we obtained were of moderate degree (.353 and .351 for the encoding and retrieval conditions, respectively). In comparison, the study by Haenschel et al. that used the same paradigm in adolescent schizophrenia patients reported effect sizes of .63 and .67 for the P1 reduction for encoding and retrieval, respectively. This suggests that the severity of the early visual processing abnormality in high schizotypes lies between the schizophrenia patients and controls. This finding is in agreement with previous studies that found moderate degree of neuropsychological disturbance in schizotypal personality when compared with patients (Siever et al. 2002). On this basis, one conclusion that can be drawn from the currently reported results is that the P1 abnormality observed in schizophrenia is not the result of florid positive or severe negative symptoms, repeated hospitalization or medication. On the same note, a recently published study found that the P1 deficit in schizophrenia patients is unrelated to disease duration, medication dose or age (Yeap et al. 2008). Instead the abnormality is probably related to mechanisms that predispose to schizophrenia, as suggested by a study that found reduced P1 amplitude in unaffected relatives of schizophrenia patients (Yeap et al. 2006). However, our sample had minimum family

history for schizophrenia and removing the family history cases did not affect the difference between the groups in terms of P1. This suggests that the early visual processing deficits are probably related to the general psychopathology that is characteristic for the schizophrenia spectrum. As such the P1 deficit is probably a more reliable index of overall susceptibility to schizophrenia and not only genetic susceptibility. It is plausible that early sensory abnormalities appear after the genetic and environmental factors have combined to produce the risk state.

6.4.2. Relevance of the P1 abnormalities to higher-order cognitive deficits

Another important finding of this study is that the P1 amplitude in response to both the encoding and retrieval stimuli correlated positively with task performance. We interpret these findings as an indication that the efficient perception of both the encoding and retrieval stimuli is crucial for later cognitive operations and abnormalities at this stage contribute to cognitive impairment. The current finding is supported by a study that used the same delayed matching-to-sample paradigm in schizophrenia patients and found that higher P1 amplitude to both encoding and retrieval stimuli predicted better accuracy in controls on the task (Haenschel et al. 2007). One other study has reported an association between P1 amplitude reduction and cognitive impairment. It demonstrated that impaired emotion recognition correlated with visual sensory dysfunction (Butler et al. 2009). These findings add to a growing body of evidence that primary abnormality in encoding exists in schizophrenia and that it affects cognitive processes by not allowing the effective transformation of the perceived stimulus into an internal representation. Direct psychophysical evidence supports this conclusion, as patients have been demonstrated to need longer periods of uninterrupted encoding to achieve stable working memory representations (Hartman et al. 2003; Fuller et al. 2005; Fuller et al. 2009). Also, the encoding abnormality can sometimes be reduced by increasing the duration of the stimulus presentations (Tek et al. 2002; Lencz et al. 2003; Fuller et al. 2009). In demonstration of this, we found abnormal performance on the WM ERP task with short stimulus presentation in the encoding phase but no difference on the PAL and IEDSS tasks that allowed longer encoding (encoding stimulus presentation times: 400

ms in WM ERP task, 2000 ms in PAL and unlimited in IEDSS). The relevance of encoding abnormalities for the formation of higher order cognitive deficits was underlined by a meta-analysis showing that the cognitive deficits in schizophrenia are not due to dysfunction in information storage, as greater maintenance periods in working memory paradigms do not worsen the deficit (Lee et al. 2005).

6.4.3. Magnocellular involvement in the P1 deficit

The pathophysiological mechanism behind the early visual processing abnormalities has consistently been linked to the magnocellular visual pathway. Evidence from psychophysical studies show that patients are particularly impaired in perceiving stimuli that are biased to activate the M-pathway (Keri et al. 1998; Slaghuis 1998; Schwartz et al. 2001; Keri et al. 2002; Keri et al. 2005). Similarly, electrophysiological studies have found a preferential disturbance in the P1, but not the N1 potentials, suggesting impaired early dorsal, but not ventral stream dysfunction (Doniger et al. 2002; Foxe et al. 2005; Butler et al. 2007). The results from our study show that the same pattern is observable in high schizotypy. The relevance of the magnocellular/dorsal disturbance lies with the specific functions it serves in the human brain. Transmission of information is significantly faster within this pathway and it has been proposed that this data is used to create a low-resolution template in the extrastriate areas. This template facilitates the processing of the high-resolution input from the ventral stream (Kveraga et al. 2007). Consequently, any dysfunction of the dorsal visual stream could disturb this early template generation and compromise the formation of stable representations of the perceived image. This interpretation is supported by data showing normal initial ventral stream input, but abnormal activity once the two streams are integrated (Ncl component in negativity closure studies) (Doniger et al. 2002).

The neurochemical basis for the magnocellular and related encoding dysfunction has been proposed to be due to an abnormality within the glutamatergic neurotransmitter system (Javitt 2009). Glutamate has been implicated in schizophrenia on the basis of studies showing that pharmacologically induced glutamate hypofunction (using ketamine, NMDA-antagonist) in healthy volunteers produces psychopathological and

cognitive disturbances similar to the ones in schizophrenia, e.g. (Krystal et al. 1999). Evidence for the importance of glutamate in early visual processing deficits was provided by a study that linked P1 reductions in schizophrenia patients to a specific haplotype of the dysbindin-1 gene (DTNBP1) (Donohoe et al. 2008). The product of this gene has been implicated in the NMDA/glutamate neurotransmission and the DTNBP1 variant has been associated with an increased risk for schizophrenia (Numakawa et al. 2004). One theory regarding the early visual processing abnormalities suggests that a basic NMDA abnormality in the visual system does not allow effective transmission of data (Javitt 2009). Another possibility is that the P1 reduction is the result of ineffective top-down regulation of the visual cortex by higher order structures. The existence of such a relationship in the brain is demonstrated by data showing unilateral P1 reduction with ipsilateral prefrontal cortex lesions (Barcelo et al. 2000). However both bottom-up and top-down processes might be simultaneously implicated, as recent evidence has shown that top-down facilitation of recognition is dependent on the fast magnocellular projections (Kveraga et al. 2007).

6.4.4. Relationship between WM load and P1 amplitude

The study also found that in both groups P1 amplitude increased with WM load during encoding, but not retrieval. This finding replicates the pattern observed in controls from the previously reported study using the same paradigm (Haenschel et al. 2007). In the original study however, this relationship was not true for the schizophrenia sample, as the encoding P1 amplitude did not increase with demand. The fact that the normal pattern of activation is sustained in high schizotypes could be interpreted in the following way: reduced P1 amplitude is an index of vulnerability to schizophrenia, but in non-clinical cases the visual cortex is more efficiently regulated by higher-order brain areas, resulting in activation with increased demand. In the developed condition this relationship decompensates and the top-down projections cannot modulate as effectively the primary sensory areas.

6.4.5. Limitations

Several important limitations in regards to the currently reported finding of early visual deficits in schizotypy need to be addressed. Firstly, based on findings that P1 amplitude is dependent on spatial attention (Mangun et al. 1998), it is often argued that the observed P1 reduction could be due to differences in the level of arousal or engagement with the task. Our data argue against such criticism. Firstly, it is now well established that both P1 and N1 amplitudes are modulated by attention (Mangun et al. 1991; Luck et al. 1993; Eimer et al. 1998; Mangun et al. 1998) and in our study there was an effect of group only on the P1 but not N1. Secondly, we only analyzed the amplitude to images from successful trials. This ensured that the reported results were only from instances when the participants were actively engaged with the task. Thirdly, the two groups did not differ in their reaction times to the task where the deficit was observed. Lastly, the two groups did not differ in their performance on the two CANTAB tasks, which both require considerable and sustained attention. Given these arguments, we believe that the effects cannot be attributed solely to difference in engagement and attention. Recent data from schizophrenia patients also argues against an effect of attention or arousal in the P1 deficit. A study using a technique that allows the selective activation of the parvocellular pathway discovered normal P1 amplitude in patients but reduced P1 component in standard visual evoked potential technique (Lalor et al. 2008). The authors argued that it would be very unlikely that an arousal mechanism should affect only one of the two visual pathways.

A second limitation is that a recently published study did not find significant difference between controls and patients with schizotypal personality disorder (SPD) in terms of P1 amplitude (Vohs et al. 2008). The P1 amplitude in the SPD group was lower in comparison with the controls and higher than the one in a sample of schizophrenia patients. This pattern coincides with the results emerging from our data but the effect was not found to be significant. One possible explanation of this discrepancy is that the SPD sample recruited for the Vohs et al. study had lower overall SPQ score compared to our sample (42.6 ± 6 vs. 49.4 ± 5) (Vohs et al. 2008). Also, the SPQ score in the Vohs et al. study was elevated mainly due to the cognitive-perceptual score (20.9±7 cognitive-perceptual; 13.0 ±7 interpersonal and 8.7 ± 5

disorganized), while the participants in our sample had more pronounced interpersonal and disorganized traits (19.5 ± 5 cognitive-perceptual; 19.5 ±5 interpersonal and 13.1 ± 2.6 disorganized). Previous studies have shown that negative and disorganized schizotypy tends to have greater cognitive similarities with schizophrenia (Kendler et al. 1991). In schizophrenia itself, negative and disorganized symptoms correlate stronger with cognitive impairment than positive symptoms (O'Leary et al. 2000; Rocca et al. 2005). Also, negative schizotypy is higher among relatives of schizophrenia patients (Tsuang et al. 2002). This has led some authors to hypothesize that negative schizotypy is the one that is more closely linked to schizophrenia (Tsuang et al. 2002). As a result the observed difference between the two studies could be regarded as further evidence for the claim that the P1 amplitude is a biomarker that reflects the level and type of psychopathology and is demonstrable in subjects with higher symptom severity.

Thirdly, it should be noted that we did not correct our results for multiple comparisons. Therefore our results regarding P1 in schizotypy should be treated with caution and may necessitate further studies to replicate the findings. Also, the study has limited power to exclude abnormalities in the N1 and P2 components despite the confidence intervals supporting the conclusions drawn on the basis of the significance values (Tables 6.2 and 6.3).

Finally, although we have used a standard approach to ERP identification, it is nonetheless possible that slow drifts or low frequency oscillations components might have been mistaken for the peaks of interest. However, given the short duration of the peaks of interest (20 and 30 ms for P1 and N1 respectively), their well-defined characteristics and the application of 0.3 Hz high-pass and 30 Hz low-pass filters, it is very unlikely that signal drifts or noise would have systematically obscured the ERPs of interest.

6.4.6. Conclusion

The findings of a significantly reduced P1 amplitude in this group of healthy volunteers with elevated schizotypal traits support claims that the schizophrenia spectrum is characterized by an early sensory deficit. The abnormality also appears to contribute to higher order cognitive deficits, particularly in cases when only short stimulus encoding is possible. This provides evidence that the P1 deficit is a trait marker for the disease that could partly underlie the cognitive impairment in schizophrenia.

CHAPTER 7

Abnormal neural oscillations in schizotypy during a visual working memory task: Support for a deficient top-down network?*

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Contribution of the thesis author: Ivan Koychev designed the study, managed ethical and research approvals, recruited the volunteers, collected and analyzed the study data, wrote the first draft of the article, coordinated the ensuing input from the co-authors and was responsible for amending the article in accordance with the input from the Neuropsychologia referees.

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Abstract

Neural oscillatory deficits may to be core features of schizophrenia spectrum disorders. In this study we aimed to test this hypothesis by examining early evoked oscillatory patterns in the EEG theta, beta and gamma bands of individuals with high schizotypal personality trait scores. We carried out an event-related experiment using a computerised delayed matching to sample working memory (WM) task on a sample of volunteers scoring high or low on the Schizotypal Personality Questionnaire (SPQ). Phase-locking factor (PLF), a measure of network synchronisation, was reduced in the beta and gamma bands in two distinct topographical regions (fronto-central and central-occipital). In addition, signal power in the beta band was decreased in the high schizotypy group in the same fronto-occipital network. These findings suggest that abnormalities in functional connectivity, already described in schizophrenia, extend to schizotypy. Further, the pattern and latency of altered neural oscillations in the high schizotypy group suggests a deficient modulation of sensory processing by higher-order structures. Such top-down deficits have been reported in schizophrenia and this data supports the idea that top-down dysfunction is a vulnerability trait that is independent of disease course, medication or symptom severity.

7.1. Introduction

There is increasing evidence that the psychotic and cognitive manifestations of schizophrenia involve a distributed abnormality affecting multiple regions and their coordination (Andreasen 1999; Friston 2005). fMRI studies find evidence of a 'dysconnectivity' syndrome affecting the efficiency of distributed dynamic coordination of neural activity (Liang et al. 2006; Liu et al. 2006).

EEG and MEG have also been used extensively to study coherent neural activity in schizophrenia by analysing the patterns of spontaneous and evoked neural oscillations (Uhlhaas et al. 2008). These oscillations have been identified as the key mechanism that allows coordination of local and global neuronal populations (Singer 1999; Fries 2009). Studies in animals and humans have shown that during cognitive acts neurons align the rhythm (phase) of their oscillations to achieve highly precise synchronization of their action potential discharges. The temporal correlation between the emergence of synchronized oscillations and various cognitive acts, such as perception, working memory and consciousness, supports the functional relevance of this mechanism (Varela et al. 2001). Also, oscillatory activity in different frequency bands has been implicated in coordinating separate cognitive processes. Oscillations in beta and gamma bands (13-30 and 30-200 Hz respectively) are implicated in the synchronization of local cortical networks and maintenance of the current cognitive set respectively (Engel et al.; Gray et al. 1989), while theta and alpha bands (4-7 and 8-12 Hz) have been proposed to underlie long-distance coordination of local higher frequency activity (von Stein et al. 2000).

Two main parameters are used to measure oscillatory activity: signal power and phase-locking factor (PLF). While the first measure provides information regarding the signal magnitude, the latter indicates the degree of synchronization of neural oscillations to the stimulus presentation, irrespective of power (Roach et al. 2008). PLF measures the consistency of this synchronization across trials, such that a PLF of zero indicates random phase distribution, while a maximum of one reflects exact alignment of phase. It provides information regarding the variability of neural

response and reductions in PLF have been interpreted as an indication of increased 'cortical noise' (Winterer et al. 2000; Winterer et al. 2004).

Many studies have reported oscillatory abnormalities in schizophrenia, some of the most common findings being decreased power and PLF of evoked oscillations (Uhlhaas et al. 2010). These are oscillations that are tightly time and phase-locked to the stimulus onset and have been linked to early encoding processes. Disruption in this activity has been associated with both perceptual and higher-order cognitive deficits (Hirano et al. 2008; Johannesen et al. 2008; Spencer et al. 2008; Haenschel et al. 2009; Uhlhaas et al. 2010). For example, studies in schizophrenia patients showed that the degree of evoked oscillatory abnormality predicts impairment on a working memory task (Haenschel et al. 2009; Haenschel et al. 2010). The relevance of oscillatory disturbance is not limited to cognition, as several studies have shown that the severity of psychotic, disorganized and negative symptoms is correlated with the extent of evoked oscillatory abnormality (Lee et al. 2003; Spencer et al. 2004; Spencer et al. 2008; Spencer et al. 2009). The implication of these findings is that disturbed oscillatory activity is a core mechanism of the disease that underpins diverse cognitive deficits and psychopathological symptoms.

Studies in schizophrenia patients however suffer from several methodological weaknesses that may be particularly relevant when interpreting these subtle neurophysiological signals. In most cases the patients have had the disease for many years and chronic polypharmacy is common (Raine et al. 1995). Furthermore, behavioural and perceptive disturbances may reduce the number of accepted trials in a cognitive experiment. This in turn affects the reliability of key oscillatory parameters such as the phase-locking factor (Roach et al. 2008). In addition schizophrenia is associated with restricted educational opportunities (Gambini et al. 1992) and reduced IQ levels (Reichenberg et al. 2007) which could lead to problems in recruiting an appropriate control group.

One way of tackling the confounding factors of chronicity, drug treatment, florid symptoms and low IQ is to recruit individuals with schizophrenia-like personality traits. This is based on theories that see schizophrenia and schizotypal personality as the two extremes in a spectrum of disorders (Meehl 1962). Extensive data has

supported this by demonstrating that the two conditions share a common psychopathological, genetic and neurobiological basis (Kendler et al. 1993; Siever et al. 2002; Siever et al. 2004). Despite these similarities schizotypal individuals are most commonly spared antipsychotic treatment, repeated hospitalizations or florid symptoms. In addition, the majority attain normal educational and IQ levels.

The currently available data regarding evoked oscillatory activity in schizotypy comes from auditory steady-state studies (experimental settings in which the sensory system is entrained by stimuli of particular frequency). The results are mixed with two studies reporting abnormalities (Hong et al. 2004; Skosnik et al. 2006) and another one that did not find evidence of disturbance (Brenner et al. 2003).

In this study we tested the hypothesis that schizotypy is associated with oscillatory abnormalities by studying the transient evoked-responses of a sample of non-medicated high schizotypal individuals using a visual working memory (WM) paradigm. We chose this paradigm as previous studies have shown that the efficiency of the early information processing predicts the performance on the task (Haenschel et al. 2007; Haenschel et al. 2009; Haenschel et al. 2010). In accordance with this we have already reported findings of early event related potential abnormalities that were related to WM deficits in the same sample and the current report is an analysis of the evoked time-frequency oscillations in the same dataset (Koychev et al. 2010). The hypothesis was that the high schizotypy group would exhibit abnormal oscillatory patterns in the earliest stages of information processing that are similar to those observed in schizophrenia patients.

7.2. Materials and methods

7.2.1. Subjects

University of Manchester research volunteering e-mail, posters and flyers list were used to recruit 45 healthy participants according to their online responses on the short version of the Schizotypal Personality Questionnaire (SPQ-B, (Raine 1991)). At the appointment, participants signed a consent form, completed the full version of the SPQ (Raine 1991) and were included if there was no current or past history of mental health disorders (established by using the Mini-International Neuropsychiatric Interview), neurological conditions, no uncorrected visual impairment and no prescribed medication. Based on the SPQ scores the participants were entered into two groups: high schizotypy one (HS) for those with scores of 43 or more and low schizotypy one (LS) for scores of 9 or below. The SPQ cut-off scores were based on the results from a previous study using SPQ in 760 students from the Manchester University (Barkus et al. 2008) and the SPQ manual (http://www-rcf.usc.edu/~raine/spqrel.html). 5 participants were excluded from the study at this stage (3 participants due to SPQ score out of range, 1 - history of depression and 1 – severe astigmatism). The participants that successfully passed the screening procedures completed the ERP experiment, as well as a semi-structured personality interview based on the Structured Clinical Interview for DSM-IV Axis II Disorders instrument.

The presence of an identifiable and typically distributed P1 event-related component was selected as a criterion for including the data into further analysis. The data from two participants were excluded at this stage in accordance with this criterion (1 due to unidentifiable P1 and 1 due to midline instead of bilateral distribution of the P1). The final groups used in the analysis were 18 high schizotypes and 20 controls and they were well-matched for age and IQ. The demographic, SPQ and family mental health history data is presented in table 7.1. The results from the SCID-II interview in the high schizotypy group revealed that 12 participants met the criteria for a personality disorder (5 paranoid, 3 paranoid and schizotypal, 2 schizotypal, 1 schizoid and 1 depressive), 5 were subtreshold (2 paranoid, 2 schizotypal and 1 schizoid) and 1 did

not meet any criteria for a personality disorder. No participants from the control group fulfilled the SCID-II criteria for personality disorders.

Table 6.1. Demographic and mental health family history data of schizotypal individuals and controls

	High schizotypes	Controls	P value
Age	23.1 ± 4.1	23.5 ± 3.4	.7
Sex			
Male	12	13	
Female	6	7	
Handedness			
Right	18	17	
Left	0	3	
IQ (NART)	114.3 ± 4.8	114.9 ± 4.8	.7
SPQ score			
SPQ total score	49.4 ± 5.3	3.1 ± 2.3	<.001
Cognitive-perceptual SPQ score	19.5 ± 5	.7 ± .9	
Negative SPQ score	19.5 ± 5	1.6 ± 1.6	
Disorganized SPQ	13.1 ± 2.6	1.0 ± 1.1	
Family history of schizophrenia			
First-degree	1	0	
Second-degree	4	3	
No history	13	17	

7.2.2. Stimuli and task – ERP experiment

A Sternberg-type delayed discrimination task (minor modifications from a previously published study (Haenschel et al. 2007)) was presented on a personal computer using E-Prime software (Psychology Software Tools, Inc., Pittsburgh, the USA) (Figure 7.1). For details see (Koychev et al. 2010).

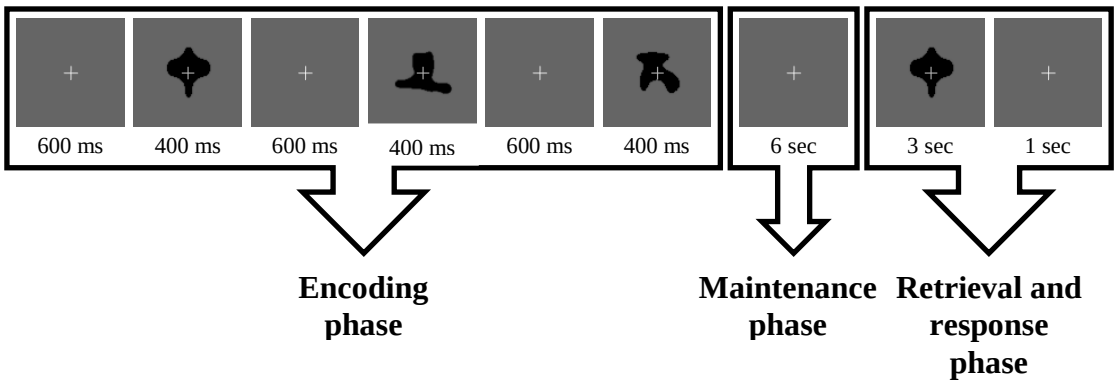

Figure 7.1. Working memory event-related potential task. During encoding one, two or three images were presented for 400 ms seconds each separated by an interstimulus interval of 600 ms. A delay period of 6 seconds ensued (maintenance phase). A target image then appeared and remained on the screen for 3 seconds and the participants were required to indicate by pressing a button whether it was shown during the encoding phase or not (retrieval phase). An interstimulus interval of 1 second separated the trials.

