The National University of Ireland Maynooth

Electrophysiological Correlates of Cognitive Processing in Adolescents Reporting Psychotic-Like Experiences

Thesis submitted to the Department of Psychology, Faculty of Science, in fulfilment of the requirements for the degree of Doctor of Philosophy, National University of Ireland Maynooth.

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My Role within the Adolescent Brain Development (ABD) Study

I was involved in the recruitment process. I travelled to nine primary schools in the Co. Kildare region and gave a ten minute presentation to fifth and sixth class students (i.e. 11-13 year olds, the two most senior primary school classes). The ten minute presentation contained information about the brain and how it changes throughout adolescence. I distributed information packs and assent and consent forms on the first visit to the schools. On the second visit to the schools I collected assent and consent forms and administered the 7-item Adolescent Psychotic-Like Symptom Screener (APSS) and the Strengths and Difficulties (SDQ) questionnaires in the classrooms. I shadowed some of the clinical interviews and helped to administer neuropsychological tests using the MATRICS Consensus Cognitive Battery (MCCB). I administered approximately forty neuropsychological tests. Administration of the MCCB took approximately one hour per participant and included ten tests of cognitive function.

The recruitment from schools in Co. Dublin was carried out by other researchers involved in the overall ABD Study. Clinical interviews using the K-SADS-PL were carried out by researchers trained in the use of the instrument and were conducted at NUI Maynooth and RCSI Education and Research Centre at Beaumont Hospital. The consensus meeting was held by three independent raters (1 psychologist and 2 psychiatrists) who were blind to the information gathered from the interviews and rated PLEs based on the psychosis section of the K-SADS-PL. Neuropsychological tests were also administered by other members of the ABD Study research team.

I mailed information packs to those participants who had indicated that they were interested in taking part in the EEG study. I contacted participants and arranged

appointments for EEG testing. I greeted participants and their parent/guardian when they arrived at the EEG laboratory. I briefed the participants about what participation in the EEG study would involve and I completed the necessary assent and consent forms with the participants and their parent/guardian. I set up the EEG equipment and recorded the data. I designed the Active Auditory Oddball Task and I processed and analysed the data presented in the present thesis.

Publications:

Rawdon, C., Murphy, J., Blanchard, M. M., Kelleher, I., Clarke, M. C., Kavanagh, F., Cannon, M. & Roche, R.A.P. (2013). Reduced P300 amplitude during retrieval on a spatial working memory task in a community sample of adolescents who report psychotic symptoms. *BMC Psychiatry*, *13*, 125.

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List of Abbreviations

A

ABD Study – Adolescent Brain Development Study

AEP – Auditory Evoked Potential

AESOP Study – Aetiology and Ethnicity of Schizophrenia and Other Psychoses Study

ADD – Attention Deficit Disorder

ANOVA – Analysis of Variance

AP – Action Potential

APSS – Adolescent Psychotic-Like Symptom Screener

ARMS – At-Risk Mental State

B

BA – Brodmann's Area

BACS SC – Brief Assessment of Cognition in Schizophrenia: Symbol Coding

BESA – Brain Electrical Source Analysis©

BOLD - Blood-Oxygen-Level-Dependent

BPVS – British Picture Vocabulary Scale

BVMT-R – Brief Visuospatial Memory Test – Revised™

C

CE – Current

C-GAS – Children's Global Assessment Scale

CNV – Contingent Negative Variation

CNVs – Copy Number Variants

COMT – Catechol-O-Methyl Transferase gene

CPT-IP – Continuous Performance Test – Identical Pairs

CRN – Correct Response Negativity

D

DA - Dopamine

DISC -1 – Disrupted in Schizophrenia 1 gene

DSM-III – Diagnostic and Statistical Manual III

DSM-IV – Diagnostic and Statistical Manual IV

DSM-IV-TR - Diagnostic and Statistical Manual IV Text Revision

DSM-5 - Diagnostic and Statistical Manual 5

DTI – Diffusion-Tensor Imaging

E

EEG – Electroencephalography

EOG – Electrooculography

EP –Evoked Potential

EPSP – Excitatory Postsynaptic Potential

ERN – Error-Related Negativity

ERP – Event-Related Potential

F

FA – Fractional Anisotropy

FEP – First-Episode Psychosis

FFT – Fast Fourier Transformation

fMRI – functional Magnetic Resonance Imaging

G

H

HEOG – Horizontal Electrooculography

HVLT-R – Hopkins Verbal Learning Test –Revised ™

I

IPSP – Inhibitory Postsynaptic Potential

J

K

K – Potassium

K-SADS-PL – Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children (6-18 Years) – Present and Lifetime Version

L

LNS – Letter Number Span

LSD - Lysergic acid diethylamide

M

M – Mean

MANOVA – Multivariate Analysis of Variance

MATRICS - Measurement and Treatment Research to Improve Cognition in Schizophrenia

MCCB – MATRICS Consensus Cognitive Battery

MEG – Magnetoencephalography

MMN – Mismatch Negativity

MRI – Magnetic Resonance Imaging

ms – Millisecond

MSP – Most Severe Past

mV - Millivolt

µV – Micro Volt

N

Na – Sodium

NAB – Neuropsychological Assessment Battery ®

NE – Error Negativity

NMDA - N-methyl-D-aspartate

NUIM – National University of Ireland Maynooth

O

P

Pc – Correct Response Positivity

Pe – Error-Positivity

PET - Positron Emission Tomography

PLEs – Psychotic-Like Experiences

PSP – Postsynaptic Potential

Q

qEEG – Quantitative EEG

R

rCBF – regional Cerebral Blood Flow

RCSI – Royal College of Surgeons in Ireland

S

SDQ – Strengths and Difficulties Questionnaire

SEM – Standard Error Mean

SES – Socioeconomic Status

SOP – Speed of Processing

T

THC – delta-9-tetrahydrocannabinol

TIAR – Two-In-A-Row

TMTA – Trail Making Test A

TMTB – Trail Making Test B

TTL – Transistor-Transistor Logic

U

UHR – Ultra High-Risk

V

VEOG – Vertical Electrooculography

W

WM – Working Memory

WMS-III – Wechsler Memory Scale –III

WMS-III SS – Wechsler Memory Scale–III: Spatial Span

WRAT-4 – Wide Range Achievement Test-4

X

Y

Z

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General Abstract

Psychotic disorders are often preceded by impaired cognitive functioning. Self-reported psychotic symptoms during adolescence have been associated with the development of a psychotic disorder in adulthood (Poulton et al., 2000; Welham et al., 2009a; 2009b). Adolescents who report psychotic-like experiences (PLEs; the non-clinical psychosis phenotype) have been shown to share many of the same schizophrenia-related risk factors as patients with schizophrenia (the clinical psychosis phenotype; Kelleher & Cannon, 2011).

The following thesis employs both behavioural and electrophysiological methods in an attempt to uncover possible correlates of PLEs in a community-based sample of young adolescent participants compared to a control group. Electroencephalographic (EEG) recording took place following a detailed clinical interview and neuropsychological testing. Neuropsychological functioning and resting state EEG data were examined. Three tasks which investigate capacities which have been proposed as trait markers for schizophrenia were chosen for use with EEG. These tasks were an Active Auditory Oddball Task, an Implicit Spatial Memory Task and a Spatial Working Memory Task. The present thesis is the first study to examine resting state data and the electrophysiological correlates of auditory and spatial processing in adolescents reporting PLEs.

In Chapter 3 the MATRICS Consensus Cognitive Battery (MCCB) was employed to test group differences on a number of tests of neuropsychological functioning. Chapter 3 also examines quantitative EEG spectral power in the delta (1.5-3.5Hz), theta (3.5-7.5Hz) and alpha (7.5-12.5Hz) frequency bands during resting state recordings in which participants had their eyes open for two minutes and eyes closed for an additional two minutes. Adolescents reporting PLEs scored more poorly on two

measures of speed of processing. No between-group differences were observed in the resting state data at anterior, posterior or fronto-temporal scalp locations.

In Chapter 4 an Active Auditory Oddball Task was employed to test group differences in the P300 event-related potential (ERP) and the N100 auditory evoked potential (AEP). Reduced amplitude of the P300 ERP to target tones has been reported in patients with schizophrenia, first-episode psychosis (FEP), groups at genetic high risk for psychosis and, most recently, in clinical at-risk groups. Reduced amplitude of the N100 AEP to non-target tones has also been reported in schizophrenia patients and first-degree relatives of patients. An increase in the amplitude of the N100 AEP component to non-target tones was observed in the PLEs group in the present thesis. No between-group-differences in mean amplitude of the P300 component to target tones were observed; however, mean amplitude to target tones at FCz was found to be significantly greater than mean amplitude to non-target tones in the control group but not in the PLEs group at fronto-central locations.

Chapters 5 and 6 investigated spatial processing and spatial working memory, respectively. No between-group differences were observed in the behavioural or electrophysiological data obtained from the Implicit Spatial Memory Task. Data from the Spatial Working Memory Task revealed no between-group differences for accuracy or reaction time. Greater reaction time variability was observed in the PLEs group relative to control group however. Reduced mean amplitude of the P300 component was observed in the PLEs group relative to the control group at parietal electrode sites.

The present thesis adds to the knowledge of PLEs in early adolescence by reporting reduced P300 during spatial working memory retrieval in this group while spatial processing and memory (as assessed by the Implicit Spatial Memory Task) remain unimpaired. This reduction in P300 amplitude may reflect disrupted neural

processes underlying stimulus evaluation and template matching during retrieval in the PLEs group. The finding of reduced P300 in the PLEs group on the Spatial Working Memory Task adds to previous findings of impaired spatial working memory in this group reported by Kelleher et al. (2012c), and expands existing findings of reduced P300 amplitude in adolescent onset schizophrenia (Haenschel et al., 2007) by revealing reduced P300 amplitude in the treatment-naïve extended psychosis phenotype.