7.2.3. Data acquisition, processing and analysis

Continuous EEG recording was obtained using ActiveTwo BioSemi electrode system (BioSemi, Amsterdam, the Netherlands) from 72 electrodes digitized at 512 Hz with an open passband from DC to 150 Hz. Data were analyzed using BESA version 5.2 (Brain Electric Source Analysis, Gräfelfing, Germany). Only trials where the participants responded correctly were included in the analysis. The epoch within each trial was defined as the period starting at 400 ms prestimulus and ending at 1000 ms poststimulus. For the encoding phase, the stimulus was defined as the last object to appear within the encoding series (object 1 in load 1, object 2 in load 2 and object 3 in load 3). For the retrieval phase, the stimulus was the target image. An automatic predefined source model was used for artifact correction in the period from 400 ms prestimulus to 1000 ms poststimulus (Ille et al. 2002). The model included topographies for horizontal, vertical eye movements and blinks. These standard templates were used to apply weighted corrections to all channels in trials in which

the signal amplitude in the horizontal or vertical channels oculomotor channels exceeded ±250 μV and ±150 μV respectively. The mean percentage acceptance rate and the standard deviation for the two groups is as follows: high schizotypes - encoding 87 ± 2 % and retrieval 89 ± 2%, controls - encoding 89 ± 2 % and retrieval 91 ± 2%. For full details on data acquisition and analysis, see (Chapter 6).

The retained trials were subjected to a complex Morlet wavelet transformation and signal power and phase-locking factor values were calculated for each time point according to Tallon-Baudry et al. in frequency steps of 1Hz (Tallon-Baudry et al. 1997). The wavelet transformation results in complex coefficients of the decomposition of EEG signal as a weighted sum of the wavelet functions. It can be seen as a convolution of signal with wavelet functions: windowed, complex sinusoids, with the distinctive property that the width of the Gaussian window is coupled to the sinusoid frequency. Therefore as the frequency increases the time resolution increases, whereas the frequency resolution decreases (Tallon-Baudry et al. 1997). Signal power is a measure of the magnitude, i.e. the absolute value of the wavelet coefficients. The phase-locking factor (PLF) is a quantitative approach for measuring the phase synchronization that tests the consistency of phases across trials in the EEG spectrum at particular frequencies. The PLF at frequency *f* and time point *t* is defined as

$$= \left| \frac{1}{L} \sum_{i=1}^{L} e^{j\varphi_{ift}} \right| = \left| \frac{1}{L} \sum_{i=1}^{L} \frac{x_{ift}}{|x_{ift}|} \right|$$

Where φ_{ift} is the phase of the complex wavelet coefficients x_{ift} and L is the number of trials. This corresponds to projecting of wavelet coefficients onto a unit circle in the complex plane, and therefore is independent of the signal power.

PLF is a measure of the phase variability across trials within each electrode. It provides information regarding the degree of synchronization between the oscillations and the event onset, separate from its signal power. PLF ranges between 0 and 1, 0 indicating completely random phase distribution across trials and 1 perfectly synchronized phase angles across trials (Roach et al. 2008). The measures were calculated for three frequency bands (4-14, 14-30 and 30-80 Hz). Peaks of activity were identified in each of the three bands by inspecting the time-frequency plots of

each group in the encoding condition. Topography plots were generated for the time and frequency ranges of these peaks and on the basis of their inspection electrodes of interest were selected. The values of the power and PLF of these groups of electrodes were extracted for each level of the task for encoding and retrieval separately.

Repeated measures ANOVA with a within-subjects factor of working memory load and between-subjects factor of group was performed on the signal power and PLF values. An additional within-subject factor of region was entered in the cases where activity was present in two separate topographical regions in the selected time and frequency windows. Two-tailed Pearson's correlations between the two regions were also ran in each WM load. In the case of a significant factor of WM load, polynomial contrast was used to determine the characteristics of the effect.

7.2.4. Ethical Approval

The study has been approved by The University of Manchester Ethics committee (reference number 08175) and has been carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

7.3. Results

7.3.1. Behavioural data

No difference between the two groups was found in terms of their reaction times. The HS group however had a significantly lower accuracy ($p = .034$). In both groups accuracy decreased with WM load ($p < .001$) and this relationship was linear ($p < .001$).

7.3.2. Time-frequency analysis data

7.3.2.1 Alpha and theta band range

There was a peak of activity in both participant groups at 150–250 ms in the 5-8 Hz band. This effect was due to a bilateral occipital increase in power (electrodes P5, P6, P7, P8, PO8, PO7, PO4, PO3, O2 and O1). The values of these electrodes were averaged into one dependent variable and entered into a repeated ANOVA with WM load as the within-subject factor and schizotypy as the between-subject factor.

5-8 Hz at 150-250 ms: Signal power

In encoding, the main effect of schizotypy was not significant. There was a main effect of WM load ($F(2, 72) = 5.672$, $p = .01$) due to its positive linear correlation with theta power ($F(1, 36) = 7.332$, $p = .01$). This effect was significantly more pronounced in LS than in HS, producing a significant WM load and schizotypy interaction ($F(2, 72) = 4.743$, $p = .01$). Post-hoc contrasts showed that the interaction was due to the two groups being statistically different at WM loads 2 and 3 in comparison with load 1 ($F(1, 36) = 5.388$, $p = .026$ and $F(1, 36) = 6.006$, $p = .019$).

In retrieval, the main effects of WM load, schizotypy and their interaction were not statistically significant.

5-8 Hz at 150-250 ms: Phase-locking factor

In encoding, there was no main effect of schizotypy or WM load. The interaction between the two factors however was of borderline statistical significance ($F(2,72) = 2.432$, $p = .09$). Polynomial contrast revealed that the relationship was linear, but in opposite direction in the two groups ($F(1,36) = 5.284$, $p = .03$). Inspection of the marginal means showed that while PLF increased with WM load in LS it decreased in HS. Post-hoc comparisons between the WM loads revealed that the group and WM load interaction was significant for WM load 3 relative to WM 1 ($F(1, 36) = 5.284$, $p = .027$).

In retrieval the main effects of WM load, schizotypy and their interaction were not statistically significant.

7.3.2.2 Beta band range

Inspection of the time-frequency plots revealed that there was a peak of activity in the 14-28 Hz band at the 50-150 ms period post-stimulus (Figure 7.2A). The topography plots (Figure 7.2B) suggested that the activation was due to two groups of electrodes: fronto-central (FCz, FC1 and FC2) and central-occipital (POz and Pz). Therefore in addition to the factors of WM load and schizotypy we added a within-subject factor of region (fronto-central and central-occipital).

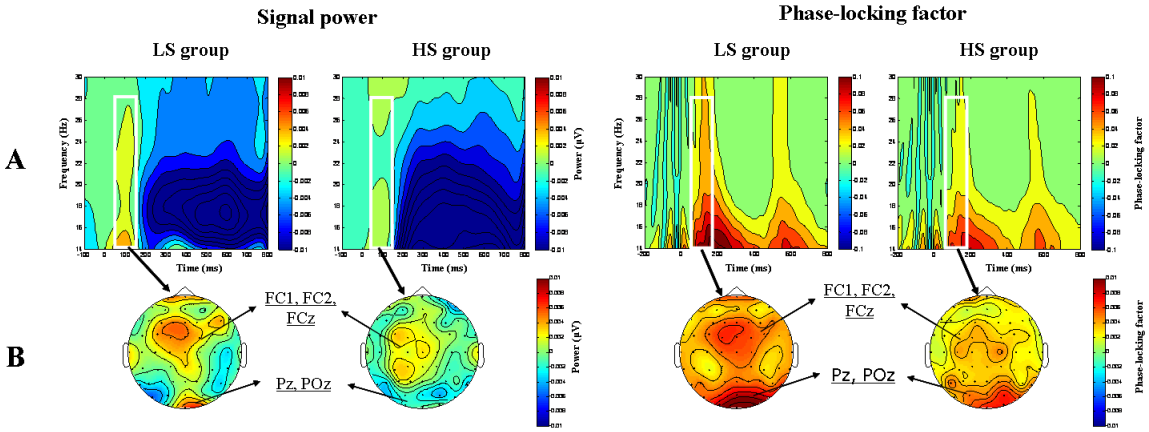

Figure 7.2. Oscillatory activity in the -200 to 800 ms period and 14-30 Hz range during encoding stage of the WM paradigm. Signal power on the left-hand side and phase-locking factor on the right-hand side. A peak of activity is identified at 50-200 ms in the 14-28 Hz band range (A). Its values for power and PLF are plotted topographically in the two schizotypy groups (B). Two groups of electrodes were selected for statistical analysis (FC1, FC2 and FCZ vs. Pz and POz). Abbreviations: LS group – low schizotypy group; HS group – high schizotypy group.

14-28 Hz at 50-150 ms: Signal Power

During encoding, the main effect of schizotypy did not reach significance ($F(1,36) = 2.522$, $p = .12$, Figure 7.2). There was no main effect of WM load or region and WM load and schizotypy did not interact.

During retrieval, LS showed significantly greater beta band activity compared to HS ($F(1,36) = 4.932$, $p = .03$). The main effect of WM load approached significance ($F(1,36) = 2.562$, $p = .08$), but it did not interact with schizotypy. Also, in both groups the activation in the occipital electrodes was greater in comparison to the fronto-central electrodes ($F(1,36) = 8.451$, $p = .01$).

14-28 Hz, 50-150 ms: Phase-locking factor

During encoding the LS group had significantly greater PLF values compared to HS ($F(1,36) = 17.119$, $p < .001$, Figure 7.2). There was no main effect of WM load nor did it interact with schizotypy. PLF was significantly greater in the occipital electrodes in comparison with the fronto-central electrodes in both groups ($F(1,36) =$

27.240, p < .001). However, the two sets of electrodes were significantly correlated in load 1 (r = .541, p <.001), load 3 (r = .426, p <.001) and in trend in load 2 (r = .317, p =.05).

In retrieval, LS had significantly greater degree of PLF in comparison to HS (F(1,36) = 20.063, p<.001). There was no main effect of WM load, but it interacted with schizotypy at trend level for significance (F(2,72) = 2.510 p = .09). As in encoding, the effect of region was highly significant (F(1,36) = 45.252, p < .001). This was due to the occipital set of electrodes having significantly greater PLF values in comparison with the fronto-central electrodes. The PLF values in the two regions were again correlated, load 1 (r = .35, p = .03), load 2 (r = .54, p < .001), and in trend at load 3 (r = .30, p = .06).

7.3.2.3. Gamma band range

A peak of activity in the 30-50 Hz band at 50-200 ms was identified (Figure 7.3). The activity was evident in two regions: fronto-central (FCz, FC1 and FC2) and central-occipital (Oz and POz). The ANOVA included a between-subject factor of schizotypy, as well as within-subject factors of WM load and region (fronto-central and central-occipital).

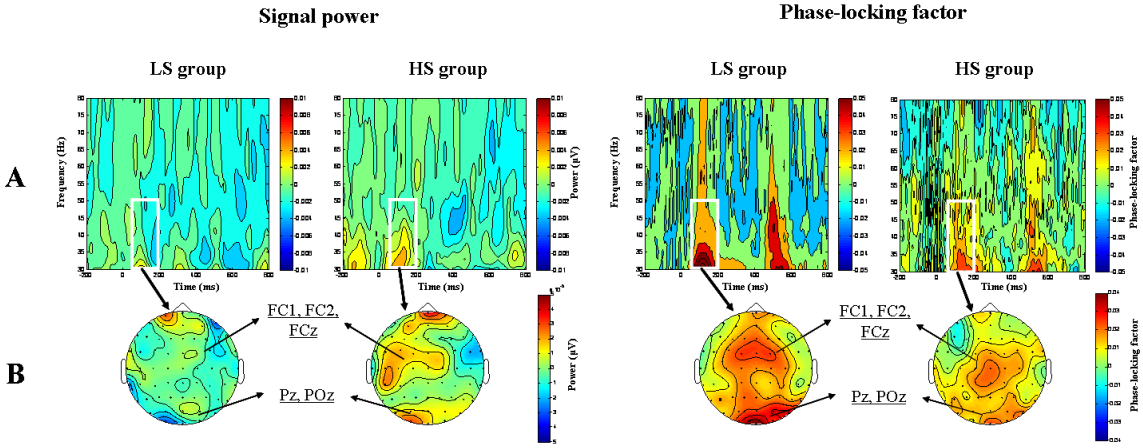

Figure 7.3. Oscillatory activity in the -200 to 800 ms period and 30-80 Hz range during encoding stage of the WM paradigm. Signal power on the left-hand side and phase-locking factor on the right-hand side. A peak of activity is identified at 50-200 ms in the 30-50 Hz band (A). Its values for power and PLF are plotted topographically in the two schizotypy groups (B). Two groups of electrodes were selected for statistical analysis (FC1, FC2 and FCZ vs. Pz and POz). Abbreviations: LS group – low schizotypy group; HS group – high schizotypy group

30-50 Hz at 50-200 ms: Signal Power

In the encoding condition, the power of gamma activity in HS was significantly greater in comparison with LS ($F(1,36) = 5.327$, $p = .03$, Figure 7.3). There were no significant main effects or interactions involving WM load, schizotypy or region. The fronto-central and occipital sets of electrodes were correlated in loads 2 and 3 (respectively $r = .31$, $p = .06$ and $r = .58$, $p < .001$).

During retrieval, there were no main effects of schizotypy, WM load, region and the interaction between load and group was non-statistically significant. The two sets of electrodes were significantly correlated in load 2 ($r = .52$, $p < .01$) and at trend for significance in load 3 ($r = .30$, $p = .07$).

30-50 Hz at 50–200 ms: Phase-locking factor

During encoding, the factor of schizotypy was statistically significant ($F(1,36) = 4.320$, $p = .04$, Figure 7.3). Gamma PLF was significantly higher in LS compared to HS. There were no main effects of WM load, region and the interaction of WM load and schizotypy was not statistically significant. The fronto-central and occipital regions were correlated in loads 1 and 3 ($r = .47$, $p < .01$ and $r = .43$, $p = .01$, respectively).

In the retrieval condition, the main effect of schizotypy was again significant, the LS group having greater PLF values compared to HS ($F(1,36) = 4.38$, $p = .04$). There was no main effect of WM load or region. WM load and schizotypy however interacted ($F(2,72) = 7.34$, $p < .01$). The contrasts revealed that this was due to a linear increase of gamma PLF with WM load in HS, but linear decrease in LS.

The significance values for the main effects and schizotypy-by-WM load interaction during encoding and retrieval are presented in tables 7.2 and 7.3 respectively.

Table 7.2. Significance values of the ANOVA factors and the interaction between WM load and schizotypy during encoding in the theta, beta and gamma bands

	Theta band		Beta band		Gamma band	
	Power	PLF	Power	PLF	Power	PLF
Schizotypy	NS	NS	NS	$p < .001$	$p = .03$	$p = .04$
WM load	$p = .01$	NS	NS	NS	NS	NS
Region	NA	NA	NS	$p < .001$	NS	NS
Schizotypy and WM load interaction	$p = .01$	$p = .09$	NS	NS	NS	NS

Table 7.3. Significance values of the ANOVA factors and the interaction between WM load and schizotypy during retrieval in the theta, beta and gamma bands

	Alpha band		Beta band		Gamma band	
	Power	PLF	Power	PLF	Power	PLF
Schizotypy	NS	NS	$p = .03$	$p < .001$	NS	$p = .04$
WM load	NS	NS	$p = .08$	NS	NS	NS
Region	NA	NA	$p = .01$	$p < .001$	NS	NS
Schizotypy and WM load interaction	NS	NS	NS	$p = .09$	NS	$p = .01$

7.4. Discussion

In this study we compared the signal power and PLF of evoked oscillations during a working memory task in a sample of non-medicated high schizotypy participants compared to a low schizotypy control group. The HS group was characterized by reduced phase-locking factor values of evoked oscillations in the beta and gamma bands in two correlated sets of electrodes (fronto-central and central-occipital). Interestingly, the gamma band signal power in the same set of electrodes was significantly increased in the HS group relative to the LS controls.

7.4.1. Phase-locking factor reductions and top-down abnormality in the schizophrenia spectrum disorders

PLF is a measure of stimulus-induced phase locking of background EEG activity and it indicates the degree of variability of neuronal responses to sensory stimuli. The beta and gamma band PLF reductions in the HS group may indicate that HS did not exhibit the same degree of synchronized and coordinated neural activity as controls. Instead of building up coherent signal, HS appears to be characterized by increased 'cortical noise'. This term was suggested by Winterer et al. to explain the common finding of decreased PLF in schizophrenia patients (Winterer et al. 2000; Winterer et al. 2004). The findings of PLF reduction in schizotypy are therefore compatible with suggestions that dysconnectivity is a core mechanism in the pathophysiology of the schizophrenia spectrum disorders.

While the PLF reduction in the occipital electrodes could indicate impaired local integration, correlated abnormalities were also seen in a set of fronto-central electrodes. We interpret this correlation as evidence for synchronized activity between the two topographical regions in the 100-250 ms period after stimulus presentation. One mechanism to explain the abnormality in this synchronized network may involve disturbed small-scale organization at the level of the occipital cortex driving higher-order cortical abnormalities, as already proposed by Butler et al. (Butler et al. 2007). Another is that the occipital abnormality is imposed by dysfunctional top-down

processes. Studies in perception support the existence of top-down factors that bias incoming signals and modulate the sensory cortex to respond more efficiently to behaviourally salient stimuli (Engel et al. 2001). Such contextual modulation of perception allows swift integration of new information with previous experience and ongoing action planning. Several research groups have already reported diminished top-down modulation of perception in schizophrenia. For example Ford et al. have demonstrated that patients lack a corollary discharge from motor to temporal cortex that normally occurs during speech initiation (Ford et al. 2004; Ford et al. 2007). As a result the dysregulated temporal cortex reacts with the same magnitude to both self- and non self-initiated speech. Decreased coupling during visual perception between frontal and visual cortex has also been reported (Harvey et al. 2011). Experiments by Dima et al. have indicated that the equilibrium between bottom-up and top-down processes in perception might be disturbed in schizophrenia. Using dynamic structural modelling (DCM) they reported that patients are less able to employ conceptually-driven top-down strategies during perception and instead rely on bottom-up processes (Dima et al. 2009; Dima et al. 2010). On a similar line, an eye-tracking fMRI study showed that during smooth pursuit patients have higher BOLD signal in occipital retinal motion regions, but diminished activity in extra-striatal regions in the frontal and temporal cortex (Hong et al. 2005). Therefore, mounting evidence suggests that perception in schizophrenia has diminished access to top-down factors and instead relies primarily on bottom-up processes to form internal representation. Our results suggest that the same might be true for milder forms of the schizophrenia spectrum, such as schizotypy.

The potential top-down abnormality in the schizophrenia spectrum has wide ranging implication. Diminished top down influences on sensory processing can help explain the increasing evidence of misattribution of salience in schizophrenia (Roiser et al. 2009). Inefficient priming of the sensory cortex by higher order structures could also account for the reports of primary perceptual deficits (Chen et al. 1999; Keri et al. 2002; Keri et al. 2004; Green et al. 2006) and decreased sensory cortex responses to stimuli (Haenschel et al. 2007; Martinez et al. 2008) in schizophrenia patients. The timing of events from our study supports this possibility: the peak in activity of the frontal-occipital network occurred earlier than the visual P1 potential (peak of activity at 110 ms and 148 ms respectively) allowing a possible causal relationship.

The pathophysiology of the proposed top-down abnormality could be driven by a localized and/or a distributed deficit. A localized deficit might be due to an abnormality specific to higher-order structures such as the prefrontal cortex. This possibility is supported in principle by a prefrontal cortex lesion study showing that unilateral prefrontal cortex lesions are associated with ipsilateral visual P1 ERP amplitude reduction (Barcelo et al. 2000). This interpretation would be in line with the literature showing prefrontal cortex abnormalities in schizophrenia and might complement the dopamine theory of schizophrenia, as it can help explain the existence of abnormalities in areas outside of the dopamine-mediated striatum and prefrontal cortex. However, a distributed abnormality, such as general neuronal dysconnectivity (Andreasen 1999), might also be responsible for the emergence of top-down dysfunction. Such a deficit would affect the integrity of long-range projections that underpin top-down modulation. In the current study we observed a pattern of inconsistent phase of oscillations in the fronto-central and occipital regions in the HS group. These results argue that the primary dysfunction is one of functional decoupling of brain regions rather than a genuine effect of higher-order structure driving lower-order deficits and therefore probably favour the dysconnectivity hypothesis.

Regardless of the underlying pathophysiology, the current results and previously published research argue that the top-down abnormality is a trait that reflects the vulnerability to schizophrenia. In an auditory MEG study that compared schizophrenia patients, ultra-high risk individuals and controls, Koh et al. found decreased alpha band PLF and power in a parieto-occipital network in both patients and at-risk individuals when compared with controls (Koh et al. 2010). The degree of PLF abnormality was higher in patients than in the ultra-high-risk group. The authors interpreted this as an indication that the extent of top-down dysfunction reflects the vulnerability to schizophrenia. Our results extend these findings by demonstrating a down-regulation of a similar neural network in schizotypy during visual perception. These results argue that the top-down modulation abnormality is a key feature of the schizophrenia spectrum and is not attributable to disease chronicity, medication or florid symptoms of schizophrenia.