Chapter 1

General Introduction

Overview

Interest has risen in psychotic symptoms as a risk factor for later psychotic disorder. While some researchers have focused on determining the percentage of people in the general population who experience psychotic symptoms (van Os, Linscott, Myin-Germeys, Delespaul & Krabbendam, 2009; Scott et al., 2009); others have focused on identifying help-seeking individuals who are thought to be clinically at-risk for psychotic disorder (Yung, Philips, Pan Yuen & McGorry, 2004; Ruhrmann et al., 2010). Higher rates of self reported 'psychotic-like experiences' (or PLEs) are often reported in adolescents relative to adults in the general population. Adolescents who report PLEs (the non-clinical psychosis phenotype) have been shown to share many of the same schizophrenia-related risk factors as patients with schizophrenia (the clinical psychosis phenotype; Kelleher & Cannon, 2011).

The following thesis employs both behavioural and electrophysiological methods in an attempt to uncover possible electrophysiological correlates of PLEs in a community-based sample of young adolescent participants. Electroencephalographic (EEG) testing took place following a detailed clinical interview and neuropsychological testing. Tasks chosen for use with EEG include an Active Auditory Oddball Task, an Implicit Spatial Memory Task and a Spatial Working Memory Task. The following introduction will begin with a brief history of the classification of psychotic disorders; followed by an overview of the etiology and risk factors associated with psychosis and an outline of theoretical models of psychosis and approaches to research. The present chapter will also include details of research in the area of PLEs and cognitive impairments associated with psychotic disorders.

1.1 Classification of Psychotic Disorders

1.1.1 Classification of Psychotic Disorders – A Brief History

Psychosis is defined as any mental disorder characterised by delusions and/or prominent hallucinations, with or without insight into their pathological nature. At its most extreme is schizophrenia, a severe form of mental illness. Schizophrenia occurs in all populations with an annual prevalence of 1.4 to 4.6 per 1000 population (Jablensky, 2000). Schizophrenia sometimes begins in childhood; however, it usually appears in late adolescence or early adulthood, with most suffers in the age group 15-35 years. Age of onset appears to be on the decrease over recent decades (DiMaggio, Martinez & Menard, 2001). The disorder is typically characterized by impairments in perception or the expression of reality, often manifested as auditory hallucinations, paranoid or irrational delusions, disorganised speech and/or thinking in the context of significant social or occupational dysfunction.

The concept of schizophrenia was originally formulated by Emil Kraepelin (1856-1926), when he described manic-depressive illness and dementia praecox (dementia meaning a decline in intellectual functioning and praecox meaning early onset). The Kraepelinian concept of dementia praecox included several subtypes such as dementia paranoides, catatonia and hebephrenia (Kring, Davison, Neale & Johnson, 2007). Eugen Bleuler (1857-1939) coined the term schizophrenia, suggesting that at the core of the illness was a separation of personality, thinking, memory and perception. Bleuler identified four symptoms which he believed to be fundamental to the illness, Bleuler's 4 'As'. Firstly, Bleuler observed a loosening of *associations* that linked together the stream of thought, thus inhibiting the patient's ability to reason. Bleuler also noted *ambivalence* as one of his 4 'As', this he proposed was the holding of

conflicting emotions and attitudes towards others. Thirdly, Bleuler proposed *autism*, or a withdrawal from the social world, as a fundamental symptom of schizophrenia, and finally he proposed inappropriate *affect* as another key symptom (Bentall, 2004).

Karl Jaspers (1883-1969) suggested *ununderstandability* as the hallmark of the psychoses and it was this that allowed the psychoses to be distinguished from the less severe psychiatric disorders, which later became known as the neuroses. In the late 1950s, Kurt Schneider identified what he determined were the *first-rank symptoms* of schizophrenia (Schneider, 1959). These included audible thoughts, voices heard arguing, voices heard commenting on one's actions, experience of influences playing on the body, thought withdrawal, thoughts ascribed to other people, thought diffusion, delusional perception and feelings, impulses and volitional acts that are experienced as the work or influence of others.

Meanwhile, as the concept of schizophrenia was evolving, so too was the concept of manic-depressive illness, which had been proposed by Kraepelin in 1898. In 1933, the term schizoaffective disorder was first used to describe an illness which combined both schizophrenic and manic-depressive symptoms, but which was distinct from both (Kasanin, 1933). Kasanin suggested that schizoaffective patients usually suffered 'marked emotional turmoil' and 'false sensory impressions' (hallucinations), but rarely experienced passivity symptoms (delusions of control). Kasanin noted these symptoms usually appeared after a stressful event despite good premorbid functioning, and recovery was often rapid.

1.1.2 Classification of Psychotic Disorders – Classification in the Diagnostic and Statistical Manual of Mental Disorders

In 1952, the first edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-I) was published; the DSM has undergone many revisions since the first edition. As a result, with advances in medicine and psychology, the symptoms and criteria which are necessary in order to obtain a diagnosis of psychotic disorders such as schizophrenia have changed somewhat in each revision, with criteria becoming more stringent in each edition over the years.

In the late 1970s researchers divided the symptoms of schizophrenia into positive and negative symptoms (Strauss, Carpenter & Bartko, 1974; Crow, 1980). The original category of positive symptoms was later divided into positive and disorganised symptoms (Lenzenwenger, Dworkin & Wethington, 1991 – see Table 1.1).

Table 1.1: *Positive, Negative and Disorganised Symptoms of Schizophrenia.*

Positive Symptoms	**Negative Symptoms**	**Disorganised Symptoms**
Delusions	Avolition (apathy)	Disorganised speech
Hallucinations	Alogia (poverty of speech, poverty of content of speech)	Disorganised behaviour
	Anhedonia	
	Flat affect	
	Asociality	

Active/positive symptoms include delusions and hallucinations; negative symptoms include avolition (inability to initiate or sustain purposeful activity), alogia (poverty of speech), anhedonia (inability to experience pleasure or interest in formerly pleasurable activity), flat affect and asociality, and disorganised symptoms include disorganised speech and behaviour.

Table 1.2: *Characteristic Symptoms of the Active Phase as outlined in the DSM-IV.*

At least two of the following, each present for a significant portion of time during a one month period (or less if symptoms successfully treated):

1) Delusions
2) Hallucinations
3) Disorganised speech (e.g. frequent derailment, incoherence or marked loosening of associations)
4) Grossly disorganised or catatonic behaviour
5) Negative symptoms (e.g. affective blunting, alogia, or avolition)

In the DSM-III-R and DSM-IV schizophrenia is characterised by the psychotic symptoms of the active phase (see Appendix I and II for the criteria necessary for a diagnosis of schizophrenia as outlined in the DSM-III-R and DSM-IV, respectively). In DSM-IV the following criteria are required for a diagnosis of schizophrenia; characteristic psychotic symptoms of the active phase (see Table 1.2); disturbance of functioning in such areas as school, work, social relations and self-care; if present during the active phase of the disturbance, major depressive or manic syndrome must be brief relative to the duration of the disturbance and continuous signs of disturbance must

persist for at least six months. In addition, it must be established that an organic factor did not initiate or maintain the disturbance and, if there is a history of autistic disorder, an additional diagnosis of schizophrenia must only be made if prominent delusions and hallucinations are also present.

In the most recent revision of the DSM, the DSM-IV-TR, criteria for schizophrenia remain the same as in the DSM-IV. The DSM-IV-TR includes other categories of psychotic disorders besides schizophrenia. The introduction of a risk syndrome for psychosis was proposed for the DSM-5, due for publication in 2013, but this has since been rejected (this will be discussed in further detail in Chapter 7; see Table 1.3 for prodromal and residual symptoms outlined in the DSM-III-R and DSM-IV). Two brief psychotic disorders exist, schizophreniform disorder and brief reactive psychosis. Schizophreniform disorder shares the same features as schizophrenia; however it is experienced for a shorter period of time, usually greater than one month but no longer than six months. Brief reactive psychosis is characterised as an episode which lasts at least one day but no longer than one month and is often brought on by a period of extreme stress. DSM-III-R and DSM-IV criteria for both disorders are outlined in Appendix I and II respectively. Another psychotic disorder, schizoaffective disorder, is also considered a schizophrenia spectrum disorder and consists of a mixture of symptoms of schizophrenia and mood disorders, i.e. it is characterised by a major depressive episode, a manic episode or a mixed episode, together with some of the symptoms of schizophrenia.

Table 1.3: *Prodromal and Residual Symptoms outlined in the DSM-III-R and DSM-IV.*

DSM-III-R	DSM-IV
1) Marked social isolation or withdrawal	1) Social isolation or withdrawal
2) Marked impairment in role (functioning as wage-earner, student or homemaker)	2) Impaired school performance
	3) Markedly peculiar behaviour
3) Marked peculiar behaviour (e.g. collecting garbage, talking to self in public, hoarding food)	4) Impaired personal hygiene/grooming
4) Marked impairment in personal hygiene and grooming, blunted, flat or inappropriate affect	5) Blunted, flat, inappropriate affect
	6) Digressive, vague, over elaborate or circumstantial speech or poverty of speech or content of speech
5) Digressive, vague, over elaborate, or circumstantial speech, or poverty of speech	7) Odd beliefs or magical thinking which influence behaviour
6) Odd beliefs or magical thinking influencing behaviour and inconsistent with subcultural norms, e.g. superstitiousness, belief in clairvoyance, telepathy, sixth sense, "others can feel my feelings", overvalued ideas, ideas of reference	8) Unusual perceptual experiences
	9) Marked lack of initiative, interests or energy
7) Unusual perceptual experience, e.g. recurrent illusions, sensing the presence of a force or person not actually present	
8) Marked lack of initiative, interest or energy	

1.2 Etiology and Risk Factors Associated with Psychosis

1.2.1 Genetic Factors

Schizophrenia is a heritable disorder with a complex genetic architecture interacting with environmental factors (Winterer et al., 2003). Genetic factors may increase vulnerability or resilience to schizophrenia (Harrison & Weinberger, 2005). While the risk of developing schizophrenia stands at 1 to 3 percent in the general population, individuals who have a relative with schizophrenia are at increased risk. This risk increases as the genetic relationship between the relative and the proband becomes closer (Kendler, Karkowski-Shuman & Walsh, 1996). The risk increases to approximately 10 percent for siblings of schizophrenic patients, 13 percent if one parent has a diagnosis of schizophrenia or 45 percent if both parents have a diagnosis of schizophrenia, and as high as 50 percent for monozygotic twins.