7.4.2. Beta band signal power in schizotypy

We also found that in the LS group the increase in evoked PLF in the fronto-central and occipital electrodes was associated with a burst of beta power activity. One of the recent hypotheses states that activity in this band signals the conformity of incoming sensory information with the current endogenous cognitive set (Engel et al. 2010). This is based on observations that paradigms that promote expectancy and endogenous top-down modulation, such as the one used in our experiment, evoke activity in the beta band (Okazaki et al. 2008; Iversen et al. 2009). In this context the finding of beta band augmentation in the LS group suggests that they treated the incoming stimuli as expected. Conversely, the beta PLF and power reduction in the HS group may indicate that their degree of expectancy regarding the sensory input was reduced. This could be attributed to the impaired top-down modulation proposed earlier.

Beta band oscillatory abnormalities in schizotypy have been reported using steady-state paradigm, in which brain oscillations are entrained in the frequency of repetitive sensory stimuli. The authors reported a negative correlation between the power of beta oscillations and SPQ scores in a sample of heavy cannabis users (Skosnik et al. 2006). The present results extend the evidence for beta band abnormalities in schizotypy to non-substance abusing individuals and to settings where conventional transient evoked response paradigms are used.

7.4.3. Gamma band signal power in schizotypy

The finding of greater fronto-central and occipital evoked gamma oscillations in the HS group was unexpected. Nonetheless, this could again mean that the sensory input in the HS participants was treated as novel. Such interpretation is based on studies showing that conditions where responses are primarily stimulus-driven (e.g. free choice versus instruction driven tasks) cause a decrease in beta and increase in gamma band activity (Pesaran et al. 2008). It should be noted however that our finding of increased gamma power is at odds with the results from another steady-state study in schizotypy which reported a decrease in the power of gamma oscillations (Hong et al.

2004). This discrepancy could be attributed to the methodological differences that exist between steady-state and transient paradigms. The former demonstrates explores the ability to sustain prolonged activity in a particular frequency band, while the latter provides information regarding the unfolding of perceptual processes under natural conditions. Therefore, reduced ability to sustain gamma oscillations in a steady-state paradigm does not automatically mean that gamma oscillations have lost their function (e.g. discriminating between stimulus and top-down driven responses).

7.4.4. Relationship between theta band oscillations and WM demand

Finally, we also observed an abnormal pattern of occipital theta band activity in response to working memory demand in the HS group. In the LS group, the power and PLF of the oscillations in the 5-8 Hz range increased with task difficulty. In contrast to controls, in HS the power of the theta oscillations remained constant and theta PLF decreased with the increase of task difficulty. Such modulation by demand was also noted in respect to the P1 ERP amplitude in the initial analysis of this dataset (Koychev et al. 2010). We therefore consider the theta-band results to be at least partially the oscillatory correlate of the P1 abnormality that we reported earlier. Also, in a study using the same working memory task a correlation was found between P1 amplitude and evoked theta but not alpha or beta band occipital activity (Haenschel et al. 2009). This is inline with extensive evidence showing that evoked theta oscillations underlie the formation of the P1 potential while alpha oscillations generate the N1 peak (Klimesch et al. 2004; Gruber et al. 2005). The finding of lesser modulation of theta oscillations by demand in the HS group relative to the LS controls can be interpreted as another manifestation of the proposed diminished top-down control in schizotypy.

7.4.5. Limitations

A potential limitation of this analysis is the method of window of interest selection for the time-frequency analysis. In a slight modification from Tallon-Baudry et al. (Tallon-Baudry et al. 1997) we defined the windows of interest based on the activity in the control group on the basis of their stronger signal. I recognize this method as a potential bias towards the TF activity in the control groups. However examination of the time-frequency plots of the high schizotypy sample did indicate the presence of activities unique to them that might have been omitted from the analysis.

It could be also argued that the effects we observe in the beta and gamma bands also represent primarily the activity that generates the P1 potential. However several lines of evidence argue against this point. Firstly, the available evidence indicates that synchronization in the theta and alpha, but not higher frequencies produce the signal that constitutes the visual P1 and N1 ERPs (Klimesch et al. 2004; Gruber et al. 2005). In accordance, the peaks in beta and gamma band activity in our study differed temporally and topographically from the P1 potential and the theta band oscillations. Specifically, the peaks in beta and gamma power and PLF began earlier (approximately 50 ms post-stimulus) than the P1 (approximately 110 ms) and peaked earlier (110 ms for gamma/beta and 148 ms for P1) than the P1. Also, while the P1 potential and its respective theta band oscillations had a bilateral occipital topographical distribution (e.g. see Figure 6.6 in Chapter 6), the evoked beta and gamma oscillations had a fronto-central and central-occipital distribution (Figures 7.2 and 7.3). We therefore conclude that the beta and gamma band results are a novel finding that is unaccounted for by the already published ERP analysis (Koychev et al., 2010).

It should also be noted that despite the considerable evidence suggesting an early dysfunctional top-down network in the schizophrenia spectrum, our finding of correlated fronto-central occipital activity could equally represent the same response that is volume conducted rather that the activation of separate neural populations. This limitation is inherent to voltage data subjected to laplacian transformation.

7.4.6. Conclusion

In summary, the results of this study indicate that neural oscillatory abnormalities are a key feature of the schizophrenia spectrum disorders. The specific pattern of the disruption indicated the existence of dysfunctional top-down modulation of perception in schizotypy. As similar top-down deficits have already been reported in schizophrenia, this data supports the idea that top-down dysfunction is a vulnerability trait for the condition that is independent of disease course, medication or symptom severity

CHAPTER 8

Core dysfunction in schizophrenia: Electrophysiology trait biomarkers

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Contribution of the thesis author: Ivan Koychev designed the study, managed ethical and research approvals, recruited the patients and volunteers, collected and analyzed the study data, wrote the first draft of the article, coordinated the ensuing input from the co-authors and is responsible for submitting the article.

Abstract

Cognition is a core symptom domain in schizophrenia that has been proposed to be due to a distributed abnormality in neural connectivity. The development of objective laboratory measures (biomarkers) to detect dysconnectivity is therefore a promising lead in defining schizophrenia etiologically. Experiments in patients using electrophysiological methods have demonstrated abnormal information processing and activation of distributed cortical networks during simple cognitive tasks. We have shown similar patterns in individuals with high schizotypal personality traits, with evidence of a down-regulated fronto-occipital network in the earliest stages of visual information processing during a working memory task. In the current study we used the same experimental paradigm to test if this dysfunctional fronto-occipital network is a manifestation of a core schizophrenia deficit. Electrophysiological recordings were acquired from twenty chronically ill, medicated patients diagnosed with either schizophrenia or schizo-affective disorder and 20 healthy volunteers while they conducted a working memory task. The patient group had significantly lower accuracy on the working memory task and a trend for slower responses. Early visual evoked potential P1 was reduced in patients. Analysis of the EEG oscillations showed decreased phase-locking factor (in the theta, beta and gamma bands) and signal power (theta frequency band). The beta and gamma oscillatory abnormalities were confined to two sets of correlated fronto and occipital electrodes. The findings of ERP and oscillatory abnormalities in patients with schizophrenia and schizoaffective disorder confirm the sensitivity of early visual information processing measures to the schizophrenia phenotype. The fronto-occipital distribution of the oscillatory abnormalities replicates our findings from a schizotypal sample and implicates a possible top-down dysfunction as a trait for the vulnerability to schizophrenia.

8.1. Introduction

Schizophrenia is currently diagnosed on the basis of psychotic symptoms (e.g. hallucinations and delusions) present for most of the time in a 4-week period along with functional impairment. The lack of specificity and longitudinal stability of psychotic features (Jansson et al. 2007) leads to operational criteria accepting the risk that etiologically, prognostically and clinically heterogeneous disorders may be lumped together in one condition (Stober et al. 2009). This complicates within- and inter-sample analysis and limits the relevance of fundamental research. In respect to genetic studies for example, none of the identified risk genes are specific to schizophrenia but rather indicate a general vulnerability to mental health disorders or personality psychopathology (Allan et al. 2008).

One way of decreasing the extreme clinical and probably etiological heterogeneity of the DSM-IV defined schizophrenia is to decompose its manifestations into distinct clinical dimensions (e.g. positive, negative, cognitive, disorganization, mood, motor symptom domains) (Tandon et al. 2009). These dimensions have been broadly replicated (Tandon et al. 2009) and discriminate with regard to treatment response and course (Davidson et al. 1997; Dikeos et al. 2006; Harvey et al. 2006). The dimensions may in turn reflect separate etio-pathogenic processes that are associated with measureable biological correlates (biomarkers or intermediate phenotypes) (Preston et al. 2005; Owen et al. 2007; Braff et al. 2008). The successful development of such biomarkers would validate the dimensions etiologically and may ultimately be better at defining specific drug targets (Thaker 2007).

A dimension that may be particularly relevant to the vulnerability to schizophrenia and therefore its core pathophysiology is the cognitive symptom domain. Cognitive dysfunction is highly prevalent in schizophrenia (Saykin et al. 1991; Keefe et al. 2005) and at-risk populations (Siever et al. 2004; Raine 2006), is present in the premorbid stages (Woodberry et al. 2008) and persists longitudinally (Rund 1998; Hoff et al. 2005). It has been hypothesized that this symptom domain may be at least partially due to impairments in the coordination of neural activity (coined ‘dysconnectivity’) (Andreasen 1999; Friston 2005). Therefore, one prominent

direction of biomarker development is to objectively define the dysconnectivity phenotype associated with cognitive dysfunction.

Defining neural connectivity patterns in schizophrenia has classically been undertaken while patients perform working memory tasks, a function considered to be a cardinal neuropsychological feature of the disease (Silver et al. 2003; Gooding et al. 2004). It is proposed to be subserved by the prefrontal cortex (Goldman-Rakic 1994) and research into connectivity using event-related fMRI e.g. (Thermenos et al. 2005) or electroencephalography e.g. (Barr et al. 2010) has therefore focused on activity within this region. Recent evidence has however indicated that WM deficit may at least partly be accounted for by early sensory deficits that disrupt information encoding (Javitt 2009). Specifically, an early event-related potential (P1) that is reduced in amplitude in patients and at-risk individuals (Butler et al. 2005; Yeap et al. 2006; Haenschel et al. 2007; Lalor et al. 2008; Yeap et al. 2008) has been shown to predict WM performance (Haenschel et al. 2007) and other executive functions (Butler et al. 2009; Dias et al. 2011). In addition, the magnitude and inter-trial consistency of evoked neural oscillations that make up the early visual ERPs are also abnormal in schizophrenia (Hong et al. 2004; Uhlhaas et al. 2006; Uhlhaas et al. 2008; Haenschel et al. 2009; Haenschel et al. 2010; Koh et al. 2010) and this oscillatory aberration has also been shown to predict cognitive performance (Haenschel et al. 2009; Haenschel et al. 2010). Therefore, P1 and evoked oscillations could represent biomarkers of a dysconnectivity process that has a causative role in the cognitive domain of schizophrenia and may act as ‘footholds’ linking the cognitive dysfunction to its aetiology.

One key limitation of using information processing biomarkers to aid the diagnostics of schizophrenia is their lack of specificity. Both P1 and evoked oscillation abnormalities have been reported in bipolar disorder (Ozerdem et al. 2008; Ozerdem et al. 2008; Yeap et al. 2009) and disorders that involve sensory or higher order cortical damage (Grayson et al. 1995; Barcelo et al. 2000; Grice et al. 2001; Weinstock-Guttman et al. 2003). A possible way to deal with this is to further characterize the temporal and spatial characteristics of early information processing in schizophrenia in view of producing a pattern that is relatively specific to the disorder. For example, the evoked oscillatory abnormalities in schizophrenia patients and at-

risk individuals have been reported to affect distributed networks linking sensory cortex with higher order structures during auditory stimulation (Koh et al. 2010). This finding fits in the suggestion that the naturally occurring top-down modulation of perception (Engel et al. 2001) may be disrupted in schizophrenia (Dima et al. 2009; Dima et al. 2010). Biomarkers of early top-down dysfunction could therefore be more specific to the schizophrenia phenotype and perhaps more informative of the pathophysiology of the cognitive deficits.

In this study we aimed to test this hypothesis by examining the early information processing patterns using EEG in a sample of medicated schizophrenia patients. In order to ensure the presence of a prominent top-down component in perception we administered a working memory paradigm which was already demonstrated to elicit the effects of cognitive demand on perception (Haenschel et al. 2007). We expected to find that the evoked oscillatory abnormalities are confined to regions of correlated activity (sensory and higher order structure topographies). Our expectation was guided by findings from a previous study by our group, in which early information processing abnormality in schizotypal personality individuals (See Chapter 6) was associated with a down-regulation of an oscillatory network linking frontal and occipital topographical regions (See Chapter 7). We therefore hypothesized that top-down dysfunction is a trait marker of the vulnerability to schizophrenia and therefore should be demonstrable in patients with schizophrenia.

8.2. Materials and methods

8.2.1. Subjects

Twenty eight patients diagnosed according to DSM-IV with schizophrenia or schizoaffective disorder were recruited from mental health care teams and clozapine clinics in Greater Manchester and Merseyside areas in the United Kingdom. Patients were included if they: i) had been diagnosed at least 1 year prior to the appointment; ii) had been clinically stable for at least 6 months prior to the appointment; iii) did not suffer from any neurological disorders; iv) had normal or corrected-to-normal vision. 7 patients were excluded due to poor performance on the working memory task: 3 patients did not complete it while 4 other patients had a below chance performance (less than 50 % correct responses). Also, the data from 1 patient was not included in the final analysis due to unacceptable signal-to-noise ratio.

26 controls were recruited from a database of responders to an online version of the Schizotypal Personality Questionnaire (SPQ) (Raine 1991). Participants who scored in the average SPQ range (9-36) were invited for an appointment where they completed the questionnaire again and were included in the study if the score remained in the 9-36 range. The SPQ cut-off scores were based on the results from a previous study using the SPQ on the same population (See Chapter 4) and the SPQ manual (http://www.rcf.usc.edu/raine/spqrel.html). All controls were free from prescribed medication (apart from the contraceptive pill) and had no history of mental health disorders as confirmed by the Mini-International Neuropsychiatric Interview. All controls reported normal or corrected-to-normal vision and had no history of neurological conditions. 6 controls were excluded before any data was recorded due to SPQ scores out of the 9-36 range.

The final groups used in the analysis consisted of 20 (5 female) patients and 20 (7 female) controls. They were well matched in terms of age, but the controls had a significantly higher IQ ($p < .001$). All included patients were taking antipsychotic medication (13 clozapine only, 1 clozapine and flupentixol, 1 clozapine and quetiapine, 1 clozapine and amisulpride, 2 risperidone depot, 1 risperidone depot and

aripiprazole and 1 on aripiprazole only). 9 of the patients were also taking selective serotonin reuptake inhibitors (SSRIs) for mood and anxiety symptoms. The demographic data of the included sample, the mean SPQ of the controls, as well as the mean duration of disease, BPRS and daily dosage (DDD) of the patient group are presented in table 8.1.

Table 8.1. Subject characteristics

	Schizophrenia patients	Controls	Significance value
Age	36.4 ± 9.0	34.7 ± 7.8	p = .54
Sex	5 female	7 female	x^2 = .496
IQ (NART)	105.9 ± 9.0	114.6 ± 4.9	p = .001
SPQ total score	NA	21.0 ± 7.8	
BPRS total score	28.4 ± 8.4	NA	
DDD	1.53 ± .51	NA	
Duration of disease	14.5 ±7.2	NA	
Family history of schizophrenia			
First-degree	2	0	
Second-degree	3	1	
Third-degree	4	0	
No history	11	19	

8.2.2. Stimuli and task – ERP experiment

A delayed discrimination task (minor modifications from a previously published study (Haenschel et al. 2007)) that probes the effect of working memory load on visual information processing was presented on a personal computer using E-Prime software (http://www.pstnet.com/) (Figure 8.1). Thirty-six non-natural objects were presented in the center of a black screen (0.6 x 0.6 visual angles). The participants were instructed to encode one, two or three subsequently presented images into WM. After the delay (maintenance) period a target probe appeared on the screen and the

participants had to indicate whether it was part of the initial sample set by pressing a button. Each block consisted of 60 trials, 20 of each working memory load. The trials were intermixed pseudorandomly. All subjects included in the analysis completed 4 blocks.

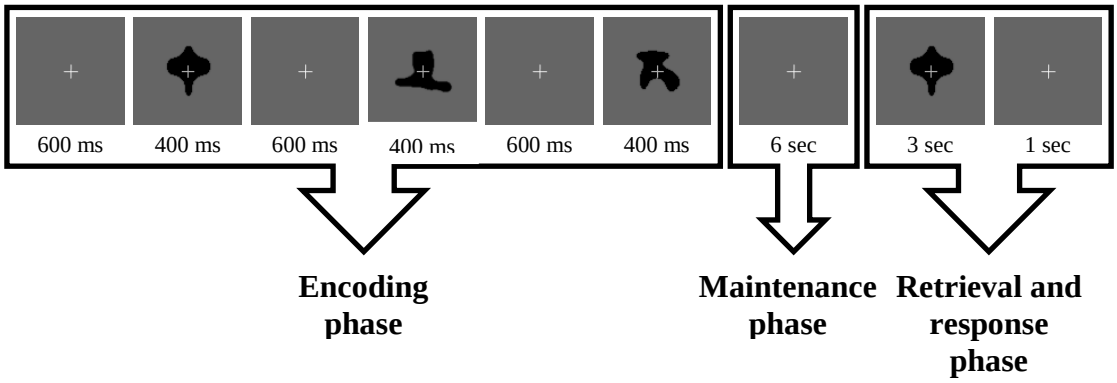

Figure 8.1. Working memory event-related potential task. During encoding one, two or three images were presented for 400 ms seconds each separated by an interstimulus interval of 600 ms. A delay period of 6 seconds ensued (maintenance phase). A target image then appeared and remained on the screen for 3 seconds and the participants were required to indicate by pressing a button whether it was shown during the encoding phase or not (retrieval phase). An interstimulus interval of 1 second separated the trials.

8.2.3. ERP data acquisition, processing and analysis

Continuous EEG recording was obtained using ActiveTwo BioSemi electrode system (BioSemi, Amsterdam, the Netherlands) from 72 electrodes digitized at 512 Hz with an open passband from DC to 150 Hz. In the BioSemi system, the classical 'ground' electrodes are replaced with two separate ones: Common Mode Sense (CMS) active electrode and Driven Right Leg (DRL) passive electrode. These 2 electrodes form a feedback loop, which drives the average potential of the subject (the Common Mode voltage) as close as possible to the ADC reference voltage in the AD-box (the ADC reference can be considered as the amplifier 'zero'). A detailed description of the

BioSemi electrode referencing and grounding convention can be found at http://www.biosemi.com/faq/cms&drl.htm.

Data were analyzed using BESA version 5.2 (Brain Electric Source Analysis, Gräfelfing, Germany). For the purpose of the analysis an averaged reference was employed. Only trials where the participants responded correctly were included in the analysis. The epoch within each trial was defined as the period starting at 400 ms prestimulus and ending at 1000 ms poststimulus. For the encoding phase, the stimulus was defined as the last object to appear within the encoding series (object 1 in load 1, object 2 in load 2 and object 3 in load 3). For the retrieval phase, the stimulus was the target image. Baseline was defined as the period -100 to 0 ms. An automatic predefined source model was used for artifact correction in the period from 400 ms prestimulus to 1000 ms poststimulus (Ille et al. 2002). The model included topographies for horizontal, vertical eye movements and blinks. These standard templates were used to apply weighted corrections to all channels in trials in which the signal amplitude in the horizontal or vertical channels oculomotor channels exceeded ±250 μV and ±150 μV respectively. The continuous data was then examined for outstanding blink artifacts and those were removed manually. The trials that survived artifact correction were averaged together with a low-pass filter of forward phase shift of 0.3 Hz (6 dB/octave) applied before the procedure. A high-pass filter of 0-phase shift of 30 Hz (24 dB/octave) was used after averaging. The mean percentage acceptance rate and the standard deviation for the two groups is as follows: schizophrenia patients - encoding 91.2 ± 6.7 % and retrieval 91.8 ± 10.1%, controls - encoding 97.8 ± 2.7 % and retrieval 98.5 ± 1.7%. This difference was statistically significant for both encoding and retrieval ($p < .001$ and $p < .01$, respectively).

Because the task was designed to probe the early visual components (P1, N1, P2), data from three pairs of occipital electrodes were used in the analysis (PO4/PO3, PO8/PO7, O2/O1). Utilizing the fact that the P1 and N1 visual potentials are well characterized (Di Russo et al. 2002), global field power was employed to identify P1 and N1 as the first two major consecutively occurring peaks of respectively positive and negative voltage in the 50-200 ms post-stimulus period. Their latencies were defined as the time points of maximum amplitude in the respective peaks. The P1

amplitude was defined as the mean amplitude of the 20 ms window around the P1 peak (local mean amplitude) (Luck 2005). The same approach was used for N1, whereby mean amplitude was calculated for a 30 ms centered on the N1 peak. The mean amplitudes and latencies of the P1 and N1 peaks were entered into repeated measures ANOVAs with within-subjects factors of WM load and electrode and a between-subject factor of group (patients and healthy volunteers). In case of a significant main effect of WM load, we used polynomial contrast to determine the character of the effect.

8.2.4. Time-frequency analysis

The retained trials were subjected to a complex Morlet wavelet transformation and signal power and phase-locking factor values were calculated for each time point according to Tallon-Baudry et al. in frequency steps of 1Hz (Tallon-Baudry et al. 1997). The wavelet transformation results in complex coefficients of the decomposition of EEG signal as a weighted sum of the wavelet functions. It can be seen as a convolution of signal with wavelet functions: windowed, complex sinusoids, with the distinctive property that the width of the Gaussian window is coupled to the sinusoid frequency. Therefore as the frequency increases the time resolution increases, whereas the frequency resolution decreases (Tallon-Baudry et al. 1997). Signal power is a measure of the magnitude, i.e. the absolute value of the wavelet coefficients. The phase-locking factor (PLF) is a quantitative approach for measuring the phase synchronization that tests the consistency of phases across trials in the EEG spectrum at particular frequencies. The PLF at frequency *f* and time point *t* is defined as

$$= \left| \frac{1}{L} \sum_{i=1}^{L} e^{j\varphi_{ift}} \right| = \left| \frac{1}{L} \sum_{i=1}^{L} \frac{x_{ift}}{|x_{ift}|} \right|$$

Where φ_{ift} is the phase of the complex wavelet coefficients x_{ift} and L is the number of trials. This corresponds to projecting of wavelet coefficients onto a unit circle in the complex plane, and therefore is independent of the signal power.

PLF is a measure of the phase variability across trials within each electrode. It provides information regarding the degree of synchronization between the oscillations and the event onset, separate from its signal power. PLF ranges between 0 and 1, 0 indicating completely random phase distribution across trials and 1 perfectly synchronized phase angles across trials (Roach et al. 2008). The measures were calculated for three frequency bands (4-14, 14-30 and 30-80 Hz). Inspection of the time-frequency plots revealed peaks of activity in the 100-250 ms period post-stimulus in subsets of each of the three time-frequency range (5-8, 14-28 and 30-50 Hz ranges). Topography plots showed that the activity was confined to two separate sets of electrodes: fronto-central (FC1, FC2, FCz, C1, C2 and Cz) and occipital (PO8, PO4, 02, O1, PO3, PO7, Oz and POZ). The mean power and PLF values of these two sets of electrodes were extracted for each level of the task for encoding and retrieval separately. The repeated measures ANOVA therefore included two within-subject factors (WM load and electrode region: occipital and fronto-central) and one between-subject factor (group: patients and healthy volunteers). Spearman's correlations were performed to determine whether the activity in the two sets of electrodes is correlated.

8.2.5. Covariate analysis

The potential influence of disease duration, symptom severity and medication dose on the electrophysiological measures was investigated by including them as covariates in a secondary analysis on the patient group only. Disease chronicity was expressed in years of illness; symptom severity was represented by the total score on the Brief Psychiatric Rating Scale (BPRS, (Overall et al. 1962); medication dose was described using Defined Daily Dose (DDD). DDD is a statistical measure of drug consumption developed by the World Health Organisation (http://www.whocc.no/ddd/definition_and_general_considera/). It is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults. DDD was preferred to the conventionally used chlorpromazine equivalents due to its good reliability (Nose et al. 2008) and the lack of agreement on the chlorpromazine equivalence of clozapine (Rey et al. 1989; Woods 2003). Significant effects were followed by correlations between the outcome variable and the covariate to determine the direction of the effect.

8.2.6. Ethical Approval

The study has been approved by 11th Regional Ethics Committee, Preston (reference number 09/H175/90) and has been carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

8.3. Results

8.3.1. Behavioural data

Data on reaction time and accuracy of responses on the task is presented on Figure 8.2. In terms of reaction times, there was a trend for slower responses in the schizophrenia group compared to controls ($F(1,38) = 3.033$, $p = .090$). There was a main effect of WM load ($F(2,76) = 95.599$, $p < .001$), the reaction time increasing linearly with demand ($F(1,38) = 130.029$, $p < .001$) in both groups.

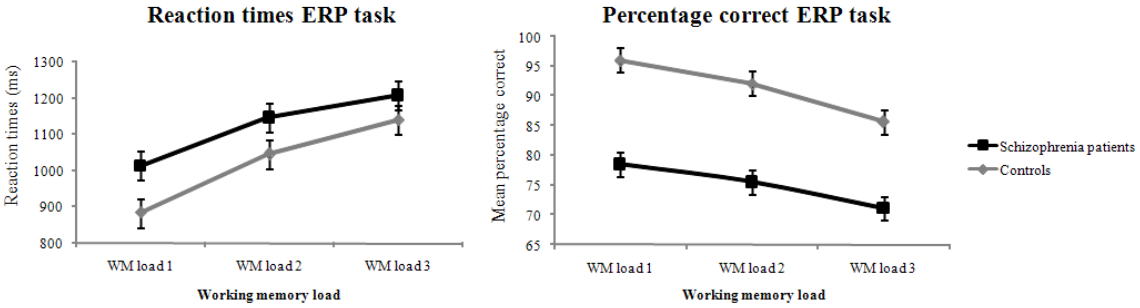

Figure 8.2. Reaction times and accuracy of the ERP task in both study groups.

8.3.2. ERP data

P1 component

The patient group had a significantly reduced P1 amplitude during encoding (P1 at 128 ms; $F(1,39) = 5.763$, $p = .02$, Figure 8.3) and retrieval (P1 at 118 ms; $F(1,39) = 7.138$, $p = .01$, Figure 8.3) compared to controls. There was no main effect of WM load on amplitude and it did not interact with diagnosis. There was no effect of group or WM load on latency, not did they interact.

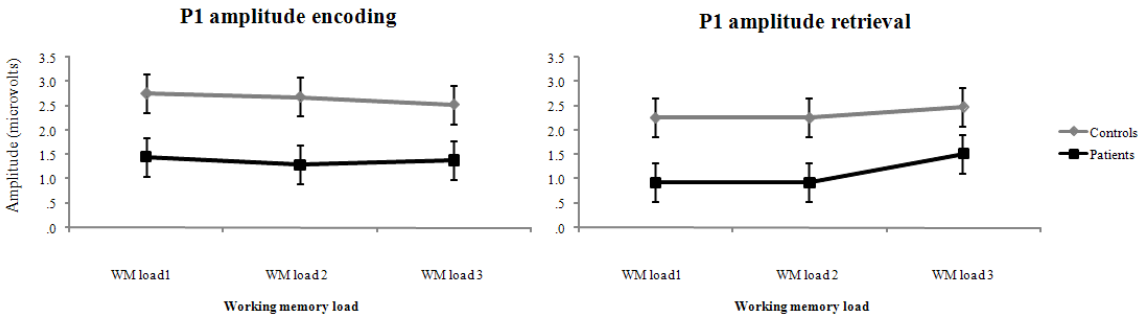

Figure 8.3. P1 amplitude in response to encoding and retrieval stimuli across the three WM loads in both groups.

N1 component

The amplitude of the N1 potential was significantly reduced in the patient group during retrieval (N1 at 180 ms, F(1,38) = 5.830, p =.02) but not encoding (N1 at 177 ms). There was no main effect of WM load, but it interacted with group during retrieval (F(2,76) = 4.354, p = .02, Figure 8.4). The effect was due to reduction of N1 amplitude with load in patients but a reversed pattern in controls (F(1,38) = 5.608, p =.02).

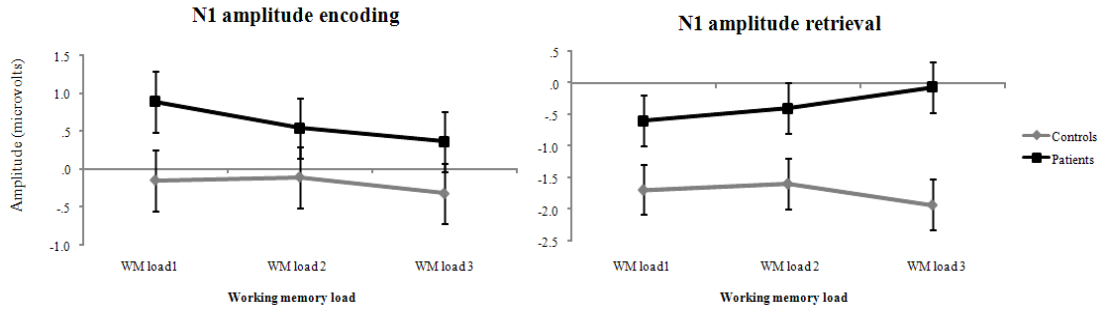

Figure 8.4. N1 amplitude in response to encoding and retrieval stimuli across the three WM loads in both groups.

8.3.3. Time-frequency analysis

8.3.3.1. Phase-locking factor data

Table 8.2 presents a summary of the results concerning PLF.

Table 8.2: Summary of PLF results						
PLF	Encoding			Retrieval		
	5-8 Hz	*16-28 Hz*	*30-50 Hz*	*5-8 Hz*	*16-28 Hz*	*30-50 Hz*
ANOVA: p values						
Group	< .001	.02	.01	< .001	.04	NS
load	NS	NS	.07	.04	NS	NS
Group-by-load	NS	NS	NS	NS	NS	NS
Clinical correlates: p values						
Severity	NS	NS	NS	. NS	NS	NS
Duration	.05	NS	NS	.08	NS	NS
Drug dose	NS	NS	NS	.06	.07	NS

PLF: Theta and alpha band range

In the *5-8 Hz* range (Figure 8.5), the patient group had significantly lower PLF values relative to the controls in both encoding ($F(1,38) = 14.730$, $p < .001$) and retrieval ($F(1,38) = 12.559$, $p = .001$). There was a main effect of WM load only during retrieval ($F(2,76) = 3.382$, $p = .039$), due to a linear increase of PLF with load. The factor electrode region was highly significant in encoding ($F1, 38) = 33.862$, $p < .001$) and at trend in retrieval ($F(1,38) = 3.451$, $p = .071$). This was due to greater PLF values in the occipital electrodes when compared with the fronto-central electrodes. The two sets of electrodes however were highly correlated in all WM loads in both encoding (WM load 1 ($r = .59$, $p < .001$), 2 ($r = .61$, $p < .001$) and 3 ($r = .76$, $p < .001$)) and retrieval (WM load 1 ($r = .58$, $p < .001$), 2 ($r = .62$, $p < .001$) and 3 ($r = .57$, $p < .001$)). There was no interaction between WM load and group.

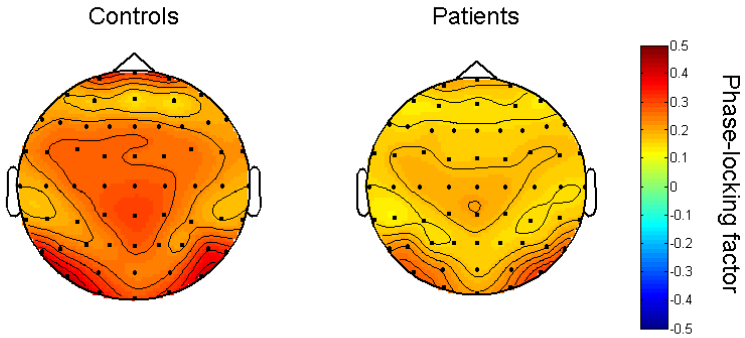

Figure 8.5. Topography plot of the phase-locking factor values of the 5-8 Hz oscillations in the 100-250 ms post-stimulus period in both study groups. View from above; frontal electrodes facing upwards and occipital electrodes facing downwards

PLF: Beta band range

In the *16-28 Hz* range (Figure 8.6), the main effect of group was significant in both encoding ($F(1,38) = .6.962$, $p = .02$) and retrieval ($F(1,38) = 4.491$, $p = .04$). This was due to higher PLF values in healthy controls relative to patients. The factor of electrode region was significant during encoding ($F(1,38) = 30.616$, $p < .001$) and retrieval ($F(1,38) = 4.407$, $p = .04$). This was due to higher values in the occipital region relative to the fronto-central region. The two sets of electrodes were correlated in encoding (WM load 1 ($r = .62$, $p < .001$), 2 ($r = .58$, $p < .001$) and 3 ($r = .34$, $p = .03$)) and in retrieval (WM load 2 ($r = .36$, $p = .02$) and 3 ($r = .44$, $p < .01$), but not WM load 1). There was no main effect of WM load nor did it interact with group.

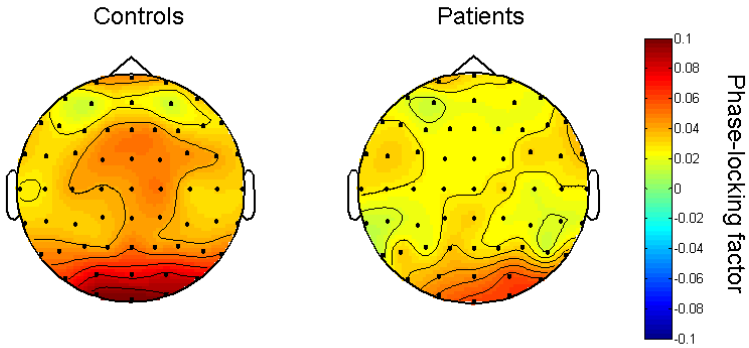

Figure 8.6. Topography plot of the phase-locking factor values of the 14-28 Hz oscillations in the 100-250 ms post-stimulus period in both study groups. View from above; frontal electrodes facing upwards and occipital electrodes facing downwards

PLF: Gamma band range

In the *30-50 Hz* range (Figure 8.7), the patient group had significantly lower PLF values during encoding only ($F(1,38) = 7.276$, $p = .01$). PLF increased in encoding with WM demand, producing a trend for significant main effect of WM load ($F(2,76) = 4.592$, $p = .07$). There was no main effect of region nor did WM load interact with group. The two electrode regions were correlated during encoding (at trend in WM load 1 ($r = .29$, $p = .07$) and significantly at WM load 3 ($r = .62$, $p < .01$)) and retrieval (WM load 1 ($r = .63$, $p < .001$), load 2 ($r = .36$, $p = .02$) and 3 ($r = .54$, $p < .01$)).

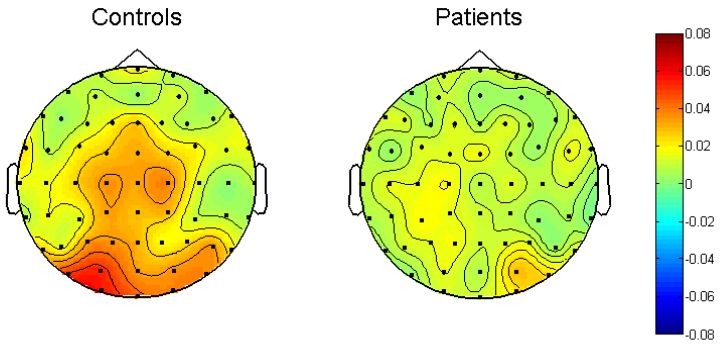

Figure 8.7. Topography plot of the phase-locking factor values of the 30-50 Hz oscillations in the 100-250 ms post-stimulus period in both study groups. View from above; frontal electrodes facing upwards and occipital electrodes facing downwards

8.3.3.2. Signal power

Table 8.3 presents a summary of the results concerning signal power.

Table 8.3: Summary of power results						
Power	Encoding			Retrieval		
	5-8 Hz	*16-28 Hz*	*30-50 Hz*	*5-8 Hz*	*16-28 Hz*	*30-50 Hz*
ANOVA: p values						
Group	.01	NS	NS	.008	NS	NS
load	NS	NS	NS	NS	NS	NS
Group-by-load	NS	.04	NS	NS	NS	.06
Clinical correlates: p values						
Severity	NS	NS	NS	NS	NS	NS
Duration	NS	NS	NS	NS	NS	NS
Drug dose	NS	.04	NS	.02	NS	NS

The only significant effects of interest occurred in the 5-8 Hz range (Figure 8.8). The controls had significantly greater signal power than the patients in encoding ($F(1,38) = 6.611$, $p = .01$) and retrieval ($F(1,38) = 7.959$, $p < .01$). The main effect of region was also significant due to the greater activation in the occipital electrodes when compared with the fronto-central ones ($F(1,38) = 9.493$, $p < .01$ and $F(1,38) = 9.901$, $p < .01$ for encoding and retrieval respectively). This effect of region was significantly more pronounced in the controls relative to the patients ($F(1,38) = 4.290$, $p = .045$) during encoding. The occipital and fronto-central electrodes were nonetheless significantly correlated in encoding (WM load 1 ($r = .58$, $p < .001$), 2 ($r = .58$, $p < .001$) and 3 ($r = .67$, $p < .001$)) and retrieval (WM load 1 ($r = .78$, $p < .001$), 2 ($r = .78$, $p < .001$) and 3 ($r = .87$, $p < .001$)). WM load exerted no main effect and did not interact with the other factors.

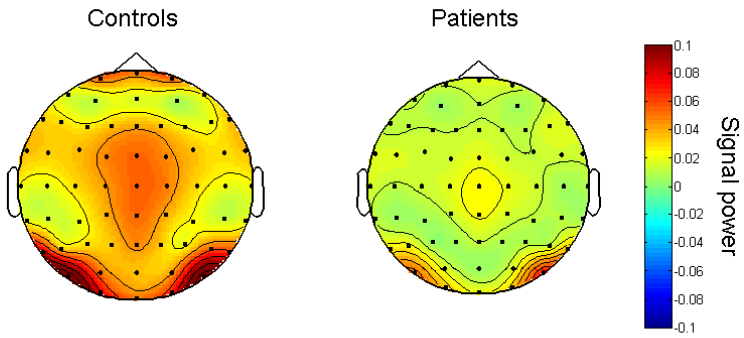

Figure 8.8. Topography plot of the signal power values of the 5-8 Hz oscillations in the 100-250 ms post-stimulus period in both study groups. View from above; frontal electrodes facing upwards and occipital electrodes facing downwards

8.3.4. Effects of symptom severity, medication and chronicity

There were no significant covariates in the ERP analysis. Symptom severity was not a significant confounding factor in any of the analyses.

The covariate of DDD was significant at trend in retrieval in the 5-8 Hz band PLF comparisons ($F(1,16) = 3.990$, $p = .06$). The effect was due to an increase of PLF with medication dose. DDD was also a significant covariate in the 5-8 Hz band signal power analysis in retrieval ($F(1,16) = 6.860$, $p = .02$) but not in encoding. The effect was due to a decrease in power with increasing medication dose.

Duration of illness approached significance in encoding and retrieval with respect to the 5-8 Hz PLF values ($F(1,16) = 4.390$, $p = .05$ and $F(1,16) = 3.442$, $p = .08$, respectively). This was due to a decrease in PLF with increase in disease duration. A similar trend was observed in respect to 14-28 Hz band PLF in retrieval ($F(1,16) = 3.850$, $p = .07$) but not in encoding.

8.4. Discussion

In this study we sought to clarify the neural oscillatory patterns that underlie early visual information processing abnormalities in schizophrenia. In a sample of medicated patients with chronic schizophrenia we found that the widely replicated reductions of in the P1 visual evoked potential were associated with reduction in the PLF values of theta, beta and gamma oscillations, as well as reductions in the signal power of theta oscillations. Importantly, these oscillatory abnormalities were confined to a fronto-occipital network that is similar to the one we described in non-medicated high schizotypy individuals using identical experiment settings (see Chapter 7). We will proceed to discuss how these individual findings relate to our goal of defining a sensitive and specific dysconnectivity biomarker of the cognitive symptom domain in schizophrenia. As cognition has been proposed to be a core, trait characteristic of the disorder we will assess the evidence regarding the trait status of the measures.

8.4.1. ERP results

Reduction in the amplitude of the early P1 VEP is a well replicated finding in schizophrenia (Butler et al. 2007; Yeap et al. 2008; Yeap et al. 2008). This abnormality has been shown to be unaffected by disease chronicity or medication dosage (Yeap et al. 2008) and was demonstrated in a sample of non-medicated first-episode patients (Yeap et al. 2008). Diminished P1 was also reported both in unaffected relatives of schizophrenia patients (Yeap et al. 2006) and schizotypal individuals (Koychev et al. 2010). This evidence argues that the reduction in P1 amplitude is a trait biomarker of schizophrenia: it is associated with the vulnerability to the disease and not the overt clinical phenotype. In support of this we did not find a correlation between symptom severity, disease duration or neuroleptic dosage and the extent of P1 amplitude reduction.

The literature concerning N1 in schizophrenia is so far inconclusive with some but not all studies reporting normal amplitude (Foxe et al. 2001; Doniger et al. 2002; Foxe et al. 2005; Dias et al. 2011). We found that the schizophrenia group had a reduced N1, an effect which reached significance only in respect to the retrieval conditions. On the

basis of data showing that N1 represents discriminatory visual processes(Vogel et al. 2000), it could be argued that the requirements for object discrimination in the retrieval condition were higher than in the encoding condition, a demand which could not be sustained by the schizophrenia patients. From this interpretation it would follow that that N1 impairment in schizophrenia can be elicited preferentially by cognitively demanding paradigms. This interpretation fits with the available literature, as the negative (Foxe et al. 2001; Doniger et al. 2002; Foxe et al. 2005) and positive (Dias et al. 2011) studies have used purely perceptual and cognitively demanding tasks respectively.

In summary, our results confirm that the early visual ERPs and P1 in particular are a sensitive trait biomarkers to the schizophrenia spectrum disorders, as we have demonstrated the abnormality both in patients and schizotypal individuals. Its role in addressing the diagnostic and classification issues of schizophrenia however may be limited by its lack of specificity as outlined in the introduction. The main value of the P1 measure may therefore lie in being used as part of a screening procedure to confirm the presence of early visual processing deficits whose specificity to schizophrenia may then be clarified using more elaborate biomarkers of dysconnectivity. Its added benefit is that it is easily transferable to animal models, which could aid drug development.

8.4.2. Oscillatory results

The finding of oscillatory abnormalities in schizophrenia patients is also in line with existing evidence. Studies commonly report reductions in evoked PLF indicating higher variability of the neuronal response (coined ‘cortical noise’ (Winterer et al. 2004)). Abnormal signal power of the evoked oscillations is also a frequent finding but some authors find increases in power, while others report diminished values (Uhlhaas et al. 2008). This raises suggestions that the abnormalities in both measures may reflect of the proposed state of neuronal dysconnectivity in schizophrenia, with PLF being the more consistent measure. The findings from our study lend some support for this: PLF reductions were evident across the theta, beta and gamma bands, while signal power reduction was present only in the theta band. Perhaps PLF is the

more sensitive measure in respect to activity in the higher frequency bands where the magnitude of the signal is not strong enough to produce reliable effects in signal power. The oscillatory abnormalities also appear to be state-independent, as both our study and previous research failed to establish significant effect of medication, duration of disease or state (See section 3.3.6 of Chapter 3 for review). Instead, the oscillatory deficits are likely to represent a vulnerability trait for schizophrenia. In demonstration of this, one study reported evoked PLF reductions in ultra high risk individuals, a finding we replicated in a study in high schizotypy (See Chapter 7).