While the increased risk of schizophrenia reported in family studies may be due to shared environmental factors as well as common genetic factors, studies of the adopted offspring of schizophrenic mothers have provided confirmation of the effects of genetic susceptibility to schizophrenia. A study carried out in Finland by Tienari et al. (2000) found that the risk of developing schizophrenia in a group of 164 adoptees who had a biological parent with schizophrenia was 8.1 percent, whereas the risk of developing schizophrenia in the 197 control adoptees was 2.3 percent.

Research on animal models of schizophrenia and from human populations has identified a number of potential genes and copy number variants (CNVs) which may be responsible for increasing genetic vulnerability for psychotic illnesses. Genes such as *Disrupted in Schizophrenia 1* (DISC-1) and deletions of fragments of chromosome 22q11 such as the *Catechol-O-methyl transferase* (COMT) gene have been investigated

as candidate risk genes for psychosis (Egan et al., 2001; Hennah et al., 2003; Chen, Wang, O'Neill, Walsh & Kendler, 2004; Harrison & Weinberger, 2005). The influence of genetics remains a complex issue, with genetic vulnerability increasing risk for psychotic disorders, in particular when combined with other risk factors.

1.2.2 Neurotransmitters

The dopamine (DA) hypothesis of schizophrenia is one of the most established and enduring hypotheses within the literature, with support from pharmacological, imaging and post-mortem data which implicate DA alterations in the disorder. Some neuroleptic drugs (also referred to as *antipsychotic drugs*) which relieve the positive symptoms of psychosis in schizophrenia are antagonists of dopamine. The DA hypothesis was originally presented by Rossum (1966) who proposed that hyperactivity of DA transmission was responsible for the disorder. While the classical DA hypothesis focused on subcortical regions, the current DA hypothesis focuses on DA imbalances in both cortical and subcortical regions. Studies suggest that hypodopaminergia in the prefrontal cortex contributes to the pathophysiology of cognitive symptoms in schizophrenia (Goldman-Rakic, Muly & Williams, 2000). An imbalance in DA with hyperactive subcortical mesolimbic projections (resulting in hyperstimulation of D2 receptors and positive symptoms) and hypoactive mesocortical DA projections to the prefrontal cortex (resulting in hypostimulation of D1 receptors, negative symptoms, and cognitive impairment) is now the predominant hypothesis (Toda & Abi-Dargham, 2007).

Until the 1990s, dopamine receptor blockade (traditional antipsychotics) was the foundation of drug treatment for schizophrenia. In the 1990s *clozapine* and *risperidone,*

which target both DA and serotonin receptors, were the first new-generation antipsychotics to become available (Julien, 2001). While antipsychotic drugs which target DA receptors relieve positive symptoms, their use is often accompanied by unpleasant side effects and they fail to target the negative and cognitive symptoms of the disorder. Even positive symptoms can persist in some individuals despite treatment with antipsychotic medication (Foussias & Remington, 2010). For this reason researchers have begun to investigate alternative targets for pharmacological interventions. Drugs which produce a schizophrenia-like state have also contributed to knowledge in this area. Drugs which are thought to be agonists of serotonin receptors (e.g. LSD - lysergic acid diethylamide) suggest that serotonin antagonism may be beneficial in antipsychotic efficacy. Drugs such as phencyclidine and ketamine are potent blockers of NMDA (N-methyl-D-aspartate)–type glutamate receptors, suggesting that NMDA antagonism results in schizophrenia-like behaviours (Julien, 2001).

The glutamate synapse has emerged as a prominent target in relation to the development of new pharmacological treatments for schizophrenia (Moghaddam & Javitt, 2012). The idea of a glutamatergic abnormality was first proposed by Kim and colleagues in 1980 and evidence from various lines of research has supported this theory. For example, post-mortem studies have reported changes in glutamate receptor binding, transcription, and subunit protein expression in the prefrontal cortex, thalamus, and hippocampus of subjects with schizophrenia (Clinton & Meador-Woodruff, 2004). It is likely that both dopaminergic and glutamatergic abnormalities are implicated in schizophrenia.

1.2.3 Obstetric and Developmental Complications

The search for risk factors for psychotic disorders such as schizophrenia has led many researchers to look at reported complications in prenatal and perinatal life as well as early infancy. Links between maternal infection and obstetric complications and the later development of psychotic disorders such as schizophrenia have been reported in the literature (Dalman, Allebeck, Cullberg, Grunewald & Köster, 1999; Clarke, Harley & Cannon, 2006). A meta-analysis carried out by Cannon, Jones and Murray (2002a) revealed three groups of complications as significantly associated with schizophrenia: 1) complications of pregnancy (bleeding, diabetes, rhesus incompatibility, and preeclampsia); 2) abnormal foetal growth development (low birth-weight, congenital malformations, and reduced head circumference) and 3) complications of delivery (uterine atony, asphyxia, emergency Caesarean section).

Obstetric complications may be an important factor in identifying those at-risk of developing schizophrenia (Ballon, Dean & Cadenhead, 2008). Preti et al. (2000) reported a two-fold increased risk of schizophrenia in people who had obstetric complications. Nonaffective psychosis has been linked to prenatal exposure to rubella also (Brown, Cohen, Greenwald & Susser, 2000). However, some researchers report no or little effect of obstetric complications on the risk of developing a psychotic disorder (Gunduz, Woerner, Alvir, Degreef & Lieberman, 1999). Yun et al. (2005) reported no differences in the frequency of obstetric complications between ultra high-risk (UHR) individuals who later converted to psychosis and those who did not.

While the risk from obstetric complications alone is not very high and many people who receive a diagnosis of schizophrenia do not report these complications in early life, it is thought they may pose a greater risk when combined with other factors,

such as genetic influences. Clarke, Tanskanen, Huttunen, Whittaker & Cannon (2009) explored the effect of prenatal exposure to pyelonephritis (an infection of the upper urinary tract) on the subsequent development of schizophrenia in a large Finnish cohort and examined this in conjunction with records on family history of psychosis. Prenatal exposure to the infection alone did not significantly increase the risk of schizophrenia; however, the effect of prenatal exposure to pyelonephritis was five times greater in those who had a family history of psychosis compared to those who did not. A recent study by Clarke et al. (2011) found that delayed attainment of milestones in infancy significantly increased the risk of later development of schizophrenia. In addition, they found that obstetric complications and delayed attainment of developmental milestones additively increased the risk of schizophrenia, reporting an odds ratio of 4.6 for the two factors together.

1.2.4 Social Factors

Higher rates of psychotic disorder have been reported among migrant communities and in urban areas (Allardyce et al., 2001; Krabbendam & van Os, 2005). In a study carried out in East London, Kirkbride, Jones, Ullrich and Coid (2012) reported that increased incidences of nonaffective psychosis may be associated with increased social deprivation, income inequality and population density. In particular, higher incidence of psychotic illness has been reported in African-Caribbean and Black African populations living in London and other areas of the U.K. (van Os, Castle, Takei, Der & Murray, 1996; Fearon et al., 2006).

Fearon et al. (2006) carried out the Aetiology and Ethnicity of Schizophrenia and Other Psychoses (AESOP) study, a population-based incidence survey of all people

with any psychosis contacting health services from a defined population in south-east London, Nottingham and Bristol during a 2-year period. The AESOP study found increased incidence rates of all categories of psychosis in African-Caribbean and Black African populations, in both males and females and across all age groups. Studies have shown that incidence rates in Caribbean countries such as Jamaica (Hickling & Rodgers-Johnson, 1995), Trinidad (Bhugra et al. 1996) and Barbados (Mahy, Mallett, Leff, & Bhugra, 1999) do not appear to be raised in relation to other countries, suggesting that this rise in incidence levels seems to be specific to migrants from these areas. Incidence rates do not appear to be raised to the same extent in Asian migrant populations; however, some studies have reported slightly elevated rates in this population (King, Coker, Leavey, Hoare & Johnson-Sabine, 1994).

Allardyce et al. (2001) reported a higher incidence of schizophrenia in the south-east London suburb of Camberwell, compared to the rural area of Dumfries and Galloway in south-west Scotland; however, they acknowledge that the difference that they have observed may be due to the large number of people from ethnic minority groups living in the Camberwell area. When they carried out a comparison of the white populations only living in these areas they did not observe a difference in incidence rates.

Other possible reasons for the elevated rates of psychotic disorders reported by ethnic minorities in urban areas may be that these groups are at a disadvantage due to their lower socio-economic background and issues of social adversity. However, while the elevated risk of schizophrenia in first generation Caribbean migrants could possibly be ascribed to the stress of migration, it has also been reported that second generation migrants from the Caribbean to the U.K. are at an increased risk of schizophrenia (Hutchinson et al., 1996; Pinto, Ashworth & Jones, 2008).

1.2.5 Adverse Experiences in Childhood

Many studies to date have focused on the link between exposure to trauma in childhood and later psychotic episodes. The development of psychotic symptoms and schizophrenia in adolescence and early adulthood has been linked to childhood sexual and physical abuse as well as exposure to domestic violence and bullying in early life (Read, Agar, Argyle & Aderhold 2003; Morgan & Fischer, 2007; Bendall, Jackson, Hulbert & McGorry, 2008; Kelleher et al., 2008).

Galletly, van Hooff and McFarlane (2011) studied children who were exposed to bushfires in South Australia in 1983 at a 20 year follow-up and concluded that exposure to multiple traumas rather than a single major trauma best increases the risk of a later episode of psychosis. An earlier study by Kelleher et al. (2008) found a significant association between psychotic symptoms in early adolescence and reports of child physical abuse, exposure to domestic violence and involvement in bullying. Contrary to previous research, Kelleher et al. (2008) did not find association between being a victim of bullying and reports of psychotic symptoms in their sample. Interestingly, an association between psychotic symptoms and being a bully/victim (i.e. both a perpetrator and victim of bullying) was observed, with 50 percent of those identified as bully/victims reporting psychotic symptoms. Harley et al. (2010) also report that exposure to traumatic events in childhood leads to an increased risk of experiencing psychotic symptoms in adolescence.