Therefore, the evoked oscillatory abnormalities appear to also be a sensitive probe for the vulnerability to schizophrenia. Their advantage over ERPs is that they provide information not only regarding the strength of the neural response but also its variability (PLF). This may be a critical measure given that the key abnormality may be not so much in frank neural damage but neural dysconnectivity. The data on the specificity of oscillatory abnormalities to schizophrenia spectrum disorders is so far limited with some evidence for disruptions in bipolar disorder (Ozerdem et al. 2008; Ozerdem et al. 2008). However, given the proposed central role of neural oscillations in coordinating brain activity (Singer 1999), it appears unlikely that oscillatory abnormalities will be restricted to schizophrenia and not feature in other conditions that involve disruption of normal neural function.

8.4.3. Top-down dysfunction pattern

A finding which furthered the case of a dysconnectivity phenomenon in our patient group was that the oscillatory abnormalities were confined to two sets of correlated fronto-central and occipital electrodes. In controls, perception of stimuli lead to increase of theta, beta and gamma band PLF and theta power in these two regions. In patients the same pattern was evident, but the degree of activation was significantly lower than in controls. Importantly, this replicates the disturbance we observed in the high schizotypy group where we found decreased PLF in the same frequency bands and in the same two sets of electrodes (See Chapter 7). These results argue that under normal conditions a network connecting sensory and higher order cortical structures is formed in the earliest stages of perception. Extensive research has highlighted that at

least a part of these connections underpin top-down information exchange (Engel et al. 2001). Top-down modulation biases the sensory cortex to process preferentially behaviourally relevant data. This control mechanism might be particularly enhanced in tasks such as ours, where the interstimulus interval is constant and the participant anticipates the appearance of the image. This suggests that the down-regulated network in patients and high schizotypes can be interpreted as evidence for disturbed top-down regulation of perception in the schizophrenia spectrum. Such top-down deficit could be a mid-point in the schizophrenia pathophysiology – arising from long-range and local dysconnectivity and causing basic perceptual and electrophysiological deficits (such as P1 amplitude reduction).

The case for top-down dysfunction in schizophrenia has already been supported by direct and indirect evidence (Dima et al. 2009; Dima et al. 2010; Koh et al. 2010). A recent MEG study exploring oscillations during auditory stimulation in patients, ultra-high-risk individuals and controls found a very similar pattern (Koh et al. 2010). The authors reported decreased alpha band PLF and power in a parieto-occipital network in both patients and at-risk individuals when compared with controls. The degree of PLF abnormality was higher in patients than in the ultra-high-risk group. Koh et al. (Koh et al. 2010) interpreted this as an indication that the extent of top-down dysfunction reflects the vulnerability to schizophrenia. Also, Dima et al. used both ERP and fMRI techniques to directly demonstrate that perception in patients is less restrained by top-down modulation than in controls (Dima et al. 2009; Dima et al. 2010). Finally, in a set of behavioural experiments Dakin et al. have shown that patients are less responsive to an optical illusion that depends on global feature integration (Dakin et al. 2005). Therefore, these data indicate that top-down abnormalities during perception might be a highly replicable finding in schizophrenia patients and high risk individuals. The temporal and spatial characteristics of this phenomenon could be used to further increase the specificity of the oscillatory abnormalities to the schizophrenia spectrum. In addition, it could provide a theoretical framework to understand the pathogenesis of perceptual and higher order level cognitive problems in schizophrenia and provide a biological correlate of the cognitive symptom domain.

8.4.4. Limitations

A potential limitation of this analysis is the method of window of interest selection for the time-frequency analysis. In a slight modification from Tallon-Baudry et al. (Tallon-Baudry et al. 1997)we defined the windows of interest based on the activity in the control group on the basis of their stronger signal. I recognize this method as a potential bias towards the TF activity in the control groups. However examination of the time-frequency plots of the patients sample did indicate the presence of activities unique to them that might have been omitted from the analysis.

Another limitation of this study is that while it suggests that the early visual processing and top-down abnormalities may be specific of the schizophrenia spectrum, it does not directly test this hypothesis by including a group from a different diagnostic entity (e.g. bipolar disorder). Some direct evidence in respect to the specificity of the P1 abnormality with data demonstrating diminished P1 in bipolar disorder (Yeap et al. 2009) and in patients with frontal cortex lesions (Barcelo et al. 2000). This suggests that early visual processing deficits may be a shared abnormality across mental health and neurological disorder. However, the etiology of these deficits may be different. Data from visual-backward masking studies for example argues that while both schizophrenia and bipolar disorder may have abnormal VBM performance, the pathophysiology of these abnormalities may occur through different visual pathway mechanisms (Green et al. 1994; Green et al. 1994).

It should also be noted that despite the considerable evidence suggesting an early dysfunctional top-down network in the schizophrenia spectrum, our finding of correlated fronto-central occipital activity could equally represent the same response that is volume conducted rather that the activation of separate neural populations. This limitation is inherent to voltage data subjected to laplacian transformation.

Finally, although we have used a standard approach to ERP identification, it is nonetheless possible that slow drifts or low frequency oscillations components might have been mistaken for the peaks of interest. However, given the short duration of the peaks of interest (20 and 30 ms for P1 and N1 respectively), their well-defined

characteristics and the application of 0.3 Hz high-pass and 30 Hz low-pass filters, it is very unlikely that signal drifts or noise would have systematically obscured the ERPs of interest.

8.4.5. Conclusion

In conclusion, this study provides evidence that the widely replicated P1 potential abnormality in schizophrenia is associated with evoked oscillatory abnormalities that are consistent with a dysfunctional top-down network. The lack of consistent relationship between these abnormalities and state indicators (symptom severity, disease duration and medication dose) along with similar findings in schizotypal individuals argue that early information processing abnormalities are part of the core schizophrenia deficit. More research into their specificity and relationship to the formation of executive function deficits can clarify their importance as biological correlates of the cognitive symptom domain in schizophrenia.

9. GENERAL DISCUSSION

Abstract

Chapter 9 is a summary of the results of this thesis placed in the context of the five hypotheses set out in Chapter 1. The proposed neuropsychological and electrophysiological biomarkers of the schizophrenia spectrum disorders are also evaluated according to the evidence of their sensitivity, specificity and reliability. The chapter concludes with a section devoted to future research directions that could be undertaken to clarify and extend the current results.

9.1 Introduction

Schizophrenia is a clinical syndrome that can feature a number of mental and behavioural phenomena. Converging data from structural and functional neuroimaging studies, as well as cognitive experiments suggests that it is underpinned by an organic cause. Despite this progress, currently there are no laboratory measures to confirm or reject the presence of schizophrenia defect. The current thesis aimed to address this limitation by developing and validating candidate biomarkers.

The development of objective measures of the disease process (biomarkers) in schizophrenia could help bridge the gap that exists between the scientific evidence for an organic abnormality in schizophrenia and its clinical diagnosis. Biomarkers hold the potential for a long overdue paradigm shift in schizophrenia research and clinical practice with wide ranging implications. These include revision of the schizophrenia classification, expansion of our understanding of its pathophysiology and augmentation of the efficacy of the currently used drug development procedures (Breier 2005).

The biomarkers that were researched in this thesis probed processes relevant to the cognitive symptom domain in schizophrenia. The rationale for this choice was based on evidence that cognition is a core component of the schizophrenia phenotype that predicts the functional and social outcome of patients (Heinrichs 2005). Furthermore, this domain remains largely unaffected by the available antipsychotic therapy and discovery of novel treatments to address this is a major unmet need (Heinrichs 2005). Therefore, research aimed at cognitive processes has the potential to fully exploit the utility of biomarkers both in respect to aetiology clarification and drug development.

This PhD focused on the potential of cognitive biomarkers to aid one specific aspect of novel drug development: the successful translation of novel compounds from the preclinical to the clinical stages. The growing interest in cognitive enhancing agents has led to a number of novel agents emerging from the preclinical stages of drug development. However, their success rate has been very poor, a trend that is mainly due to lack of efficacy at Phase 2 and 3 clinical trials (Hurko 2009; Hurko 2010). One strategy to counter this trend is to try and identify the compounds destined to fail as

early as possible in their development. One possibility is to test the potential of a novel drug to improve cognition in small Phase 1 clinical trials involving surrogate populations for schizophrenia. These are populations that feature some of the characteristics of the main disorder without having the full-blown condition. Such proof of concept studies require the availability of validated cognitive biomarkers to swiftly assess the effect of the novel compound on cognition. The work in this thesis therefore concentrated on defining the sensitivity and reliability of several promising cognitive and information processing biomarkers to the phenotype of schizophrenia and its surrogate populations. Another line of work was to explore the response of the biomarkers to psychotropic medication, as well as their possible relevance to the pathophysiology of the schizophrenia spectrum. In accordance with this, several hypotheses were stated at the onset of this thesis. They were based on previous research on the cognitive impairment associated with schizophrenia and the next chapter will review the evidence relevant to each hypothesis in turn.

9.2. Hypothesis 1: Schizophrenia is the extreme of a spectrum of disorders that is characterized by cognitive deficits

The first hypothesis was based on the idea that schizophrenia lies on a continuum with related mental health disorders of varying severity. The evidence for this comes from studies that show elevated vulnerability of individuals with familial history of schizophrenia to certain psychiatric illnesses (schizoaffective disorder) and personality disorders (schizotypal, paranoid and schizoid personality disorders) with similar clinical features (Kendler et al. 1993; Kendler et al. 1993; Kendler et al. 1993; Kendler et al. 1994). This has led researchers to propose that these disorders and schizophrenia form a spectrum of disorders with common pathogenesis, *i.e.* the schizophrenia spectrum (Meehl 1989; Lenzenweger 2006).

Developing biomarkers that probe dysfunction in the milder disorders of the schizophrenia spectrum can help to determine the core deficit in schizophrenia, to inform understanding of its pathophysiology, and to validate drug targets. These populations can also be used for early assessment of novel drug efficacy, which represents the major focus of this thesis.

Existing evidence has already pointed out that cognition might be a shared abnormality in the schizophrenia spectrum. Indeed, a number of cognitive abnormalities are present in schizotypal personality disorder and in the unaffected relatives of schizophrenia patients (Raine 2006; Allen et al. 2009). Their severity is typically intermediate between that of patients and healthy volunteers at low risk for schizophrenia, consistent with a continuum of symptom severity in schizophrenia.

9.2.1. Prediction 1.1:

Schizotypy is associated with cognitive deficits similar to these found in schizophrenia.

The first prediction was therefore that subjects with psychometrically defined schizotypy will also feature cognitive deficits similar to those found in the clinical population. The experiment reported in Chapter 4 used a number of candidate neuropsychological biomarker to compare the cognitive performance of a large cohort of high (HS) and average (AS) scoring schizotypes. There was an overall effect of schizotypy on tasks that tested working memory and verbal fluency performance.

The results in Chapter 5 extended these data by demonstrating that the working memory impairment is also evident when comparing high and low schizotypy. In the same study high schizotypy scores were associated with worse performance than low scorers on an antisaccade eye-tracking task.

Further, in Chapter 6 a modified Sternberg working memory paradigm was administered to high and low schizotypy scorers. Again, working memory performance in high schizotypy was significantly impaired relative to controls.

The relevance of these results to schizophrenia was underlined in Chapter 8, in which the Chapter 6 working memory paradigm was administered to a sample of patients. As expected, the schizophrenia patients performed significantly worse than the healthy volunteer group. In accordance with previous research working memory impairment in the high schizotypy group was between that of patients and controls.

These results support the prediction that psychometrically defined schizotypy is characterised by cognitive deficits. Whilst this is unsurprising given the evidence of cognitive impairment in clinically defined Schizotypal Personality Disorder (SPD), the results from Chapter 4 demonstrate the utility of psychometrically defined schizotypy for identifying individuals exhibiting schizophrenia-like cognitive deficits. It should be noted, however, that an effect of schizotypy effect was only evident for the most taxing conditions in the tasks. This suggests that the study designs chosen for these experiments may have led to the recruitment of a high functioning schizotypy sample presenting only subtle cognitive abnormalities. These recruitment factors were: 1) exclusion of volunteers with previous mental health history; 2) exclusion of volunteers who smoked heavily or had history of drug dependence. The case for a high functioning HS group in Chapter 4 was supported by their higher number of years of education relative to AS controls. Despite this, the effect of schizotypy was still evident on the more difficult cognitive tasks, probably aided by the large sample size reported in Chapter 4. This highlights the importance of the inclusion and exclusion criteria as major factors influencing the detectability of cognitive abnormalities in psychometrically defined schizotypy.

9.2.2. Prediction 1.2:

Schizotypy will feature abnormalities in trait but not state dependent cognitive domains as it represents a less extreme deviation from the norm than schizophrenia

The second prediction regarding hypothesis 1 stated that schizotypy will feature abnormalities in some but not all cognitive domains relative to schizophrenia. There were two sets of findings that supported this prediction.

Firstly, in Chapter 5 two tests demonstrated no effect of schizotypy: the Salience Attribution (SAT) and the Smooth Pursuit Eye Movement (SPEM) tasks. The SAT results appear to contradict one previous study that found a link between schizotypy and aberrant salience attribution (Roiser et al. 2009). In this study, Roiser et al. found a correlation between Introvertive Anhedonia OLIFE scores and aberrant salience

attribution, a pattern that was not replicated here. The current results are, however, in line with pharmacological evidence showing that SAT is a state biomarker given that i) Roiser et al. (2009) report a normalisation of aberrant salience with adequate antipsychotic treatments and ii) imaging studies have demonstrated that the antipsychotic drugs haloperidol (Pessiglione et al. 2006) and olanzapine (Abler et al. 2007) attenuate reward-related activity in ventral striatum. In light of this evidence the response of SAT abnormalities to antipsychotic treatment reported by Rosier et al (2009) suggests that the underlying abnormality might have been secondary to acute psychotic state. The lack of frank psychosis in schizotypy sample could therefore account for the negative result reported in Chapter 5.

Secondly, the SPEM test also yielded a negative schizotypy effect in Chapter 5. The average and high schizotypy groups in Chapter 5 were recruited as part of a larger sample (same as the one reported in Chapter 4) and the SPEM analysis of this larger cohort also revealed no effect of group. As discussed in Chapter 5, this result adds to a background of mixed results regarding the effect of schizotypy on SPEM. Indeed some studies have found no effect (Siever et al. 1994), while another found reduced gain but normal saccade rate (Gooding et al. 2000). Also, a large study reported disrupted SPEM performance in extremely high scorers on the disorganisation subscale of the SPQ (Smyrnis et al. 2007). A pattern begins to emerge when Thaker et al.'s studies on schizotypy individuals with and without family risk of schizophrenia are considered (Thaker et al. 1996). They show that the SPEM abnormality is specific to the schizotypal individuals who have family history of schizophrenia and argued that the SPEM deficit is specifically associated with the familial risk for schizophrenia. It could therefore be speculated that the mixed results in the SPEM schizotypy literature could be due to the varying levels of genetic load in the different sample. Smyrnis et al. (2007) did not report the genetic loading in their sample, but the established link between negative and disorgantisational schizotypal traits and familial risk for schizophrenia (Kendler et al. 1995) suggest that the positive SPEM result could have been due to genetic loading. Indeed, only a small proportion of the Chapter 5 sample reported having a first-degree relative with schizophrenia. One could also argue that the negative result in our study might have been due to the high functioning of our sample. However, we did not find a significant effect of years of education or IQ on the SPEM measures.

9.2.3. Limitations to the data corroborating with Hypothesis 1

The schizotypy effect also did not reach significance on the spatial working memory task in Chapter 4 and on two CANTAB tasks that probed memory and executive function in Chapter 6. These results contrast with the schizotypy effect on working memory tasks in the same studies. This discrepancy could be attributed to the difference in presentation times in these tasks. The working memory paradigms that detected an effect used presentation times of 400 ms (Chapter 4) and 1 second (Chapter 6), while the negative results came from tasks using encoding periods that were either longer (2 seconds in the case of the executive function CANTAB task in Chapter 6) or unlimited (Spatial Working Memory task in Chapter 4 and memory CANTAB task in Chapter 6). As argued earlier, these data highlight the importance of early information processing for the formation of higher-order cognitive deficits. A relationship between indices of early information processing abnormality and cognitive impairment has already been demonstrated in schizophrenia patients (Butler et al. 2007; Haenschel et al. 2007). The findings of reduced early visual evoked potentials in schizotypy argue that this pattern is generalisable to the whole schizophrenia spectrum.

The choice of control group is likely to have been an important contributing factor in the case of SWM task in Chapter 4. This was demonstrated in Chapter 5 by the significant difference obtained when low rather than average schizotypes are used as controls against the high schizotypes. In addition, as it was argued earlier, the high schizotypy sample in Chapters 4 and 5 may have been particularly high functioning. Therefore, several confounding factors might have concealed the schizotypy effect in respect to the SWM and CANTAB tasks.

The conclusions from the experiments aimed at addressing hypothesis 1 indicate that i) psychometrically defined schizotypy has detectable cognitive deficits; ii) the cognitive deficits are confined to working memory, verbal fluency and antisaccade eye-tracking measures; iii) cognitive studies in psychometrically defined schizotypy should employ tasks that are sufficiently difficult to demonstrate the schizotypy

effect; iv) not all tasks that detect an abnormality in schizophrenia are sensitive to the schizotypy effect which could be due to state-dependence or specificity to genetic risk rather than schizotypy symptoms *per se*; v) the choice of exclusion and inclusion criteria may affect the likelihood of detecting the cognitive abnormalities associated with schizotypy.

9.3. Hypothesis 2: Cognitive abnormality in the schizophrenia spectrum is a continuously distributed trait

The work relating to hypothesis 2 sought to further clarify the relationship between schizotypy and cognitive impairment. As pointed out in Chapter 5, there are two competing frameworks addressing this issue. The threshold model derived from Matthysse's and Meehl's works (Matthysse et al. 1986; Meehl 1989) states that cognitive abnormalities are present only in the "disease" end of the schizophrenia spectrum: extremely high schizotypy scorers and schizophrenia-related mental health disorders (Figure 9.1, dashed line). Therefore, according to this theory, there should be no difference in the neurocognitive performance of non-high schizotypy scorers. The second theoretical framework defines schizotypal personality traits as continuum from health to schizophrenia ("full dimensional model"). Authors, such as Eysenck, argue that there is no need to introduce arbitrary cut-off points above which schizotypy lies (Eyseneck et al. 1976; Claridge 1994). Instead, the vulnerability to schizophrenia has a continuous distribution in the population and is correlated with both schizotypal symptoms and neurocognitive deficits (Figure 9.1, solid line). According to this model, average schizotypy scorers will have performance that is inferior to the low scorers and superior to the high scorers.

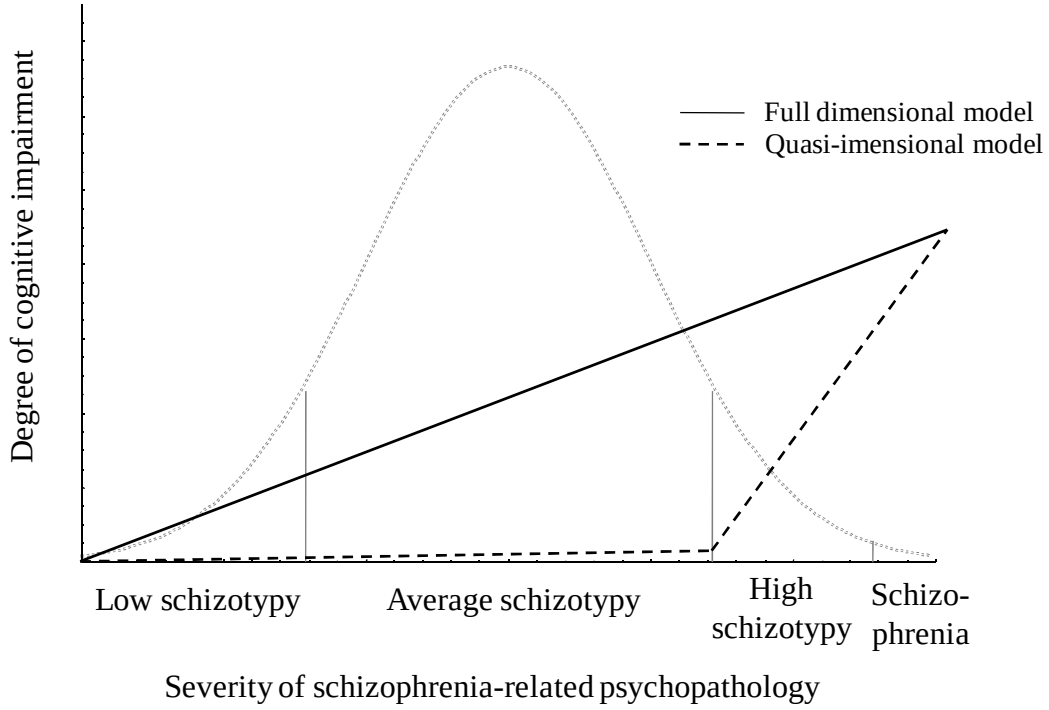

Figure 9.1. Relationship between severity of schizophrenia-related psychopathology and cognitive impairment according to the threshold (dotted) and full dimensional (solid) models of schizotypy. Degree of cognitive impairment on the vertical axis, severity of schizophrenia-related psychopathology on the horizontal axis. A dotted bell-shaped curve in the background describing the frequency of schizophrenia-related psychopathology in the general population.