1.2.6 Substance Abuse

The influence of substance abuse on the development of psychotic disorders has been explored in the past decade, in particular the effects of exposure to delta-9-

tetrahydrocannabinol (THC), the psychoactive component in cannabis. Cannabis is one of the most commonly used illegal drugs in terms of both frequency of use and dosage (Casadio, Fernandes, Murray & Di Forti, 2011). The link between cannabis use and psychosis is particularly well established, with many studies reporting that cannabis use increases the odds of the user experiencing psychotic symptoms (see Table 1.4). For example, Andreasson, Allebeck, Engstrom and Rydberg (1987) found that Swedish conscripts who had smoked cannabis by the age of conscription were at a two-fold increased risk of developing schizophrenia at both 15 and 27 year follow ups. At the 27 year follow up it was also observed that heavy cannabis users were 6 times more likely to receive a diagnosis of schizophrenia than non-users (Zammit, Allebeck, Andreasson, Lundberg & Lewis, 2002). Results of a systematic review carried out by Moore et al. (2007) suggest a 40 percent increased risk in participants who had ever used cannabis, with this figure rising to 50-200 percent increased risk for those participants who used it most heavily.

Harley et al. (2010) report that in a sample of adolescents, while self reports of cannabis use lead to increased risk of experiencing psychotic symptoms, the additive effects of using cannabis and experiencing childhood traumas (such as childhood abuse and domestic violence) lead to an even higher risk of experiencing psychotic symptoms. Other studies have suggested that cannabis use along with genetic vulnerability for psychosis may additively increase the risk of developing a psychotic illness. For example, a study by Caspi et al. (2005) found that a functional polymorphism of the COMT gene moderated the influence of adolescent cannabis use on developing adult psychosis.

Table 1.4: *Longitudinal studies in the general population regarding the role of cannabis as risk factor for schizophrenia - adapted from Casadio et al. (2011).*

Country and Author	**Study N**	**Follow up**	**Odd ratio (95% CI) (adjusted risk)**
United States	4494	NA	2.4 (1.2-7.1)
(Tien & Anthony, 1990)			
Sweden	50, 053	15 years	2.3 (1.0-5.3)
(Andreasson et al., 1987)		27 years	3.2 (1.7-5.5)
(Zammit et al., 2002)			
The Netherlands	4045	3 years	2.8 (1.2-6.5)
NEMESIS			
(van Os et al., 2002)			
Israel	9724	4-15 years	2.0 (1.3-3.1)
(Weiser et al., 2002)			
New Zealand (Christchurch)	1265	3 years	1.8 (1.2-2.6)
(Fergusson et al., 2003)			
New Zealand (Dunedin)	1034	15 years	3.1 (0.7-13.3)
(Arseneault et al., 2002)			
The Netherlands	1580	14 years	2.8 (1.79-4.43)
(Ferdinand et al., 2005)			
Germany	2437	4 years	1.7 (1.1-1.5)
EDSP			
(Henquet et al. 2005)			
United Kingdom	8580	18 months	1.5 (0.55-3.94)
(Wiles et al., 2006)			
Greece	3500	NA	4.3 (1.0-17.9)
(Stefanis et al., 2004)			

Comorbid substance abuse in patients with schizophrenia is also thought to carry many consequences; these consequences include the possibility of experiencing more positive symptoms, an increased risk of relapse of psychosis, heightened risk of violence, heightened risk of suicide, more medical comorbidities, legal complications including increased risk of incarceration, and a greater propensity to anti-psychotic side effects (Buckley, Miller, Lehrer & Castle, 2009).

1.2.7 Neuroanatomy

Enlargement of the ventricles and prefrontal cortex dysfunction are among the most well-replicated findings in schizophrenia (Kring et al., 2007). Post-mortem studies of the brains of schizophrenia patients and neuroimaging studies have consistently reported enlargement of the ventricles in the disorder (Johnstone, Frith, Crow, Husband & Kreel, 1976; Marsh, Suddath, Higgins & Weinberger, 1994). In line with a number of other studies, Wright et al. (2000) reported lower cerebral volume in patients with schizophrenia compared to control participants, as well as higher ventricular volumes in the schizophrenia patients, in particular in the left and right body of the lateral ventricle.

Reductions in frontal, prefrontal and temporal lobe grey matter volume of schizophrenia patients have also been reported in the literature (Buchanan, Vladar, Barta & Pearlson, 1998; Shenton, Dickey, Frumin & McCarley, 2001). In addition, reductions in the volume of the temporal lobe bilaterally and subcortical temporal lobe structures such as the amygdala and the hippocampus have also been reported (Lawrie & Abukmeil, 1998, Wright et al., 2000). Reductions in grey matter volume have recently been shown in individuals at-risk of schizophrenia (Job, Whalley, Johnstone & Lawrie, 2005). A study by Pantelis et al. (2003) reported reduced grey matter volumes

in the right prefrontal cortex, insular and temporal cortex, the right basal ganglia and the cingulate cortex bilaterally in those UHR participants who converted to psychosis compared to those who did not convert to psychosis. Follow-up scans in the UHR participants indicated that further reductions in grey matter volume in the cingulate gyri, the left parahippocampal gyrus, left fusiform gyrus, the left orbitofrontal cortex and one region of the left cerebellar cortex.

The possibility of hypofrontality in schizophrenia has also been proposed, meaning a reduction of functioning in the prefrontal cortex (Andreasen et al., 1992; Andreasen al., 1997). Other authors have proposed that a "disconnection syndrome" may underlie structural and functional abnormalities in schizophrenia; more specifically, it has been suggested that schizophrenia patients show a different pattern of distributed cerebral interactions between the prefrontal and temporal cortices (Friston & Frith, 1995).

1.2.8 Psychopathology

Depression, anxiety and, as outlined above, substance abuse often accompany a diagnosis of schizophrenia (Green, Canuso, Brenner & Wojcik, 2003; Buckley et al., 2009). In a review of the literature, Buckley et al. (2009) state that there is clearly an increased prevalence of these disorders in patients with schizophrenia which is higher than those rates found in the general population, and that there is evidence that symptoms of these disorders are present at all stages of psychotic illness, including the prodrome, FEP and chronic schizophrenia. The presence of these co-morbidities with schizophrenia can make the diagnostic process more difficult as depressive symptoms could be incorporated as negative symptoms of schizophrenia or, indeed they may occur

in response to the onset of a psychotic disorder. In addition, anxiety may arise due to paranoid thoughts, hallucinations or delusions.

Ohayon and Schatzberg (2002) studied the prevalence of major depressive episodes with psychotic features in a general population sample of 18,980 people surveyed in five European countries. About 16.5 percent of all subjects endorsed at least one key depressive criterion, and of those, 12.5 percent reported delusions and/or hallucinations. Of the 454 subjects diagnosed with a full DSM-IV major depressive episode, 18.6 percent experienced delusions and/or hallucinations, yielding a prevalence of major depressive episode with psychotic features of 0.4 percent in their sample. It was also observed that subjects who reported feelings of worthlessness or guilt were most likely to have psychotic features.

Many studies report an increase in the suicide rate among individuals with schizophrenia, as well as increased rates of suicidal ideation and self-harm. It is suggested in the literature that there is a 10 percent lifetime risk of suicide in patients with a diagnosis of schizophrenia (De Hert, McKenzie & Peuskens, 2001); however, other researchers have suggested that this figure may be lower at 4.9 percent for lifetime risk of suicide among schizophrenics, with suicide and suicide behaviours occurring generally near the onset of illness, early in the disease (Palmer, Pankratz & Bostwick, 2005; Bertelsen et al., 2007).

1.3 Theoretical Models of Psychosis and Approaches to Research

1.3.1 Models of Psychosis – The Neurodevelopmental Model

Rapoport, Addington and Frangou (2005) state that schizophrenia is a complex and severe brain disorder, which to date has a poorly defined etiology and pathophysiology. They elucidate that for more than two decades, the 'neurodevelopmental' model has been accepted as the prevailing explanatory theory of schizophrenia. According to Polanczyk et al. (2010) two models of schizophrenia currently exist within the literature; the neurodevelopmental theory and the dimensional model of schizophrenia which documents the presence of psychotic symptoms in the general population.

The neurodevelopmental model proposes that individuals who later develop schizophrenia often show signs of neurodevelopmental deficits as children. In its simplest form this neurodevelopmental theory suggests that schizophrenia is the behavioural outcome of an aberration in neurodevelopmental processes that begins long before clinical symptoms appear and is caused by a combination of environmental and genetic factors (Cardno et al., 1999; Singh, McDonald, Murphy & O'Reilly, 2004; Rapoport et al., 2005). Abnormalities in behavioural, emotional, social, cognitive and motor development have been reported in at-risk populations and it has been hypothesised that these deficits signal the starting point of a risk pathway to psychotic disorder in which nonaffective psychosis is the endpoint (Jones, Rodgers, Murray & Marmot, 1994; Marenco & Weinberger, 2000; Murray, Lappin & DiForti, 2008; Welham, Isohanni, Jones & McGrath, 2009a). Polanczyk et al. (2010) propose that to date the neurodevelopmental theory has not emphasised the emergence of positive symptoms of psychosis during childhood, and in their view it is unknown whether or

how such symptoms should be incorporated into the theory alongside the other childhood neurodevelopmental risks which the theory considers.

1.3.2 Models of Psychosis – The Dimensional/Continuum Model

The dimensional model proposed by researchers such as van Os, Hanssen, Bijl and Ravelli (2000) has directed a considerable amount of scientific attention to the existence of psychotic symptoms in the general population (see Figure 1.1). These symptoms are usually below the threshold for the diagnosis of disorder; however, a substantial amount of research over the past decade reports the existence of such symptoms within the general population. These sub diagnostic symptoms are thought to be the mild end of a risk continuum on which psychotic disorder (such as schizophrenia) exists at the extreme end of the continuum (Dutta et al., 2007; van Os et al., 2009; Polanczyk et al., 2010).

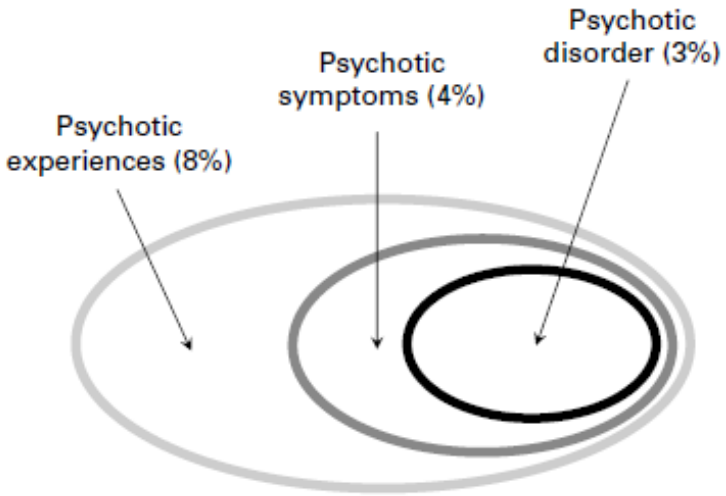


Figure 1.1: *The Dimensional Model of Schizophrenia – from van Os et al. (2009).*

Polanczyk et al. (2010) critique the fact that the dimensional model to date has focused mainly on the existence of such symptoms in adulthood and has not emphasised the existence of such symptoms in childhood; therefore it is unknown if and how such symptoms would fit into this approach. However, Polanczyk et al. (2010) propose that these two literatures (the neurodevelopmental approach and the dimensional approach) suggest the possibility that psychotic symptoms signal neurodevelopmental processes that are already known to lead to schizophrenia, and that these symptoms in childhood are part of the dimension of schizophrenia risk.

Dutta et al. (2007) state that the final diagnosis of a psychotic illness is merely the endpoint of a risk pathway; however, this risk pathway is not necessarily an inevitable trajectory into psychosis (see Figure 1.2). Dutta et al. (2007) explain that the pathway outlined in Figure 1.2 involves the development of prepsychotic symptoms, which progress to frank but infrequent psychotic symptoms, followed by further progression to persistent psychotic symptoms and ultimately the development of social impairment due to these psychotic symptoms. Dutta et al. (2007) explain that moving up or down the pathway depends on a number of propsychotic and antipsychotic factors. Propsychotic factors could include biological vulnerability or cannabis use, whereas individual resilience could be considered an antipsychotic factor.

Cougnard et al. (2007) proposed the psychosis-proneness-persistence-impairment model. They suggest that while the majority of people who report subclinical symptoms of psychosis do not display any psychotic illness at follow-up, the experience of subclinical psychotic symptoms during development can result in poorer outcomes if subjects are exposed to additional environmental risk factors (cannabis use, trauma and urbanicity). They propose that genetic factors also interact with

environmental factors to increase the chance of subclinical psychotic symptoms persisting, resulting in the eventual diagnosis of a psychotic disorder.

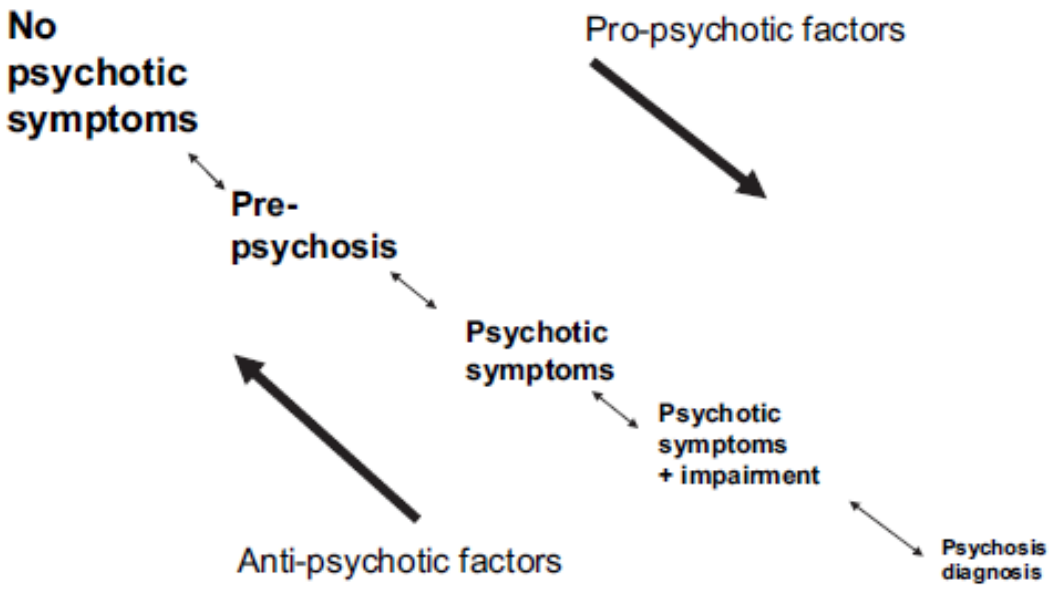


Figure 1.2: *A Risk Pathway to the Diagnosis of Psychosis – from Dutta et al. (2007).*

1.3.3 Approaches to Research

Many approaches have been adopted in an attempt to gain a better understanding of the developmental pathways to psychotic disorders such as schizophrenia. In addition to research involving participants who have psychotic disorders and those who have

recently experienced a first episode of psychosis (FEP), some research groups have taken the 'ultra high-risk' approach and begun to study participants who are considered to be in the prodromal stage of schizophrenia, or at an increased risk of entering this phase, i.e. at clinical high-risk. This provides another alternative to the traditional genetic high-risk approaches which examined risk factors for the development of psychotic disorders in offspring of schizophrenia patients, unaffected twins and other relatives of patients.

However, Dutta et al. (2007) comment that while DSM-IV criteria for schizophrenia include the prodromal phase as a construct, it best describes a *retrospective* concept because it cannot be defined until there is an established psychotic illness. Psychotic disorders such as schizophrenia are usually characterised by a prodromal period preceding the onset of full psychotic symptoms (Beiser, Erickson, Fleming & Iacona, 1993; Yung & McGorry, 1996; Olsen & Rosenbaum, 2006). Ballon et al. (2008) agree that the term "prodromal" can only truly be used retrospectively, and propose that these groups of subjects should be considered as "at-risk" for schizophrenia rather than truly within the prodrome phase.

In addition, other approaches such as the 'genetic' high-risk approaches generally involve the offspring of parents with psychotic disorders or other first-degree relatives, whereas the 'symptomatic' high-risk approaches involve studying individuals who report psychotic-like experiences (PLEs; also referred to as psychotic-like symptoms or subclinical psychotic symptoms - the non-clinical psychosis phenotype). This 'symptomatic' high-risk approach to research, involving individuals who report these subclinical psychotic symptoms, has provided a unique high-risk paradigm for studying the developmental trajectory to psychosis. Much work to date detailing such groups has been carried out retrospectively using large birth cohort studies. These

studies provide details on large samples with data available detailing the conversion to psychotic disorders as well as other disorders.

1.4 Psychotic-Like Experiences

1.4.1 Psychotic Symptoms in the General Adult Population

In recent years the importance of extending research in the area of psychosis to include those who report psychotic symptoms in the general population has been highlighted as a new approach to identifying individuals at increased symptomatic risk for developing a psychotic disorder (Kelleher et al., 2012a; 2012b). Contrary to the idea that psychosis is an all or nothing occurrence, as outlined in section 1.3.2, van Os and colleagues suggest that psychosis may exist as a continuous phenotype in nature (van Os et al., 2000; Johns & van Os, 2001; van Os et al., 2009). This idea was previously proposed by Strauss (1969) who suggested that psychotic symptoms reported in clinical samples have been shown to be points on a continuum of function. While the traditional medical model of schizophrenia assumes a categorical view of schizophrenia and its core symptoms, the dimensional approach proposes that schizophrenia is not a "discrete illness entity"; instead this approach proposes that psychotic symptoms of schizophrenia differ instead in qualitative ways from normal experiences and behaviours (Johns & van Os, 2001).

Van Os et al. (2000) suggest that their findings imply that the psychosis phenotype as it exists in nature may be nearly 50 times more prevalent than the narrow

medical concept. Stefanis et al. (2002) also propose that dimensions of clinical psychosis have a distribution in the general population, while Rössler et al. (2007) state that the expression of symptoms of psychosis is continuous and characterised by differing levels of severity and persistence. A more recent meta-analysis carried out by van Os et al. (2009) reported that the median prevalence of these symptoms in the general population is between 5 and 8 percent. A study by Hanssen, Bak, Bijl, Vollebergh and van Os (2005) used interviews in a study of the general adult population in the Netherlands and found that 8 percent of those who reported PLEs were clinically psychotic 2 years later. However, they noted that the emotional context and severity of the experience could drive the rate of persistence to a maximum of 16.7 percent. The past decade of research illustrates a non-ambiguous continuum between the clinical and non-clinical psychosis phenotypes in the general population (Kelleher & Cannon, 2011).

1.4.2 Psychotic-Like Experiences in Childhood

Reports of PLEs are often higher in adolescence than in adulthood (Poulton et al., 2000; Spauwen, Krabbendam, Lieb, Wittchen & van Os, 2003; Yoshizumi, Murase, Honjo, Kaneko & Murakami, 2004; Scott et al., 2009). Reports of PLEs are often higher when self-report questionnaires are used (Dhossche, Ferdinand, van der Ende, Hofstra & Verhulst, 2002; Laurens et al., 2007; Kelleher, Harley, Murtagh & Cannon, 2011). Yoshizumi et al. (2004) reported that 21 percent of 11-12 year olds who completed their questionnaire reported experiencing hallucinations. In a nationally representative Australian sample, Scott et al. (2009) reported that 8.4 percent of adolescents experienced auditory and/or visual hallucinations. Horwood et al. (2008) found that

nearly 40 percent of children in their sample self-reported at least one or more psychotic symptoms in response to questions about 12 psychotic items; when the same children were followed-up using a semi-structured clinical assessment, this figure fell to 13.7 percent.