This theoretical debate has implications that reach beyond the pathophysiology of the schizophrenia spectrum. In the context of this thesis, concerned with proof-of-concept studies of novel cognitive enhancing agents in schizotypy, this issue is particularly relevant, as it can help guide the choice of the most appropriate control group in such clinical trials. This is particularly important in light of the marginal size of the schizotypy effect reported in Chapter 4.

9.3.1. Prediction 2.1:

Cognitive performance decreases with increase of schizotypal personality traits

This prediction was addressed in Chapter 5 where the cognitive performance of low, average and high schizotypy scorers is compared. On three of the tasks that were sensitive to the effect of schizotypy, there was a linear relationship between schizotypy and cognitive performance (N-back, SWM and antisaccade tasks). These results are generally in line with reports on the correlation between schizotypy scores and executive function in a healthy population. Some (Park et al. 1997; Gooding et al. 2006; Matheson et al. 2008) but not all (Jahshan et al. 2007; Noguchi et al. 2008) have found an inverse relationship between schizotypy scores and neurocognitive performance. One of the studies that did not find such a correlation also failed to detect impairment of executive function in the high scorers (Jahshan et al. 2007). It could therefore be hypothesised that the tasks in the negative studies were not sufficiently difficult to demonstrate the subtle schizotypy deficit. Therefore, these results and previously published data collectively argue in favour of the full dimensional model and by extension to the choice of low over average schizotypy group in comparisons versus high scorers to detect a schizotypy effect on cognition.

The practical implications of this research are evident when the results from the SWM task in Chapter 4 and 5 are compared. While the comparison between average and high schizotypes did not reach significance in Chapter 5, adding a group of low schizotypy scorers produced a significant main effect of schizotypy. These data argue that perhaps some of the true main effects of schizotypy and schizotypy-by-drug interactions in Chapter 4 might have been obscured by a suboptimal choice of control group.

9.3.2. Limitations to the data corroborating with Hypothesis 2

A potentially serious limitation of the results from Chapter 5 is the fact that unlike the average and high schizotypy groups the low schizotypy group was not treated with placebo. One could therefore argue that the difference between the low and average schizotypy groups was due to a placebo effect in the average group, rather than a genuine linear relationship between schizotypy and cognitive ability. Several points argue against this. Firstly, if a placebo effect was behind the difference between two otherwise indistinguishable groups, one would expect that a number of tasks and measures would be affected. However, the positive results related only to the working memory and antisaccade tasks while SAT and SPEM were unaffected. Moreover, on the verbal fluency task the average schizotypy group performed better than the low schizotypy. Therefore, the pattern of differences argues against a generalised placebo effect being a major contributing factor for the difference in cognition between the average and low schizotypy groups. Secondly, if the placebo effect was one of fatigue, then it would be expected that the difference in cognition between the two control groups would be accompanied by latency differences. However, there was no effect of schizotypy group on the reaction times of any of the three tasks where a linear effect of schizotypy was evident. Thus we believe that the working memory and antisaccade-specific differences between average and low schizotypes are unlikely to be due to a placebo effect.

Another important limitation of the Chapter 5 results is that they did not include a correlation between the level of schizotypal symptoms and cognitive impairment. Such an approach would be a more direct way of testing the prediction than comparing the performance of low, average and high schizotypy scorers. However, the choice of SPQ cut-off scores for average and high schizotypy in the Chapter 4 study design lead to a poor spread of schizotypy scores present in the database. A large sample study exploring directly the proposed correlation would be an appropriate future research direction.

In conclusion, these results provide indirect support for the hypothesis that cognitive abnormality in schizotypy is a continuously distributed trait. In the light of proof-of-

concept studies, these data argue in favour of using low schizotypy scorers in cognitive comparisons against high scorers to maximise the size of the schizotypy effect.

9.4. Hypothesis 3: The cognitive deficits in schizophrenia are modulated by dopamine

Hypothesis 3 dealt with the neurochemical basis of the cognitive abnormality in the schizophrenia spectrum. Converging evidence from neuroimaging studies in patients using metabolic tracing neuroimaging (Ingvar et al. 1974) and fMRI (Weinberger et al. 1986; Wolkin et al. 1992; Kawasaki et al. 1993) has indicated that the cognitive deficit associated with schizophrenia is due to a prefrontal cortex dysregulation. Therefore, if cognitive abnormality is generalisable to the schizophrenia spectrum disorder as hypotheses 1 and 2 suggest, does this translate into a frontal cortex dopamine dysfunction that is continuously distributed and correlated with the risk for schizophrenia?

9.4.1. Prediction 3.1:

Cognitive deficits would be affected by drugs altering dopamine

This issue was addressed in Chapter 4 where the schizotypy effect on cognition was challenged with acutely administered risperidone, amisulpride and nicotine in a double-blind placebo-controlled design. Full D_2-receptor antagonists such as risperidone have been shown to impair cognition in healthy volunteers when administered acutely (Barch 2004). Nicotine is an agonist to the nicotinic receptor of the acetylcholine system and as a result has a general neurostimulating effect. Amisulpride is also a D2 receptor antagonist, but when given in small doses (less than 10 mg per kg) has a dopamine enhancing action due to binding to the presynaptic D2 receptors (Schoemaker et al. 1997). The dose used in Chapter 4 was 400 mg and as none of the included participants in this study weighed less than 40 kg, this should be considered a small dose with predominantly dopamine enhancement effects.

The results showed that out of the three agents only amisulpride reversed the schizotypy effect on cognition: it improved the high schizotypy group but impaired the average schizotypy group. This effect was significant in respect to the N-back and verbal fluency task, while the SWM results showed the same trend but did not reach statistical significance. We interpreted these results in the light of the theories that see the relationship between prefrontal dopamine and cognition as a reversed U-shape curve (Figure 9.2). According to this model intact cognition requires optimal prefrontal cortex dopamine activity, with hypo- and hyperdopaminergic states leading to cognitive impairment (Barch 2005). Studies in humans and in primates support this by showing that dopamine enhancement benefits the poor baseline performers while impairing the individuals with high level of cognitive abilities (Barch 2004). In Chapter 4, the improvement of the high schizotypy group by dopamine enhancement suggests that they had low baseline dopamine activity which approached optimum levels with the pharmacological challenge. In contrast, the average schizotypy results indicate that their baseline prefrontal dopamine activity was nearer to the top of the curve and that dopamine enhancement tipped them into hyperdopaminergic state. These results suggest that a moderate degree of prefrontal hypodopaminergia is a trait of the schizophrenia spectrum. This conclusion is supported by a study showing improvement of cognition in Schizotypal Personality Disorder after a 4-week treatment with a combined D1/D2-receptor agonist (McClure et al. 2010). The moderate degree of cognitive impairment would also suggest that the frontal hypodopaminergic state in high schizotypy is of intermediate severity in between that of schizophrenia patients and healthy volunteers (Figure 9.2).

Whether the frontal hypodopaminergia trait is continuously distributed and correlated with schizotypal symptoms in non-high schizotypy healthy volunteers is unclear. The full dimensional model would predict that average schizotypy has lower baseline dopamine activity compared to low schizotypy (figure 9.2A) while the threshold model would argue that both groups have optimum or near-optimum dopamine activity (Figure 9.2B). The linear relationship between schizotypal personality traits and cognitive ability established in Chapter 5 favours the full dimensional model but there is currently no direct pharmacological evidence to support this.

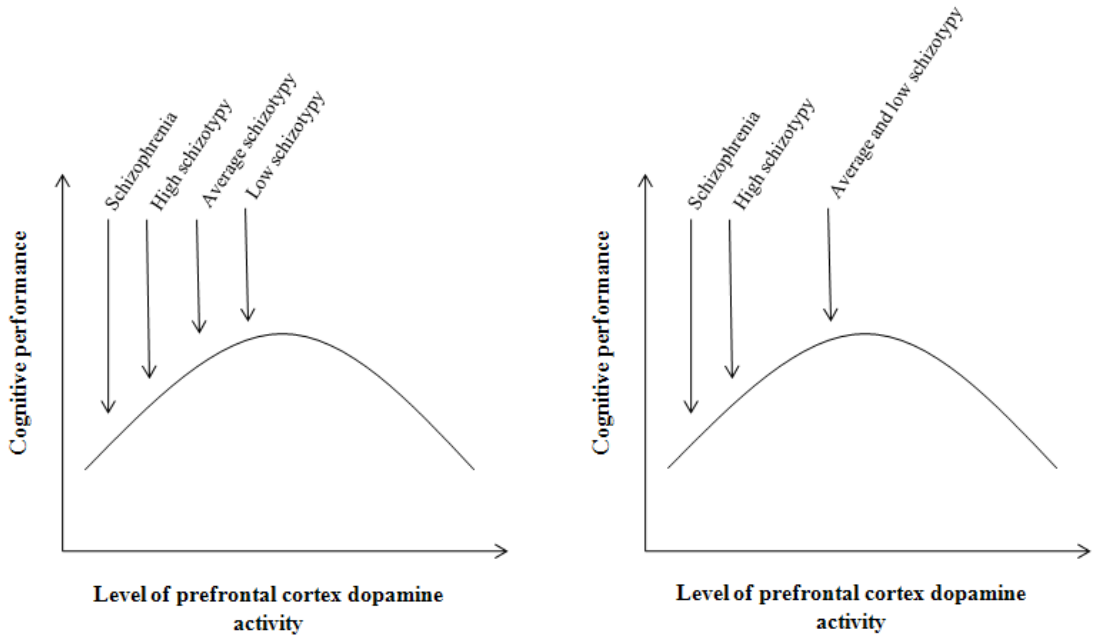

Figure 9.2. Relationship between extent of schizophrenia spectrum psychopathological symptoms and frontal dopaminergic activity according to the full dimensional and threshold model.

One way to test this hypothesis would be to challenge the cognitive performance of low, average and high schizotypy scorers with a potent dopamine agonist at gradually increasing doses (for example low, moderate and high doses of methylphenidate). A result that would support the dimensional model would see average but not low schizotypes improve under the very low agonist dose, while both groups should be impaired by moderate and high doses (Figure 9.3). In contrast, the threshold model would be supported by a uniform response by the average and low schizotypy groups to the agonist challenge, irrespective of the dose.

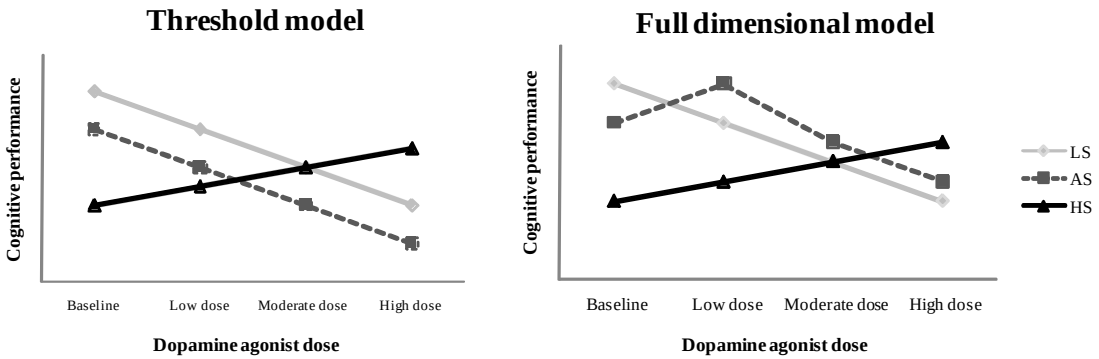

Figure 9.3. Hypothetical relationship between cognitive performance in schizotypy and low, moderate and high doses of a dopamine agonist according to the threshold and full dimensional models. Abbreviations: LS – Low schizotypy; AS – Average schizotypy; HS – high schizotypy.

9.4.2. Limitations to the data corroborating with Hypothesis 3

It should be noted that the study featuring in Chapter 5 has several limitations that may have affected the results relevant to Hypothesis 3. Firstly, as discussed previously some of the tasks might have been of insufficient difficulty allowing ceiling effects to obscure the true relationship between dopamine and schizotypy. Secondly, despite the evidence linking low dose amisulpride to enhancement of dopamine action and the direction of our results, it is nonetheless an indirect method to test Hypothesis 3. Given that both the average and high schizotypy samples were high functioning, a full dopamine agonist might have been better suited as it would have produced stronger results, particularly in respect to selective impairment of the control group. Finally, as it was argued earlier, choosing a different control group (low schizotypy instead of average schizotypy) might have maximised the effect of schizotypy and its interaction with the study drug.

Despite the shortcomings of this study design, its large sample size ensured the detection of a consistent pattern implicating prefrontal cortex hypodopaminergia in genesis of the cognitive abnormality in schizotypy.

9.5. Hypothesis 4: Cognitive impairment in schizophrenia is part of a larger information processing abnormality

The rationale for this hypothesis rests on growing evidence against a centralised aberration driving the various deficits and symptoms in schizophrenia. Instead, the pattern of behavioural, structural and cognitive abnormalities in this syndrome are more consistent with a distributed neural defect affecting most if not all cortical areas and levels of neural functioning.

9.5.1. Prediction 4.1:

Information encoding in both schizotypes and schizophrenia patients is associated with gross electrophysiological abnormalities – reductions in early visual ERPs

One set of results in schizophrenia that has been particularly difficult to reconcile with a localised prefrontal cortex abnormality are the reports of purely perceptual problems in patients (Javitt 2009). Experiments using EEG and MEG have demonstrated electrophysiological correlates of these early perceptual deficits (Javitt 2009). It is therefore possible that a pervasive information processing abnormality may underpin both the perceptual and higher-order executive problems in schizophrenia. The relevance of this hypothesis to the schizophrenia spectrum model was tested by examining the characteristics of early visual information processing in high schizotypes and schizophrenia patients. In line with suggestions of visual processing deficits being trait markers of schizophrenia (Yeap et al. 2008), we hypothesised that both patients and high schizotypes will have abnormal early visual evoked potentials.

The experiment in Chapter 8 replicated previous reports of attenuated P1 visually evoked potential in schizophrenia patients (Yeap et al. 2008). P1 is considered an indicator of the quality of the early visual processing, underpinning basic pattern detection. Reductions of P1 amplitude have been reported in multiple sclerosis (Fulgente et al. 1996; Weinstock-Guttman et al. 2003) and in patients with prefrontal cortical lesions (Barcelo et al. 2000), providing evidence for the involvement of sensory and prefrontal cortices, respectively. This suggests that the neural generators

of P1 are modulated by converging bottom-up and top-down projections and such a deficit may potentially be caused by a localised (prefrontal or sensory visual cortex aberration) or a distributed abnormality. Therefore, from a pathophysiological point of view the P1 deficit does not contribute significantly to the debate of whether a centralised or a distributed abnormality contributes to symptoms of schizophrenia. Decomposing the temporal and spatial characteristics of the signal that constitutes P1 potential could help address this issue, an approach we have taken in the analysis aimed at testing Hypothesis 5.

Whatever the underlying pathology of the P1 amplitude reduction in schizophrenia, the results from Chapter 6 demonstrate that it is present across the schizophrenia spectrum. The finding of P1 deficit in a psychometrically defined schizotypy argues that the same finding in schizophrenia patients in Chapter 8 and previous studies is not the result of repeated psychotic episodes, chronic medication or profound negative symptoms. Instead, the aberration is more likely to be a trait marker of schizophrenia, a biological manifestation of the core pathophysiology associated with the risk for schizophrenia. In support of this conclusion, one study found a P1 reduction in a sample of first-degree relatives of schizophrenia patients (Yeap et al. 2006). In conclusion, we consider the findings from Chapters 6 and 8 to support our prediction that the ERP abnormality will be present across the schizophrenia spectrum.

9.5.2. Prediction 4.2:

Early perceptual deficits correlate with cognitive deficits

The second prediction focused on the relationship between the quality of early visual processing and cognitive performance. Specifically, we predicted that P1 amplitude would correlate with performance on the WM task. This was based on two previous studies showing that P1 amplitude predicts cognitive performance in schizophrenia patients (Haenschel et al. 2007; Butler et al. 2009). The results from Chapters 6 and 8 in this respect were inconclusive. In Chapter 6 we found a modest correlation between WM task performance and the P1 amplitude. However, this relationship was not replicated in Chapter 8 for either of the two groups. One possible explanation for this discrepancy is the decision to use the P1 amplitude of the correct trials only. If a true

relationship between P1 and cognition exists, one would expect to see a lower P1 for the incorrect trials. This type of analysis however is restricted by the number of incorrect trials in the healthy volunteer groups. Low and average schizotypes had less than 10 % error rate leaving far too few trials for a reliable statistical comparison. The schizotypy and schizophrenia groups made more incorrect trials. The analysis of incorrect trials in these populations however is limited by the possibility that the participants may not have been attending the trials at all. Therefore, the electrophysiological information from these trials may be irrelevant to the question of whether encoding deficits correlate with cognitive performance.

9.5.3 Limitations to the data corroborating with Hypothesis 4

One approach that may clarify the relationship between P1 and cognition would require the administration of a more challenging cognitive task to healthy volunteers only. Careful design of the task could ensure that the volunteers are making a similar number of correct and incorrect trials. A simple t-test might be sufficient to demonstrate a difference in the amplitude of the P1 potentials between correct and incorrect trials.

In conclusion, we believe that our findings support the case that the schizophrenia spectrum is characterised by broad information processing abnormalities, as manifested by the reduction in P1 potential amplitude. The predictive validity of such indicators of early visual processing with regards to cognitive performance may need further clarification.

9.6. Hypothesis 5: The information processing deficit is underpinned by dysconnectivity

As mentioned in the previous section, the finding of a P1 abnormality across the schizophrenia spectrum makes no assumption regarding its pathophysiology: either localised or distributed abnormality could cause a P1 deficit. Based on the mounting evidence of dysconnectivity in schizophrenia, Hypothesis 5 proposed that the early

visual deficits in the schizophrenia spectrum are the product of a distributed, rather than a localised deficit.

This hypothesis was addressed by analysing the local and long-range oscillatory patterns during visual perception in a sample of high schizotypy individuals (Chapter 7) and schizophrenia patients (Chapter 8).

9.6.1. Predictions 5.1 and 5.2.

Prediction 5.1: Schizotypes and schizophrenia patients both have local sensory cortex connectivity abnormalities: abnormalities in the power and PLF of neural oscillations.

Prediction 5.2: Both groups have evidence of dysfunctional long-range connectivity during tasks that require top-down modulation: down-regulation of networks connecting the sensory and higher-order cortices

In both studies there was a very similar pattern of local sensory cortex abnormalities in the schizotypy and schizophrenia samples. There was evidence for PLF and power reduction in early theta band activity (approximately 150–250 ms post-stimulus). This burst of activity had bilateral occipital distribution, similar to the P1 potential which was also abnormal in these two groups. This observation and the studies showing that theta and alpha band synchronization give rise to the P1 potential (Klimesch et al. 2004; Gruber et al. 2005), suggest that the theta band results are oscillatory correlates of the P1 potential reduction. An interesting finding in our studies was that both the high schizotypes and schizophrenia patients lacked a normally occurring up-regulation of the theta band visual cortex response with task demand. These results argue in favour of a significant top-down contribution to the deficit.

In addition to the theta band results, oscillatory abnormalities were also evident in beta and gamma frequency bands, particularly in respect to the PLF. This higher frequency activity burst occurred earlier than the theta band activity and had a central

occipital distribution. This evidence suggested that the observed higher-frequency activity represented a process that was not accounted for by the ERP analysis. The occipital beta and gamma band activity was also correlated with an increase in activity at a fronto-central site that occurred at the same time window and frequencies range. This correlation in activity was interpreted as an indication that the two regions (central-occipital and fronto-central) were functionally coupled during the earliest stages of perception. The fact that they precede the theta band activation, as well as the P1 and N1 potentials, suggests that this fronto-occipital network may be involved in a top-down driven preparation of the visual cortex for stimulus encoding. This interpretation would be in line with research showing that perception in schizophrenia patients is constrained to a lesser extent by top-down factors (Dima et al. 2009; Dima et al. 2010). The findings from Chapter 7 extend this to schizotypy individuals and suggest that the perceptual problems in the schizophrenia spectrum may be primarily the result of a top-down dysfunction.

9.6.2. Limitations to the data corroborating with Hypothesis 5

The issue of whether this top-down dysfunction is the product of a localised higher-order abnormality, e.g. prefrontal cortex or a dysfunctional long-range connectivity is not directly addressed by the analyses featured in Chapters 7 and 8. However, the fact that PLF but not power is reduced argues in favour of a disorder of connectivity. If a localised prefrontal cortex was driving the dysfunction, as in the case of prefrontal cortex lesions, one would expect a reduction in the power of the oscillations. Instead the results reveal a pattern of increased variability of the neural responses in two functionally correlated brain regions. This pattern is consistent with generalised dysconnectivity aberration that leads to inconsistent neural activity on both a local and a global level. However, the data supporting such interpretation is, so far, indirect and more focused research is needed to determine the origin of top-down dysfunction in schizophrenia.

Experiments using pharmacological or transmagnetic stimulation (TMS) challenges in healthy volunteer populations may be useful in exploring the putative role of top-down dysfunction in the pathogenesis of schizophrenia. Firstly, a glutamate

antagonist, such as ketamine may be used to induce a temporary hypodopaminergic state in healthy volunteers (See Chapter 3 for detailed review). As glutamate is the major excitatory neurotransmitter (Meldrum 2000), it has been argued that such an intervention would induce a connectivity deficit that will be distributed and not specific to a brain region. Therefore, if a ketamine challenge replicates the pattern of oscillatory abnormality observed in the schizophrenia spectrum, it could be claimed that the top-down dysfunction is indeed the product of a generalised dysconnectivity.