In the past decade, researchers have begun to examine the role that PLEs in childhood and adolescence may play in predicting later psychosis. The presence of psychotic symptoms in adolescence has been identified as a potential risk marker for the development of schizophrenia in adulthood (Poulton et al., 2000; Welham et al., 2009b). This has led researchers such as Rössler et al. (2007) to believe that the causes of clinical psychotic disorder and pathways to the development of the disorder can be studied long before the disorder becomes clinically relevant.

Poulton et al. (2000) proposed one of the first findings that provided evidence for the continuity of psychotic symptoms from childhood to adulthood. They state that it is important to determine whether continuity of psychotic symptoms over the lifetime can be identified, as has been seen in other disorders such as depression (Harrington, Fudge, Rutter, Pickles & Hill, 1990). Poulton et al. (2000) state that a compelling childhood risk factor for schizophrenia would have the following characteristics; it would bear a moderate-to-strong statistical relationship to later schizophrenic outcomes, it would not falsely identify large numbers of children at-risk who will never develop schizophrenic symptoms, and it would predict psychoses with specificity instead of posing generalised risk of many other disorders. In a 15-year longitudinal study, Poulton et al. (2000) reported that 42 percent of those diagnosed with schizophreniform disorder at age 26 had reported 1 or more psychotic symptom at age 11 years. A follow-forward analysis showed that strong symptom children were 16 times more likely to have a schizophreniform diagnosis by age 26 years than were control children. Poulton

et al. (2000) state that self-reported psychotic symptoms at age 11 years predicted a very high risk of a schizophreniform diagnosis at age 26 years (odds ratio, 16.4; 95 percent confidence interval, 3.9-67.8).

Cannon et al. (2001) found an association in children between the later development of schizophrenia and abnormal suspiciousness or sensitivity and relationship difficulties with peers, while disturbances in eating and hysterical symptoms in childhood were linked with affective psychosis in adulthood. Wellham et al. (2009) found that self-reported auditory hallucinations at age 14 years were associated with increased risk of psychotic disorder at age 21 years. A study by Bartels-Velthuis, van de Willige, Jenner, van Os and Wiersma (2011) reported a low rate of persistent auditory vocal hallucinations when an original group of 7-8 year olds were assessed at a 5-year follow-up. However, self-reported PLEs are thought to decrease from childhood through adolescence to adulthood, and their young sample of 7-8 years olds in the original study may be the cause of such low persistence levels of PLEs in the follow-up study.

1.4.3 Psychotic-Like Experiences - Criterion and Construct Validity

Kelleher and Cannon (2011) provided evidence in favour of the criterion and construct validity of PLEs in relation to the psychosis phenotype. A wide range of risk factors for schizophrenia (the clinical psychosis phenotype) have recently been investigated in individuals who reported PLEs (the non-clinical psychosis phenotype) (Kelleher & Cannon, 2011). Details of these shared risk factors have been compiled in Table 1.5.

Kelleher and Cannon (2011) state that psychotic symptoms may fall within a spectrum of experiences; however, these symptoms are associated with increased risk of

psychotic disorder and show criterion and construct validity for clinical psychosis. They state that these findings indicate that the non-clinical psychosis phenotype represents a valid population for studying the aetiology of clinical psychosis and suggest a shared genetic aetiology between the clinical and nonclinical phenotypes.

Much remains to be learned about psychosis by broadening the scope of research to include the non-clinical psychosis population. As outlined in Table 1.5, research has suggested that those who report PLEs (the non-clinical phenotype) share many of the same risk factors as those who are diagnosed with schizophrenia (the clinical phenotype). In section 1.2 many of the commonly investigated risk factors for psychotic disorders such as schizophrenia were discussed.

Psychotic disorders such as schizophrenia are heritable and those with a relative with schizophrenia are at increased risk of the disorder (see section 1.2.1). Higher levels of subclinical psychotic experiences have been reported in non-ill relatives of patients with schizophrenia (Kendler, McGuire, Gruenberg & Walsh, 1995). Lataster, Myin-Germeys, Derom, Thiery and van Os (2009) have also shown concordance of PLEs among monozygotic twins, but not dizygotic twins. It has also been suggested that obstetric and developmental complications may play a role in the later development of psychotic disorders (see section 1.2.3). Zammit et al. (2009) reported an association between definite non-clinical psychosis-like symptoms in adolescence and maternal infection during pregnancy, maternal diabetes, need for resuscitation and reduced 5 minute Apgar scores.

Table 1.5: *Aetiological and risk factor continuity between clinical and non-clinical psychosis phenotypes – adapted from Kelleher and Cannon (2011).*

Category	Risk Factor	Schizophrenia	PLEs	Publication
Genetics	Familial	+	+	Hanssen et al. (2006)
	Heritable	+	+	Polanczyk et al. (2010)
				Lataster et al. (2009)
Obstetric and developmental deficits	Obstetric complications	+	+	Clarke et al. (2006)
	Maternal infection	+	+	Zammit et al. (2009)
	Neuromotor deficits	+	+	Cannon et al. (2002a)
	Winter/Spring birth	+	-	Blanchard et al. (2010)
	Paternal age	+	-	Zammit et al. (2008)
				Polanczyk et al. (2010)
Social	Urbanicity	+	+	Krabbendam & van Os (2005)
	Migration	+	+	Fearon et al. (2006)
	Ethnic minority	+	+	Johns et al. (2002)
	Low socio-economic background	+	+	Laurens et al. (2008a)
		+	+	Scott et al. (2006)
	Unemployed	+	+	
	Unmarried/divorced			
Adverse childhood experiences	Traumatic childhood physical or sexual experiences	+	+	Kelleher et al. (2008)
				Lataster et al. (2006)
	Bullying/victimization	+	+	Campbell & Morrison (2007)
	Paternal domestic violence	+	+	Schreier et al. (2009)
		+	+	Mackie et al. (2011)
	Maternal expressed emotion: negativity			Nishida et al. (2008)
	Maternal expressed emotion: warmth	+	-	Polanczyk et al. (2010)

Substance abuse	Cannabis use	+	+	Miettunen et al. (2008)
	Tobacco use	+	+	Harley et al. (2010)
				Henquet et al. (2005)
				Johns et al. (2004)
				Wiles et al. (2006)
Neuroanatomy	Hypofrontality	+	+	Jacobson et al. (2010)
	Frontotemporal disconnection	+	+	‘’
	Grey matter abnormalities	+	+	‘’
	White matter abnormalities	+	+	‘’
Intelligence, Cognition and Language	IQ	+	+	Cannon et al. (2002b)
	Verbal fluency	+	+	Johns et al. (2004)
	Receptive language	+	+	Horwood et al. (2008)
				Blanchard et al. (2010)
	Expressive language	+	-	Krabbendam et al. (2005a)
Psychopathology	Depressive symptoms	+	+	Nishida et al. (2008)
				Kelleher et al. (2012a)
	Anxiety symptoms	+	+	Scott et al. (2009)
				Kelleher et al. (2012a)
	Suicidal ideation	+	+	Polanczyk et al. (2010)
				Nishida et al. (2010)
				Kelleher et al. (2012e)
				Kelleher et al. (in press)
	Self-harm	+	+	Polanczyk et al. (2010)
				Nishida et al. (2010)
	Antisocial behaviour	+	+	Polanczyk et al. (2010)

+, positive finding; -, negative finding

Higher rates of schizophrenia and other psychotic disorders have been reported in migrant communities and among ethnic minorities, as well as in urban areas and areas of social disadvantage (see section 1.2.4). Higher incidence of schizophrenia is frequently reported in African-Caribbean migrants living in the U.K. in particular in suburban London (Fearon et al., 2006). Similar results with regards to PLEs have also been reported in both adults of African-Caribbean descent who report PLEs and children (Johns, Nazroo, Bebbington & Kuipers, 2002; Laurens, West, Murray & Hodgins, 2008a).

An association between childhood trauma, for example exposure to domestic abuse or child physical and sexual abuse, has also been established in the literature (see section 1.2.5). Similar findings have been reported in relation to PLEs, with associations between peer victimisation and reported PLEs observed in a number of studies (Campbell & Morrison, 2007; Schreier et al., 2009; Mackie, Castellanos-Ryan & Conrod, 2011). Kelleher et al. (2008) reported a link between experiencing PLEs in adolescence and being both the victim and perpetrator of bullying. An association between PLEs and exposure to domestic violence was also reported.

An association between abuse of substances such as cannabis and schizophrenia has been widely reported in the past (see section 1.2.6). Similar results have been reported in relation to PLEs (Henquet et al., 2005; Miettunen et al., 2008). Interestingly, Harley et al. (2010) reported that while cannabis use led to increased reports of PLEs in their adolescent sample, cannabis use in conjunction with exposure to traumatic events during childhood further increased the likelihood of reporting PLEs.

Jacobson et al. (2010) recently reported prefrontal-temporal dysfunction in addition to cingulate and insular dysfunctions in a group of adolescents who reported

PLEs. In addition, Jacobson et al. (2010) reported white matter decreases in this at-risk group using diffusion-tensor imaging (DTI). Some grey matter differences were also observed, with grey matter increases in the at-risk group within middle and superior temporal gyri, angular gyrus and orbitofrontal gyrus, while grey matter decreases were seen within the inferior temporal gyrus. However, the result of increases in grey matter is in opposition to reports of reduced grey matter in schizophrenia (see section 1.2.7).

In addition, lower IQ scores (Cannon et al., 2002b; Horwood et al., 2008) and deficits in receptive language (Blanchard et al., 2010) have been observed in adolescents who report PLEs as well as in schizophrenia. Speed of processing deficits have previously been reported in patients with schizophrenia and FEP (Dickinson, Ramsey & Gold, 2007; Mesholam-Gately, Giuliano, Goff, Faraone & Seidman, 2009). Deficits in speed of processing have also been observed in adolescents reporting PLEs (Blanchard et al., 2010; Kelleher, Clarke, Rawdon, Murphy & Cannon, 2012c; Kelleher et al., 2012d).

Comorbid diagnoses of depression and anxiety are common in schizophrenia (see section 1.2.8). Adolescents who report PLEs have been shown to be at an increased risk of other psychopathologies including anxiety, suicidal ideation, self harm and depressive disorders (Nishida et al., 2008; Scott et al., 2009; Kelleher et al., 2012a; 2012e; in press). A study carried out by Yung et al. (2006) found a relationship between self-reported bizarre experiences and persecutory ideas and increased levels of distress, depression, poor functioning and the presence of mood disorders in a sample of 15 to 24 year olds who attended a youth mental health clinic in Australia but were not considered prodromal for psychosis. Nishida et al. (2010) reported that adolescents who experience PLEs may be at increased risk of suicidal feelings and deliberate self-harm. ‘Spied upon’ and ‘heard voices’ PLEs were significantly associated with increased risk of

suicidal feelings and deliberate self-harm, and 'thoughts read' PLEs were significantly associated with suicidal feelings. In addition, the risk of these behaviours increased as more types of PLEs were experienced. Saha et al. (2011) reported that endorsement of what they called 'delusion-like experiences' among adolescents resulted in a 2 to 4 times greater likelihood of reporting life-time suicidal ideation, plans or attempts.

1.5 Cognitive Impairments in Psychotic Disorders and At-Risk Populations – Evidence from Neuropsychology, Electrophysiology and Imaging Studies

1.5.1 Overview

In addition to the perceptual, social and emotional disturbances observed in schizophrenia, cognitive disruptions are also frequently reported which include impairments of attention, concentration and memory and both receptive and expressive language. Again, like some of the risk factors outlined in sections 1.2. and 1.4, these cognitive impairments may also be present long before the diagnosis of a clinical psychotic disorder and the need for treatment. Consistent with the neurodevelopmental model of psychosis, these neurocognitive impairments may precede the expression of psychotic illness and therefore may act as a vulnerability marker for psychosis.

Erlenmeyer-Kimling et al. (2000) suggest that deficits in verbal memory, gross motor skills and attention are relatively specific to schizophrenia risk. Cannon et al.

(2002a) found an association between neuromotor impairments, as well as receptive language and cognitive impairments and psychotic symptoms in children assessed at biennial intervals between the ages of 3 and 11 years. Pflueger, Gschwandtner, Stieglitz and Riecher-Rössler (2007) found verbal intelligence, executive functions and, in particular, working memory best discriminated between a group defined as at-risk mental state (ARMS) and a control group. Research in relation to cognitive disruptions such as attention, speed of processing/context updating and memory will be discussed in more detail in sections 1.5.2 and 1.5.3, respectively.

1.5.2 Attention, Speed of Processing, Context Updating and Language

Deficits in attention have been proposed to be fundamental to disturbed cognitive processing in patients with schizophrenia (Neuchterlein, Dawson, Ventura, Miklowitz & Konishi, 1991; Fioravanti, Carlone, Vitale, Cinti & Clare, 2005; Carter et al., 2010). Attention impairments have also been highlighted as being relatively specific to schizophrenia risk (Erlenmeyer-Kimling et al., 2000) and have been shown in FEP and prodromal populations (Bilder et al., 2000). Impaired attention may be a vulnerability marker for schizophrenia (Liu, Chen, Chang & Lin, 2000). Impairments of attention have been linked to reduced activity in the anterior cingulate cortex (Carter, MacDonald, Ross & Stenger, 2001) and electrophysiological studies have reported a reduction in the error-related negativity (ERN) of the event-related potential (ERP) recording in schizophrenia (Mathalon et al., 2002). ERN (Gehring, Goss, Coles, Meyer & Donchin, 1993; Luck, 2005) or error negativity (NE; Falkenstein, Hohnsbein, Hoormann & Blanke, 1990; Falkenstein, Hohnsbein, Hoormann & Blanke, 1991) is a response-locked ERP that is observed when participants make an error on a speeded

response task and is thought to reflect pre-conscious conflict monitoring processes. Laurens et al. (2010) provided evidence for reduced ERN in adolescents presenting a triad of putative antecedents of schizophrenia using a Go/No Go task.

A reduction in mismatch negativity (MMN) is a robust finding in the ERP literature in relation to schizophrenia (Umbricht & Krljes, 2005). It has been reported in schizophrenia patients (Mitchie, 2001), FEP and most recently in prodromal populations (Atkinson, Michie & Schall, 2012). MMN is an auditory ERP component that occurs in response to any violation of the regularity of the recent auditory past, and is usually observed in a passive auditory oddball task. That is, when a stimulus which deviates in frequency, duration, intensity or location is presented among a set of non-deviant stimuli. MMN is thought to be a measure of preattentive information processing or sensory memory and is usually best observed as a difference wave between standard and deviant tones which usually peaks between 100 and 240ms after the presentation of the deviant stimulus (Näätänen, 1995). A study by Bodatsch et al. (2011) reported that duration MMN was significantly reduced in at-risk subjects who converted to first-episode psychosis compared to those subjects who did not convert. Brockhaus-Dumke et al. (2005) also reported a trend towards MMN amplitude in a putatively prodromal group being intermediate between schizophrenia patients and controls; however, their result did not reach statistical significance. The earlier part of the P300 component, the P3a, has been studied in schizophrenia, with reports of a reduced P3a in response to novel irrelevant stimuli in an active oddball task (Turetsky, Bilker, Siegel, Kohler & Gur, 2009). Reduced duration deviant MMN has recently been reported in adolescents reporting PLEs (Murphy et al., 2013).

It has recently been proposed that speed of processing may be one of the core deficits of psychotic disorders such as schizophrenia (Dickinson et al. 2007; Rodriguez-

Sanchez et al., 2007; Dickinson, 2008). Speed of processing deficits have recently been reported in FEP (Mesholam-Gately et al., 2009) and in the psychosis prodrome and adolescents who reported PLEs (Kelleher et al., 2012c; 2012d). Blanchard et al. (2010) found that adolescents who reported PLEs exhibited significant impairments in receptive language (as measured by the British Picture Vocabulary Scale), motor function (as measured by the Pegboard Test) and executive function/speed of processing (as measured by the Trail Making Test). Murphy et al. (2012) used a computerised version of the British Picture Vocabulary Scale (BPVS; Dunn, Whetton & Burley, 1997) to assess receptive language in a group of adolescents who reported PLEs. The PLEs group performed more poorly on the difficult levels of the task and reduced amplitude of the P300 component in the PLEs group compared to the control group was observed.

1.5.3 Memory

In a review of the literature, Wood et al. (2003) state that working memory may represent a neurocognitive trait marker for schizophrenia, as it is considerably impaired throughout the illness, it involves neural circuits deemed dysfunctional in the disorder and has been associated with negative symptoms. Working memory impairments have been observed in schizophrenia patients and FEP (Kim, Glahn, Nuechterlein & Cannon, 2004; Gooding & Tallent, 2004; Zanello, Curtis, Badan Bâ & Merlo, 2009). In addition, deficits in working memory have been observed in groups defined as genetically at-risk of developing schizophrenia, as well as relatives of schizophrenia patients (Glahn et al., 2003; Brahmbhatt, Haut, Csernansky & Barch, 2006; Horan et al., 2008; Bachman et al. 2009). More recently, impairments in working memory have been reported in groups

considered clinically at-risk of psychosis such as prodromal/UHR groups (Brewer et al., 2005; Smith, Park & Cornblatt, 2006; Pflueger et al., 2007; Frommann et al., 2011) and groups who report PLEs (Laurens et al., 2008b).

Results from imaging studies and electrophysiological research have added further to our understanding of working memory deficits in schizophrenia. As outlined in section 1.2.7, schizophrenia is associated with changes in neuroanatomy including prefrontal cortex dysfunction (Kring et al., 2007). The prefrontal cortex is one of the key areas involved in working memory and alterations in activity in the prefrontal cortex, in particular the dorsolateral prefrontal cortex, have been observed in schizophrenia patients during working memory tasks (Manoach et al., 1999; Manoach et al., 2000; Perlstein, Carter, Noll & Cohen, 2001; Callicott et al., 2003; Cannon et al., 2005; Schlösser et al., 2008).

Results from functional Magnetic Resonance Imaging (fMRI) studies of genetically and symptomatically at-risk groups have provided evidence that activations maybe be reduced in a number of areas prior to the onset of a clinical psychotic disorder. In a study of verbal working memory in participants defined as ARMS, Broome et al. (2009) found activation in the at-risk group was intermediate relative to that of the control group and the FEP group. Specifically, activation was reduced for the psychosis group relative to the at-risk group and the at-risk group relative to the control, in the inferior frontal and anterior cingulate cortex during the verbal fluency task, and in the inferior frontal, dorsolateral prefrontal and parietal cortex during the *n*-back task. Spatial working memory studies have reported a decrease in activity in the dorsolateral prefrontal and inferior parietal cortex in genetically high-risk groups (Keshavan et al., 2002) and in the medial prefrontal cortex in ARMS groups (Broome et al., 2010).

In terms of electrophysiological studies, the most common finding in the literature is the elicitation of a sustained parietal positivity to the test probe in working memory tasks (irrespective of whether probe type is positive or negative) with a monotonous increase in latency as memory set size increases (Marchand, Lefebvre & Connolly, 2006). In other words, as the number of items to be remembered increases so does the ERP latency and activity at parietal electrodes. The P3b component is associated with the updating of working memory (Bramon, Rabe-Hesketh, Sham, Murray & Frangou, 2004). Electrophysiological studies of working memory in schizophrenia patients and populations at-risk for schizophrenia will be discussed in Chapter 6, section 6.1.