The results of this experiment could be complemented by a study using TMS to induce a localised disruption to the fronto-central topographical region described in Chapters 7 and 8. If the top-down dysfunction in schizophrenia is the product of a localised disruption in this brain region, one would predict that the TMS would recreate the PLF oscillatory abnormalities reported in the current thesis. Alternatively, if dysconnectivity is implicated then the TMS-driven abnormalities in the occipital cortex should be of a different character, possibly involving reductions in both PLF and power of occipital higher frequency band oscillations.

In conclusion, the results from Chapters 7 and 8 broadly support the predictions in regards to Hypothesis 5: there was evidence for a local sensory cortex dysconnectivity underlying the early information processing abnormalities in the schizophrenia spectrum. In addition, the pattern of abnormalities suggested that an earlier, top-down mediated process may be implicated in the sensory cortex dysfunction. Therefore the results suggest a dysconnectivity mechanism in the pathophysiology of this top-down abnormality, but more research is needed to provide corroborative evidence for this.

9.7. A proposal for a framework of the relationships between the various manifestations of schizophrenia

Overall, the current findings showed that schizotypy is associated with abnormalities in two cognitive functions – working memory and inhibition. The ERP experiments indicated that these cognitive deficits are part of a larger pattern of information processing abnormalities affecting local and long-range connectivity. These abnormalities appear to be continuously distributed in the population and are likely to be correlated with psychopathological indicators of risk for schizophrenia, such as schizotypal personality traits.

One framework to try and explain the relationship between these manifestations of the schizophrenia spectrum phenotype in presented in Figure 9.4. The cause of the disorder is likely to be the product of an interaction between genetic and environmental factors resulting in an abnormality that affects normal neurodevelopment (Tandon et al. 2009). This neurodevelopmental abnormality has variable severity according to the number of risk and protective factors and is distributed continuously in the population. A key manifestation of this core developmental abnormality is an abnormality of inter-neuronal connectivity, affecting the capacity of spontaneous neural oscillatory activity to transmit information effectively (Andreasen 1999). Oscillatory activity of the glutamatergic pyramidal cortical cells is governed primarily by the activity of GABA-mediated inter-neurons (Fries et al. 2007). Therefore, dysconnectivity is likely to involve both these neurotransmitter systems early in the pathophysiological cascade (Deakin et al. 1989; Krystal et al. 1999). The deficit brought about by a neural connectivity defect is likely to be pervasive and could account for the various manifestations of schizophrenia, including the aberration of early information processing (e.g. reductions in P1 peak amplitude), executive function abnormalities (e.g. working memory and inhibition deficits), as well as the various psychopathological features of the schizophrenia spectrum disorders (e.g. disorganised behaviour, cognitive-perceptual and interpersonal symptoms). All these pathophysiological events happen before the development of the psychotic illness or even in at-risk individuals who will ultimately remain unaffected by psychotic disorders. The gravity of the original risk factors, or

experiencing additional environmental insults, may cause certain individuals from this at-risk group to develop the ultimate complication of the basic neurodevelopmental abnormality – schizophrenia. The development of psychotic illness leads to a dramatic increase in severity of the trait abnormalities, as well as the emergence of new, state-specific deficits.

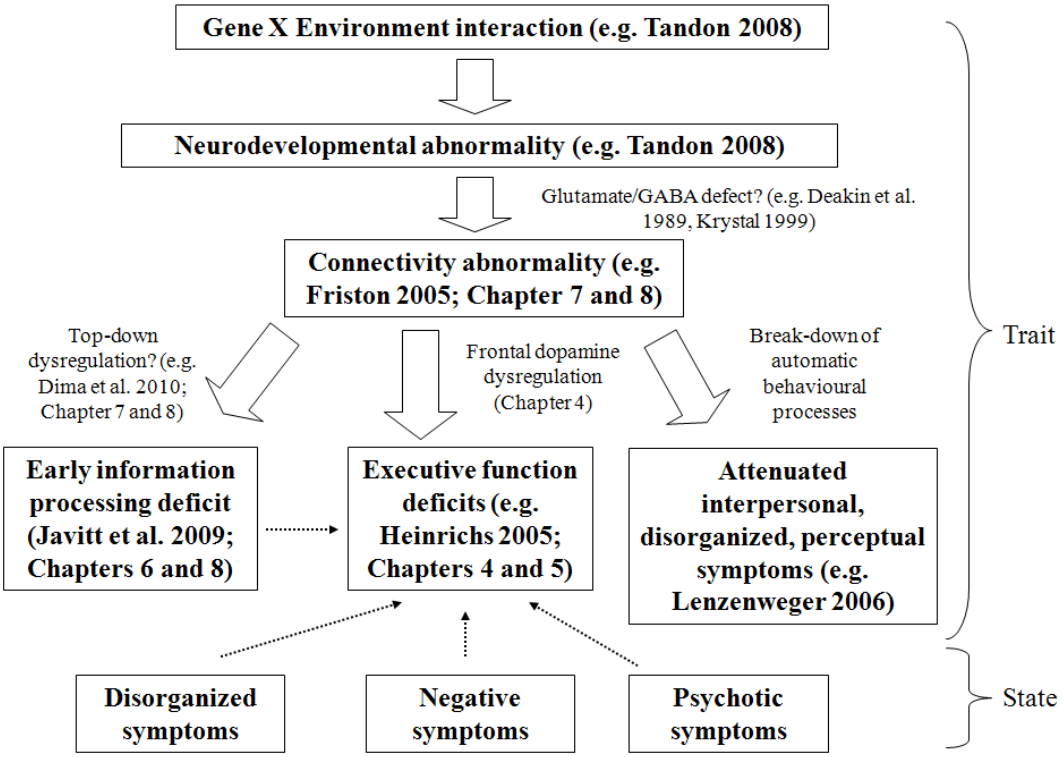

Figure 9.4. Proposed framework to explain the relationships between the various manifestations of schizophrenia. Dysfunctional connectivity with a neurodevelopmental pathogenesis drives diverse trait abnormalities. Transition from the vulnerability stage into psychosis manifests itself through state-related symptoms that augment the expression of the trait abnormalities.

9.8. Relevance of the findings to proof-of-concept biomarker studies in the schizophrenia spectrum disorders

The main focus of the thesis was the development of biomarkers to objectively and reliably define the core schizophrenia pathology, as well as foster drug development through proof-of-concept studies in surrogate populations. Cognitive biomarkers were the measures of interest due to their relevance to the key unmet need of cognitive impairment in schizophrenia and the good evidence for similar cognitive deficits in the surrogate population of schizotypal individuals. Biomarkers are evaluated in terms of their sensitivity to the disease process and therapeutic intervention, specificity and reliability. The following section will provide a review of the evidence presented in this thesis in respect to the extent that the behavioural cognitive and electrophysiological measures of interest satisfy these criteria.

9.8.1. Sensitivity to the schizophrenia spectrum phenotype: Neuropsychological measures

The experiments showed that tasks probing several but not all cognitive functions can be used to detect the schizophrenia spectrum phenotype. Working memory tasks stand out as the most reliable in this respect, but caution should be exerted in the design of the paradigm. As Chapter 4 and 5 showed, tasks that allow only brief encoding (e.g. N-back) may be more suitable than paradigms with unlimited stimulus presentation (SWM).

The results also demonstrate that the antisaccade task was sensitive to the schizophrenia spectrum phenotype. However, schizotypy effect was evident only in respect to the antisaccade error rate, but not in other eye-movement measures such as spatial accuracy or latency of the saccades. This implies that the detected abnormality may be due to a general inhibitory deficit rather than an eye-tracking dysfunction per se. Therefore, paradigms probing inhibition may be useful as biomarkers in schizotypy proof of concept studies.

Measures such as SAT and SPEM appear to be sensitive to state- and genetic-risk related abnormalities and their use in proof of concept studies in schizotypy may be limited.

An important consideration that was shown to affect the sensitivity of a biomarker is the choice of control group. Specifically, choosing an average over a low schizotypy group may obscure the schizotypy effect. Therefore in proof of concept studies the sensitivity of working memory and inhibitory paradigms may benefit significantly by instead comparing low and high schizotypy groups.

9.8.2. Sensitivity to the schizophrenia spectrum phenotype: Electrophysiological measures

The results from Chapter 6 and 8 suggest that the amplitude of the P1 visual evoked potential peak is a sensitive measure of the information processing deficit associated with schizophrenia and schizotypy. This is in line with previous research showing that the P1 deficit is highly replicable in schizophrenia patients (Yeap et al. 2008). P1 could be used in proof of concept studies as a method to screen for individuals with early information processing deficits. Combining this approach with other indicators of risk for cognitive impairment, such as schizotypy, could allow the identification of groups with homogeneous schizophrenia spectrum-related cognitive impairment. Equally, P1 in itself could be used as a biomarker to detect the effect of drugs designed to improve cognitive abilities through efficient information encoding.

The evoked oscillations also distinguished well schizophrenia spectrum individuals from healthy volunteers (Chapter 7 and 8). Out of the two outcome variables of oscillatory activity (power and PLF), PLF appeared to be the more sensitive measure, particularly in the higher-frequency bands (beta and gamma). The specific topographical distribution and timing of the beta and gamma PLF abnormalities suggested that they may be biomarkers for a top-down dysfunction in the schizophrenia spectrum. Power differences were noted mainly in respect to the theta band oscillations suggesting that theta band activity may be the oscillatory correlate of the P1 deficit.

Therefore, proof of concept studies in schizotypy could use theta band power and PLF to confirm and possibly augment the sensitivity of the P1 peak biomarker. Additionally, beta and gamma band PLF could be employed to assess the potential of interventions aimed am improving long-range connectivity in schizophrenia.

9.8.3. Sensitivity to drug challenges: Neuropsychological measures

The data from Chapter 4 showed that tasks sensitive to the schizophrenia spectrum phenotype are also responsive to psychotropic challenges. Specifically, acute enhancement of dopamine function was associated with improvement of cognitive function while dopamine antagonism led to worsening of cognition. These data support the idea that cognitive biomarkers probing working memory and inhibition-related cognitive processes are adequate outcome measures for the assessment of cognitive enhancing agents in schizophrenia spectrum populations.

9.8.4. Sensitivity to drug challenges: Electrophysiological measures

The current thesis did not explore the sensitivity of the electroencephalographic measures to drug challenge, and this is a recognised limitation. Two studies addressing this are underway at the point of the submission of this thesis. The first one examines the effect of premedication with risperidone on the cognitive and electroencephalographic effects of the NMDA-receptor antagonist ketamine. The second one probes only the effects of ketamine on ERP and evoked oscillatory activity using the same WM task as the one reported in Chapter 6, 7 and 8.

9.8.5. Specificity to the schizophrenia spectrum: Neuropsychological and electrophysiological measures

The current thesis did not address the issue of specificity of the behavioural and electroencephalographic biomarkers and this represents another limitation. The available evidence suggests that cognitive impairment is present in a number of

mental health diagnostic entities (Martinez-Aran et al. 2004) and this pattern is likely to extend to connectivity measures.

The greatest promise for specificity may lie in biomarkers that probe for topographical and temporal patterns of neural connectivity which may be different in the separate major psychiatric disorders. The down-regulated fronto-occipital PLF network in schizotypy may be a particularly promising biomarker in this respect. More research is needed to test the hypothesis that major psychiatric disorders, such as bipolar disorder and schizophrenia, differ in the patterns of their long-range connectivity.

9.8.6. Test-retest and inter-site reliability: Neuropsychological and electrophysiological measures

The current thesis did not investigate the test-retest reliability of the two types of biomarkers. The available evidence suggests that executive function and eye-tracking measures have good reliability (See Chapter 3 for detailed review). More research is needed to establish the reliability parameters for the electroencephalographic biomarkers, however.

Chapter 4 examined the inter-site reliability in respect to the cognitive biomarkers and no significant differences were noted between the three UK sites. The analysis of the eye-tracking data from the same dataset did not find any effects of site either. Inter-site reliability of the electroencephalographic measures was not explored and this is another area that will require clarification before these biomarkers can be used in proof of concept studies.

9.9. Future research directions

The work featuring in this thesis can be extended in a variety of directions, some of which have already been touched upon.

Firstly, future research should continue to characterise the pathophysiology of the information processing abnormality in the schizophrenia spectrum. As it was mentioned previously, the work in this thesis suggests a distributed rather than localised cause but falls short of unequivocally proving this. Section 9.6.2 outlined two complementary experiments using NMDA-challenge and TMS that may help to address this limitation of the current thesis. In addition, further analysis of the datasets reported in Chapters 6, 7 and 8 may provide more evidence to support either hypothesis. One approach would be to analyse the inter-electrode coherence within and between the prefrontal and occipital cortices in the period immediately before the onset of the stimulus. Reduced within-prefrontal cortex synchrony that precedes the fronto-occipital network activation would argue in favour of primary localised prefrontal cortex deficit. Simultaneous disruption of intra- and inter-regional synchrony would serve the case of a dysconnectivity deficit. Additionally, examination of the inter-electrode coherence and induced oscillations during the delay periods of the WM paradigm could indicate whether the schizophrenia spectrum individuals fail to support distributed or localised prefrontal cortex networks during sustained cognitive effort.

Secondly, as it was outlined earlier, the question of whether the frontal hypodopaminergia trait is continuously distributed in the general population is still unclear. Addressing this question using a study, such as the one suggested in section 9.3. (dopamine agonist challenge of cognitive performance in low, average and high schizotypy) could help define the neurotransmitter basis of the risk for schizophrenia. The results of such a study could help to map the line beyond which mental health states become abnormal. It could also help to define the likely benefits and ethical caveats associated with cognitive enhancement in the general population.

Thirdly, the lack of a schizotypy effect on the SPEM task in Chapter 5 indicates the complex link between genetic and psychopathological risk for schizophrenia (Thaker et al. 1996). Some authors have already argued that perhaps two types of schizotypy exist in respect to their genetic background - 'true genetic' and 'wild' types - and that distinct pathophysiological mechanisms may be involved (Bergman et al. 2000). Future research may focus on defining the relative importance of these factors for the formation of specific cognitive deficits. One design that may be well suited to address this would compare the cognitive performance of four groups of volunteers: i) relatives of patients with high levels schizotypal personality traits; ii) relatives of patients with low levels of schizotypal personality traits; iii) volunteers with no family history of schizophrenia with high levels schizotypal personality traits; iv) volunteers with no family history of schizophrenia with low levels schizotypal personality traits. Recruitment for such a study would be demanding, but its results may provide important information on the contributions of genetics and psychopathological factors to the formation of cognitive and information processing abnormalities.

Fourthly, as outlined in section 9.6, a number of key characteristics that define the usefulness of a biomarker are yet to be explored in respect to the cognitive and electroencephalographic measures used in this thesis. Further exploration of reliability, specificity and sensitivity to drug action is required to justify their use in proof of concept studies of novel cognitive enhancing agents.

A fifth direction would be to further define the causal link between early information processing abnormalities and higher-order cognitive deficits. This type of research would identify the potential for cognitive improvement with therapies aimed at improving the encoding capabilities.

Lastly, the main rationale for pursuing agents rests on the evidence showing that cognitive deficits are linked to worse functional outcome (Green 1996). There is however relatively little evidence that improving cognition in developed cases of schizophrenia will automatically lead to better functional outcome (Breier 2005). Meta-analyses and reviews of studies using cognitive remediation therapy to improve cognition in schizophrenia have indicated that modest improvement in cognitive abilities does not readily translate into better functioning (Kurtz et al. 2001; Pilling et

al. 2002; Krabbendam et al. 2003; McGurk et al. 2007). Therefore, once a compound demonstrates an effect on cognition, one of the next key research priorities would be to explore its relevance to the ultimate unmet need in schizophrenia: functional outcome.

9.10. Conclusion

In conclusion, both cognitive and electroencephalographic biomarkers showed good sensitivity to the schizophrenia spectrum phenotype. Together with the evidence for sensitivity to drug action in the case of the cognitive measures, these results argue in favour of the feasibility of proof of concept studies using such biomarkers to detect the effect of novel agents on cognition in schizophrenia spectrum populations. The results in this thesis indicate that several key considerations should be taken into account when designing a proof of concept study in schizotypy. These are as follows: i) choice of biomarkers that probe trait rather than state-dependent cognitive abnormalities; ii) manipulation of the difficulty of a cognitive biomarker, to avoid floor or ceiling effects; iii) Choice of control group that would allow the demonstration of maximum schizotypy effect; iv) Inclusion of a dopamine enhancing comparator drug to examine critically the benefit provided by the novel compound.

The lack of specificity of the biomarkers evaluated here to schizophrenia probably reflects the non-specific nature of the cognitive abnormalities in mental health disorders. This should not be solely as a limitation, given that any agents found to be effective in improving cognition in one psychiatric population are likely to be beneficial in other mental health disorders.

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APPENDIX 1: Schizotypy Personality Questionnaire (SPQ)

Please answer each of the items by circling either Yes or No. Answer **all** items even if unsure of your answer. When you have finished, check over each one to make sure that you have answered them.

1. Do you sometimes feel that things you see on the TV or read in the newspaper have a special meaning for you?	Yes	No
2. I sometimes avoid going to places where there will be many people because I will get anxious.	Yes	No
3. Have you had experiences with the supernatural?	Yes	No
4. Have you often mistaken objects or shadows for people, or noises for voices?	Yes	No
5. Other people see me as slightly eccentric (odd).	Yes	No
6. I have little interest in getting to know other people.	Yes	No
7. People sometimes find it hard to understand what I am saying.	Yes	No
8. People sometimes find me aloof and distant.	Yes	No
9. I am sure I am being talked about behind my back.	Yes	No
10. I am aware that people notice me when I go out for a meal or to see a film.	Yes	No
11. I get very nervous when I have to make polite conversation.	Yes	No
12. Do you believe in telepathy (mind-reading)?	Yes	No
13. Have you ever had the sense that some person or force is around you, even though you cannot see anyone?	Yes	No
14. People sometimes comment on my unusual mannerisms and habits.	Yes	No
15. I prefer to keep to myself.	Yes	No
16. I sometimes jump quickly from one topic to another when speaking.	Yes	No
17. I am poor at expressing my true feelings by the way I talk and look.	Yes	No
18. Do you often feel that other people have got it in for you?	Yes	No
19. Do some people drop hints about you or say things with a	Yes	No

double meaning?		
20. Do you ever get nervous when someone is walking behind you?	Yes	No
21. Are you sometimes sure that other people can tell what you are thinking?	Yes	No
22. When you look at a person, or yourself in a mirror, have you ever see the face change right before your eyes?	Yes	No
23. Sometimes other people think I am a little strange?	Yes	No
24. I am mostly quiet when with other people.	Yes	No
25. I sometimes forget what I am trying to say	Yes	No
26. I rarely laugh and smile.	Yes	No
27. Do you sometimes get concerned that friends or co-workers are not really loyal or trustworthy?	Yes	No
28. Have you ever noticed a common event or object that seemed to be a special sign for you?	Yes	No
29. I get anxious when meeting people for the first time.	Yes	No
30. Do you believe in clairvoyancy (psychic forces, fortune telling)?	Yes	No
31. I often hear a voice speaking my thoughts aloud?	Yes	No
32. Some people think I am a very bizarre person.	Yes	No
33. I find it hard to be emotionally close to other people.	Yes	No
34. I often ramble on too much when speaking.	Yes	No
35. My "non-verbal" communication (smiling and nodding during a conversation) is poor.	Yes	No
36. I feel I have to be on my guard even with my friends.	Yes	No
37. Do you sometimes see special meaning in advertisements, shop windows, or in the way things are arranged around you?	Yes	No
38. Do you often feel nervous when you are in a group of unfamiliar people?	Yes	No
39. Can other people feel your feelings when they are not there?	Yes	No
40. Have you ever seen things invisible to other people?	Yes	No

41. Do you feel that there is no one you are really close to outside of your immediate family or people you can confide in or talk to about personal problems?	Yes	No
42. Some people find me a bit vague and elusive during a conversation.	Yes	No
43. I am poor at returning social courtesies or gestures.	Yes	No
44. Do you often pick up hidden threats or put-downs from what people say or do?	Yes	No
45. When shopping do you get the feeling that other people are taking notice of you?	Yes	No
46. I feel very uncomfortable in social situations involving unfamiliar people.	Yes	No
47. Have you had experiences with astrology, seeing the future, UFOs, ESP or a sixth sense?	Yes	No
48. Do everyday things seem unusually large or small?	Yes	No
49. Writing letters to friends is more trouble than it is worth.	Yes	No
50. I sometimes use words in unusual ways.	Yes	No
51. I tend to avoid eye contact when conversing with others.	Yes	No
52. Have you found that it is best not to let other people know too much about you?	Yes	No
53. When you see people talking to each other, do you often wonder if they are talking about you?	Yes	No
54. I would feel very anxious if I had to give a speech in front of a large group of people.	Yes	No
55. Have you ever felt that you are communicating with another person telepathically (by mind reading)?	Yes	No
56. Does your sense of smell sometimes become unusually strong?	Yes	No
57. I tend to keep in the background on social occasions.	Yes	No
58. Do you tend to wander off the topic when having a conversation?	Yes	No
59. I often feel that others have it in for me.	Yes	No

60. Do you sometimes feel that other people are watching you?	Yes	No
61. Do you ever suddenly feel distracted by distant sounds that you are not normally aware of?	Yes	No
62. I attach little importance to having close friends.	Yes	No
63. Do you sometimes feel that people are talking about you?	Yes	No
64. Are your thoughts sometimes so strong that you can almost hear them?	Yes	No
65. Do you often have to keep an eye out to stop people from taking advantage of you?	Yes	No
66. Do you feel that you are unable to get "close" to people?	Yes	No
67. I am an odd, unusual person.	Yes	No
68. I do not have an expressive and lively way of speaking.	Yes	No
69. I find it hard to communicate clearly what I want to say to people.	Yes	No
70. I have some eccentric (odd) habits.	Yes	No
71. I feel very uneasy talking to people I do not know well.	Yes	No
72. People occasionally comment that my conversation is confusing.	Yes	No
73. I tend to keep my feelings to myself.	Yes	No
74. People sometimes stare at me because of my odd appearance.	Yes	No

APPENDIX 2: Brief Version of the SPQ (SPQ-B)

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

1. People sometimes find me aloof and distant.
2. Have you ever had the sense that some person or force is around you, even though you cannot see anyone?
3. People sometimes comment on my unusual mannerisms and habits.
4. Are you sometimes sure that other people can tell what you are thinking?
5. Have you ever noticed a common event or object that seemed to be a special sign for you?
6. Some people think that I am a very bizarre person.
7. I feel I have to be on my guard even with friends.
8. Some people find me a bit vague and elusive during a conversation.
9. Do you often pick up hidden threats or put-downs from what people say or do?
10. When shopping do you get the feeling that other people are taking notice of you?
11. I feel very uncomfortable in social situations involving unfamiliar people.
12. Have you had experiences with astrology, seeing the future, UFOs, ESP or a sixth sense?
13. I sometimes use words in unusual ways.
14. Have you found that it is best not to let other people know too much about you?
15. I tend to keep in the background on social occasions.
16. Do you ever suddenly feel distracted by distant sounds that you are not normally aware of?
17. Do you often have to keep an eye out to stop people from taking advantage of you?
18. Do you feel that you are unable to get "close" to people?
19. I am an odd, unusual person.
20. I find it hard to communicate clearly what I want to say to people.
21. I feel very uneasy talking to people I do not know well.
22. I tend to keep my feelings to myself.

APPENDIX 3: O-LIFE Questionnaire

These questions relate to your thoughts, feelings, experiences and preferences. There are no right or wrong answers or trick questions so please be as honest as possible. For each question please choose either YES or NO and circle this on the form. Please do not spend too much time thinking about it – choose the answer closest to your own.

	Experience	
1. Do you often hesitate when you are going to say something in a group of people whom you more or less know?	Yes	No
2. Do you often overindulge in alcohol or food?	Yes	No
3. Are the sounds you hear in your daydreams really clear and distinct?	Yes	No
4. Do you enjoy many different kinds of play and recreation?	Yes	No
5. Do your thoughts sometimes seem real as actual events in your life?	Yes	No
6. Does it often happen that nearly every thought immediately and automatically suggests an enormous number of ideas?	Yes	No
7. When in a group of people do you usually prefer to let someone else be the centre of attention?	Yes	No
8. Do you frequently have difficulty in starting to do things?	Yes	No
9. Has dancing or the idea of it always seemed dull to you?	Yes	No
10. When you catch a train do you often arrive at the last minute?	Yes	No
11. Is trying new foods something you have always enjoyed?	Yes	No
12. Do you often change between intense liking and disliking the same person?	Yes	No
13. Have you ever cheated at a game?	Yes	No
14. Are there very few things that you have ever really enjoyed doing?	Yes	No
15. Do you at times have an urge to do something harmful or shocking?	Yes	No
16. Do you often worry about things you should not have done or said?	Yes	No

17. Are your thoughts sometimes so strong that you can almost hear them?	Yes	No
18. Are you usually in an average sort of mood, not too high and not too low?	Yes	No
19. Would you take drugs, which may have strange or dangerous effects?	Yes	No
20. Do you think you could learn to read other's minds if you wanted to?	Yes	No
21. When in a crowded room, do you often have difficulty in following a conversation?	Yes	No
22. No matter how hard you try to concentrate, do unrelated thoughts creep into your mind?	Yes	No
23. Are you easily hurt when people find fault with you or the work you do?	Yes	No
24. Do you stop to think things over before doing anything?	Yes	No
25. Have you ever felt that you have special, almost magical powers?	Yes	No
26. Are you much too independent to really get involved with other people?	Yes	No
27. Do ideas and insights sometimes come to you so fast that you cannot express them all?	Yes	No
28. Do you easily lose your courage when criticised or failing in something?	Yes	No
29. Can some people make you aware of them just by thinking about you?	Yes	No
30. Does a passing thought ever seem so real it frightens you?	Yes	No
31. Have you ever blamed someone for doing something you know was really your fault?	Yes	No
32. Are you a person whose mood goes up and down easily?	Yes	No
33. Does your voice ever seem distant or far away?	Yes	No
34. Do you think having close friends is not as important as some people say?	Yes	No
35. Are you rather lively?	Yes	No
36. Are you sometimes so nervous that you are "blocked"?	Yes	No
37. Do you find it difficult to keep interested in the same thing for a	Yes	No

long time?		
38. Do you dread going into a room by yourself where other people have already gathered and are talking?	Yes	No
39. Does it often feel good to massage your muscles when they are tired or sore?	Yes	No
40. Do you sometimes feel that your accidents are caused by mysterious forces?	Yes	No
41. Do you like mixing with people?	Yes	No
42. On seeing soft thick carpet have you sometimes had the impulse to take off your shoes and walk barefoot on it?	Yes	No
43. Do you often have difficulties in controlling your thoughts?	Yes	No
44. Do the people in your daydreams seem so true to life that you sometimes think they are real?	Yes	No
45. Are people usually better off if they stay aloof from emotional involvements with people?	Yes	No
46. Can just being with friends make you feel really good?	Yes	No
47. Is your hearing sometimes so sensitive that ordinary sounds become uncomfortable?	Yes	No
48. Have you often felt uncomfortable when your friends touch you?	Yes	No
49. When things are bothering you do you like to talk to other people about it?	Yes	No
50. Do you have many friends?	Yes	No
51. Would being in debt worry you?	Yes	No
52. Do you think people spend too much time safeguarding their future with savings and insurance?	Yes	No
53. Do you ever have the urge to break or smash things?	Yes	No
54. Do you often feel that there is no purpose to life?	Yes	No
55. Do you worry about awful things that might happen?	Yes	No
56. Have you ever felt the urge to injure yourself?	Yes	No
57. Would it make you nervous to play the clown in front of other people?	Yes	No
58. Have you felt that you might cause something to happen just by thinking too much about it?	Yes	No

59. Have you had very little fun from physical activities like walking, swimming or sports?	Yes	No
60. Do you feel sometimes so good at controlling others that it sometimes scares you?	Yes	No
61. Are you easily distracted from work by daydreams?	Yes	No
62. Are you easily confused if too much happens at the same time?	Yes	No
63. Do you ever have a sense of vague danger or sudden dread for reasons that you do not understand?	Yes	No
64. Is it true that your relationships with other people never get very intense?	Yes	No
65. Have you sometimes had the feeling of gaining or losing energy when certain people look at you or touch you?	Yes	No
66. Do you worry too long after an embarrassing experience?	Yes	No
67. Do you love having your back massaged?	Yes	No
68. Do you consider yourself to be pretty much an average kind of person?	Yes	No
69. Have you ever taken advantage of someone?	Yes	No
70. Would you like other people to be afraid of you?	Yes	No
71. Have you ever thought you heard people talking only to discover that it was in fact some nondescript noise?	Yes	No
72. Have you occasionally felt that your body did not exist?	Yes	No
73. Do you often feel lonely?	Yes	No
74. Do you often have an urge to hit someone?	Yes	No
75. Do you often experience an overwhelming sense of emptiness?	Yes	No
76. On occasions, have you seen a person's face in front of you when no one was in fact there?	Yes	No
77. Is it fun to sing with other people?	Yes	No
78. Do you often have days when indoor lights seem so bright that they bother your eyes?	Yes	No
79. Have you wondered whether spirits of the dead can influence the living?	Yes	No
80. Do people who try to get to know you better usually give up after a while?	Yes	No

81. Do you often feel ‘fed up’?	Yes	No
82. Have you felt as though your head or limbs were somehow not your own?	Yes	No
83. When you look into the mirror does your face sometimes seem quite different from usual?	Yes	No
84. Do people who drive carefully annoy you?	Yes	No
85. Would you call yourself a nervous person?	Yes	No
86. Can you usually let yourself go and enjoy yourself at a lively party?	Yes	No
87. Do you ever suddenly feel distracted by distant sounds that you are not normally aware of?	Yes	No
88. Do you sometimes talk about things you know nothing about?	Yes	No
89. When in the dark do you often see shapes and forms even though there's nothing there?	Yes	No
90. Have you sometimes sensed an evil presence around you, even though you could not see it?	Yes	No
91. Is it hard for you to make decisions?	Yes	No
92. Do you find the bright lights of a city exciting to look at?	Yes	No
93. Does your sense of smell sometimes become unusually strong?	Yes	No
94. Do you usually have very little desire to buy new kinds of food?	Yes	No
95. Do you ever feel that your speech is difficult to understand because the words are all mixed up and don't make sense?	Yes	No
96. Do you often feel like doing the opposite of what other people suggest, even though you know they are right?	Yes	No
97. Do you like going out a lot?	Yes	No
98. Do you feel very close to your friends?	Yes	No
99. Do you ever feel sure that something is about to happen, even though there does not seem to be any reason for you thinking that?	Yes	No
100. Do you often feel the impulse to spend money which you know you can't afford?	Yes	No
101. Are you easily distracted when you read or talk to someone?	Yes	No
102. Do you feel that making new friends isn't worth the energy it takes?	Yes	No

103. Do you believe in telepathy	Yes	No
104. Do you prefer watching television to going out with other people?	Yes	No

Thank you very much for taking the time and effort to fill this in.

APPENDIX 4: National Adult Reading Test (NART)

Instructions for NART: These words are pronounced differently to how they read. Please speak each word out loud and clearly so that the experimenter can hear. Please try to pronounce each word as best you can even though some of the words may be quite difficult.

List of words (2nd edition)

CHORD	SUPERFLUOUS
ACHE	SIMILE
DEPOT	BANAL
AISLE	QUADRUPED
BOUQUET	CELLIST
PSALM	FACADE
CAPON	ZEALOT
DENY	DRACHM
NAUSEA	AEON
DEBT	PLACEBO
COURTEOUS	ABSTEMIOUS
RAREFY	DETENTE
EQUIVOCAL	IDYLL
NAIVE	PUERPERAL
CATACOMB	AVER
GAOLED	GAUCHE
THYME	TOPIARY
HEIR	LEVIATHAN
RADIX	BEATIFY
ASSIGNATE	PRELATE
HIATUS	SIDEREAL
SUBTLE	DEMESNE
PROCREATE	SYNCOPE
GIST	LABILE
GOUGE	CAMPANILE

APPENDIX 5: Neurocognitive Biomarkers for the MATRICS Domains

N-back task

A computer controls the presentation of a series of alphabet letters on a colour monitor and record responses on clearly marked response keys. Participants are instructed not to respond until they see two specific letters following one another with a varying number of letters between the two target letters. The letters remain on the screen for 1 second and a blank screen of 1 second separates the stimuli. The letters are presented in a centrally and have dimensions of 4 visual degrees vertically and horizontally. This task has three levels of difficulty each increasing the load on working memory. In the 1-back test the two target letters are separated by one letter, in the 2-back test the target letters are separated by two letters and so on. Consequently, the 1-back test exerts the lowest load on working memory and the 3-back task the highest. There are also blocks to control for attending to the task where participants simply need to respond when they see a target letter (attention or 0-back). Before the beginning of the task participants complete a practice trial consisting of 1 block of each condition. During the main task participants complete 3 blocks of each condition (attention, 1-back, 2-back and 3-back). The 12 blocks are intermixed pseudorandomly. At the beginning of each block a title screen informs the participant what the condition is. In each block 14 stimuli are presented pseudorandomly, so that there are 3 target and 11 non-target images. Overall, there is a maximum of 9 correct answers and 33 errors of commission per working memory load. The outcome variables are the percentage of correct responses, number of errors of commission and the latencies of correct and incorrect responses.

Spatial working memory task (SWM)

A computer controls the presentation of stimuli on a colour monitor and records responses made via the computer mouse. Participants are given the task of searching treasure troves for coins. There is the same number of coins as there are treasure chests. The participants attempt to search for all the coins without choosing treasure chests they have previously searched or already found coins in on previous choices. The task has one practise attempt with 3 treasure chests, followed by test blocks which include four repetitions each with four treasure chests, six chests, and eight

chests. Between each block the configuration of the boxes on the page is altered so as to reduce the likelihood of stereotypical searching strategies. The levels of task difficulty are increased by increasing the number of treasure chests to be searched. Once the participants complete four successful choices at each level of task difficulty they move on to the next level of difficulty. The SWM task involves the maintenance and manipulation aspects of working memory. The performance indices for this task are number of completed trials for the 8 treasure chest blocks (maximum score 4), number of within trial errors (already searched a chest within that trial), number of between trial errors (where they have previously found coins), and searching strategy score.

Verbal fluency task

Letter and category verbal fluency and word production is assessed during a succession of one minute periods. For the letter verbal fluency test participants are asked to verbally report as many words as they can beginning with the letters F, A and S in one minute for each letter (FAS condition). The experimenter writes down the words. For the category fluency test participants are first asked to name all the vegetables and animals they can think of in one minute for each category (category naming condition). Participants are then asked to verbally report as many words as they can in one minute, alternately from two categories: fruit and furniture (category swap condition). The main outcome variable of all three conditions is the number of correctly produced words. For the FAS and category naming conditions, the number of set and repetition errors is recorded. The number of correct transitions is an outcome variable in the category swap condition.

APPENDIX 6: Eye Movement Procedures

General Set-up

The eye movement procedures take place in a window-less, light-dimmed, quiet room. The lights are dimmed in order to secure accurate eye movement recordings yet without subjecting the participants to complete darkness.

The general set-up of the procedures involves the participant sitting in a comfortable chair in front of a desk-mounted computer screen. The distance between the participant's eyes and the screen is 57 cm. Participants with contact lenses or glasses are allowed to wear these during assessments.

In order to minimise head and body movements the participant is required to keep still and rest their arms on the desk. Additionally, a custom built chin rest is used to further reduce head movements.

Equipment for the Recording of Eye Movements

Eye movements will be recorded using an eye movement tracker such as the Eyelink 1000 Desktop System (SR Research Ltd., Mississauga, Ontario, Canada). The Eyelink system is a video-based pupil tracker with high resolution and fast data acquisition (1000 Hz sampling frequency). The "desktop mount" version of this well-established and widely used system avoids any contact between hardware and the participant's head as it tracks the participant's eye with a camera positioned below the monitor on the desktop. This set-up minimises any discomfort to the participant.
The research team at the Institute of Psychiatry has previously conducted several hundred experimental sessions examining eye movements in healthy individuals and patients with schizophrenia (Ettinger et al. 2003, 2004a,b, 2005, 2006). Only minimal problems with compliance have been encountered in the patient and volunteer groups, and there are no reports of discomfort or physical damage to any participants.

Procedure

The participant is seated in the chair and is given some preliminary instructions concerning the eye movement experiments. These instructions include a brief lay language description of the technical principles of eye movement recording, a

statement regarding its risks (e.g. dry eyes), and a brief introduction to the tasks that are to be conducted. Participants are told that they will be required to sit in the chair provided, keep their head in a chinrest, and respond to a simple visual stimulus presented on a computer screen. The eye movement measurement device is shown to the participants. They are also told that they will be given more detailed instructions regarding each individual task as the assessment proceeds.
Once the participant has indicated that they are comfortable with the equipment they are asked to rest their head on the chin rest provided, and to bring their arms forward to rest on the desk (to ensure minimal body movements during the procedures). The chinrest consists of a height-adjustable, small plastic cup shaped to accommodate the participant's chin. The participant is informed that they will have to keep still in that position, moving their head or body as little as possible.

Next the eye-tracker is calibrated. This requires the participant to focus their gaze successively, as instructed by the experimenter, on one of three small dots presented on the computer screen. The stimuli are presented in the mid-horizontal plane on the screen, corresponding to amplitudes of 0°, -12°, and +12° of centre (thus corresponding to three of the target positions later used in the actual tasks). Calibration takes about 5 minutes. Re-calibration (lasting only several seconds) is carried out before each task.

Once the eye-tracker is calibrated a brief verbal warning is issued by the experimenter and the lights in the room are dimmed. The participant is given a few seconds to adjust their eyes to the new light conditions before the first task begins. Each task is initiated individually by the experimenter. The participant can talk to the experimenter between tasks (but is strongly encouraged not to speak during a task). Anonymised file names are entered for data saving and the task is started once the participant is ready. The experimenter reminds the participant before each new block to keep their head still.

Four different sets of eye movement tasks are carried out, in the following order: (1) fixation, (2) smooth pursuit, (3) prosaccade, and (4) antisaccade (NB: the order can be counter-balanced if necessary).

Stimuli and Tasks

The target stimulus that is displayed on the computer screen consists of a small, white dot of circular shape (0.2° of visual angle), presented against a black background for all tasks.

In the ***fixation task***, the target appears for 30 seconds in each of three locations (centre=0°, left=-12°, right=+12°). The participant is required to keep their eyes on the target as closely as possible.

In the ***smooth pursuit eye movement (SPEM) task*** the target moves horizontally at a sinusoidal waveform (frequency 0.4Hz) across the screen for 60 seconds (range ±12°). The participant is required to keep their eyes on the target as closely as possible. Participants are allowed 10 seconds practice before the actual task begins.

In a ***prosaccade trial*** (or reflexive saccade trial) the target jumps from the central location to a peripheral location (±6°, ±12°). The participant is required to keep their eyes on the target as closely as possible. There are 60 such trials, with each trial lasting on average 2.5 seconds (overall task duration on average is 2.5 minutes). Participants perform 4 practice trials before the actual task.

In an ***antisaccade task*** the target again jumps from the central location to a peripheral location (±6°, ±12°), with the same timing as in the prosaccade task. In this task however, the participant is required to look at the target while it is in the central location and then look immediately in the opposite direction when it jumps to the side. For example, if the target jumps to 12° on the right, the participant has to look to 12° to the left of the centre. Participants perform 4 practice trials before the actual task.

APPENDIX 7: Salience Attribution Test

On the Salience Attribution Test (SAT), participants make a speeded response to the onset of a probe (white square) in order to earn money. The maximum win for all trials is set at £20. Prior to the main test, participants complete a computerized tutorial. Two practice sessions are embedded into the tutorial to familiarize participants with the test and provide a measure of baseline response time (RT). On these practice sessions, a fixation cross appears on the computer screen at the beginning of each trial. Following a variable interval (minimum 0.5 seconds, maximum 1.5 seconds) the probe appeared, and participants respond by pressing a button as quickly as possible. Participants are instructed to try to respond before the box disappears. During the first practice session the probe is on the screen for randomised variable periods, with a maximum duration of 1.5 s, minimum duration 0.5 s and mean duration 1 s. Feedback is provided after 2 s as: (i) "Good" if the participant responds before the box disappears, (ii) "Try to respond faster" if they respond after the box disappears, (iii) "Too early" if they respond before the box appeared, and (iv) "No key pressed" if they do not make a response. On the second practice session, the mean probe duration is set to be the mean RT from the first, ensuring participants are responding as quickly as possible and to link task difficulty to individual performance. The standard deviation (SD) of the fastest half of the trials (SDF) is also calculated, and is used to set the minimum and maximum probe durations for the second practice session (mean from first practice session ± 2*SDF). For the main test, the mean, minimum and maximum probe durations are calculated from the second practice session in the same way. No reinforcement is provided during the practice sessions.

Participants then complete two blocks of 64 trials on the main test, where money is available on 50% of trials. The likelihood that money is available on a trial is signaled by one of four conditioned stimuli (CSs) that appear at the top and bottom of the screen before the onset of the probe. CSs vary on two different visual dimensions: color (blue or red) and shape (animal or household object). Therefore, there are four different types of CS: blue animals; red animals; blue household objects and red household objects. One of these dimensions (e.g. color) is task-relevant so that one level of the dimension is reinforced on 28/32 (87.5%) of the trials while only 4/32

(12.5%) trials of the other are reinforced. For example, if 'color' is the reinforced dimensions, 14/16 blue animals and 14/16 blue household objects will be reinforced, compared to only 2/16 red animals and 2/16 red household objects. The other dimension, in this example 'shape', are task-irrelevant, so that 16/32 (50%) of both levels are reinforced. Participants are not informed of these contingencies.

At the beginning of each trial a fixation cross appeared; after 1000ms, while the fixation cross remains on-screen, one of the four CSs is displayed at the top and bottom of the screen and remains on-screen until the end of the trial. After a variable period of time (between 0.5 and 1.5 s) the probe appears and participants attempt to respond before it disappears. The probe duration is calculated according to the participant's responses on the second practice block, as described above. After 2.25 s, auditory and visual feedback is presented for 1.5 s. Four different versions of the SAT are used, each with a different stimulus feature (blue, red, animal or household object) reinforced with high probability. Each participant is administered the same version for both blocks of the SAT.

If the trial is not reinforced, the message "Sorry – no money available" is displayed. If the trial is reinforced, participants win between 5 and 100 pence, depending on the latency of their response. On reinforced trials where participants either make no response or respond after the probe has disappeared, the message "Missed: 5 pence" is displayed. If participants respond prematurely (<100ms after the onset of the probe), the message displayed is "Too early: 5 pence". On reinforced trials where participants respond before the probe disappears, but slower than their mean RT, the message "Hit – good: 10 pence" is displayed. When participants respond more quickly than their mean RT, the message "Quick – very good: X pence" is displayed (for responses up to 1.0 SDFs faster than their mean) and "Very quick– excellent: X pence" (for responses faster than their mean by 1.5 SDFs). The reward is scaled according to X = 10 + 90 x (mean RT – trial RT)/(3 x SDF), up to a maximum of 100 pence. For example, a response 1 SDF faster than the mean is reinforced with 40 pence, while a response 2 SDFs faster is reinforced with 70 pence. The money won on each trial is added to the participant's running total for that block. On reinforced trials, a 0.5 s tone is sounded, frequency: (300 + (10 x X)) Hz. At the end of each block, participants

indicate, using 10mm visual analogue scales (VAS), their estimate of the reinforcement probabilities for each of the four different CSs.