1.6 Aims and Objectives

Studying adolescents who are considered symptomatically at-risk of psychosis (i.e. those who are experiencing subclinical symptoms of psychosis) provides an opportunity to examine susceptibility to the development of psychosis. Further research in this area may therefore provide an opportunity for earlier diagnosis and intervention. The current research project aims to uncover possible behavioural and electrophysiological markers associated with PLEs in a young adolescent population.

In the present thesis, auditory processing, spatial cognition and spatial working memory, will be explored in a group of participants reporting PLEs. Chapter 2 which follows provides a summary of the methods used in the following thesis. Details of participant recruitment and earlier stages of the ABD Study such as the clinical

interviews and neuropsychological testing carried out will be outlined. The electrophysiological methods used throughout this thesis and the physiological basis of ERPs will be described in detail. The data collection and analyses techniques employed will be discussed followed by a brief summary of the tasks and methods employed in Chapters 3, 4, 5 and 6 respectively.

Chapter 3 will investigate group differences on a number of neuropsychological tests from the MATRICS Consensus Cognitive Battery. Group differences on tests of speed of processing, attention, working memory, verbal learning, visual learning, reasoning and problem solving will be examined. EEG activity during resting state will also be explored. A two-tone active auditory oddball paradigm will be employed in Chapter 4 to explore electrophysiological correlates of auditory processing. Behavioural differences in accuracy to target and non-target tones and reaction time to target tones will be assessed. Mean amplitude of the P300 component to target tones will be explored with reduced mean amplitude of this component anticipated in the PLEs group. In addition the amplitude of the N100 auditory evoked potential (AEP) to both target and non-target tones will also be explored with reduced amplitude anticipated in the PLEs group.

Chapter 5 will assess spatial processing using an implicit spatial memory task in adolescents who report PLEs and a control group using behavioural measures and EEG techniques. Differences in accuracy scores and reaction times will again be explored between the groups. Between-group differences in the amplitude and latency of the P300 waveform will again be explored with reduced amplitude anticipated in the PLEs group relative to the control group. Behavioural and ERP correlates of spatial working memory in adolescents who report PLEs and a control group will be explored in Chapter 6. In this chapter, behavioural differences in accuracy scores and reaction times

will be explored while participants complete a computerised spatial working memory task. Differences in the mean amplitude and latency of the P300 ERP component during retrieval on the spatial working memory task will be explored.

Chapter 2

General Methods

Overview

The purpose of the following chapter is to provide a more detailed description of the methods used in the experimental chapters of the present thesis than is possible to include within each experimental chapter separately. Another purpose of the following chapter is to outline the context in which the present thesis took place and to outline *why* the behavioural and in particular the electrophysiological tools used were chosen, how they compare to other neuroimaging techniques available and *how* the behavioural and electrophysiological tools were employed.

The present thesis was carried out as part of the Adolescent Brain Development Study carried out by Royal College of Surgeons in Ireland and Beaumont Hospital, a project which was supervised by Professor Mary Cannon (henceforth referred to as the ABD Study). Prior to taking part in the electrophysiological part of the ABD Study, participants went through a screening process in schools and completed a clinical interview and neuropsychological testing (details of this process are outlined below in section 2.1).

Section 2.2 contains background information on electrophysiology and electroencephalography (EEG), a brief history of the method, the physiological basis of event-related potentials (ERPs), as well as a detailed account of the limitations of electroencephalography and its advantages and disadvantages for research. Section 2.3 contains a detailed account of the data collection and analysis process while section 2.4 contains information about the tasks that were chosen for inclusion in the present thesis.

2.1 Participant Recruitment, Clinical Interviews and Neuropsychological Testing

2.1.1 Participant Recruitment

Participants were recruited from local primary schools in Co. Kildare and north Co. Dublin. Initial contact was made by letter to each school principal, inviting the school to take part in the ABD Study being carried out by the Royal College of Surgeons in Ireland and Beaumont Hospital in collaboration with the National University of Ireland Maynooth under the supervision of Professor Mary Cannon. Consent was obtained from each school principal to visit the school on two occasions to recruit participants from fifth and sixth classes (i.e. 11-13 year olds, the two most senior primary school classes). On the first visit to the schools, a brief presentation was given to pupils outlining details of the study. Information sheets and consent forms were distributed to pupils to take home to their parents/guardians (see Appendix III and IV). On the consent form, parents/guardians were asked to tick a box to indicate consent for their child to take part in the first part of the study and complete the questionnaire in class. Parents/guardians were also asked to tick a second box and leave contact details if they would like to hear about the next part of the study which included the clinical interview, neuropsychological testing and EEG study.

During the second visit to the schools participants from whom consent was obtained were screened using a questionnaire comprising of questions from the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997; Goodman, Meltzer & Bailey, 1998) and a 7-item Adolescent Psychotic-Like Symptom Screener (APSS; Kelleher et al., 2011-details outlined below). Contact details were also obtained on the consent forms from those participants and their parents/guardians who wished to take part in the next part of the study, i.e. the clinical interviews and the subsequent EEG

study. Letters were sent by post to these participants containing further details of the clinical interviews, neuropsychological testing and the EEG study, and follow-up calls were made to arrange appointments (see Figure 2.1 for a full timeline of school visits and data collection for the ABD Study).

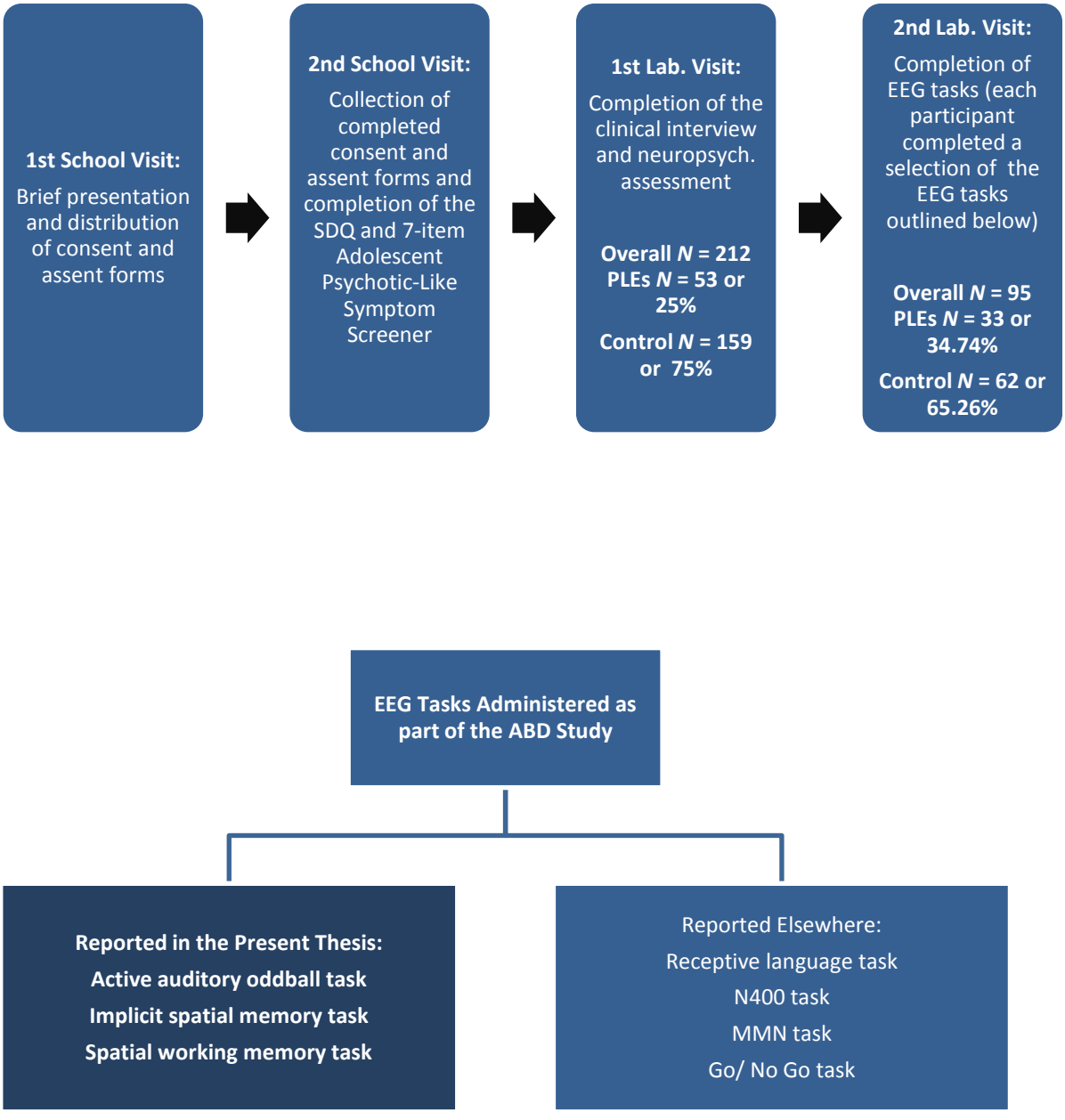


Figure 2.1: *Timeline of school visits and data collection for the ABD Study.*

2.1.2 Questionnaires

Participants were screened in schools using a questionnaire comprising of questions from the SDQ (Goodman, 1997; Goodman et al., 1998) and the 7-item APSS (Kelleher et al., 2011; see Appendix V).

2.1.2.1 The Strengths and Difficulties Questionnaire.

A self-report version of the SDQ, a brief behavioural screening questionnaire, for 11-16 year old was administered within the classroom (Goodman et al., 1998). The SDQ contains 25 items on psychological attributes, some positive and others negative. These 25 items are divided between 5 scales; emotional symptoms (5 items), conduct problems (5 items), hyperactivity/inattention (5 items), peer relationship problems (5 items) and prosocial behaviour (5 items).

2.1.2.2 The Adolescent Psychotic-Like Symptoms Screener.

The 7-item APSS (Kelleher et al., 2011) contained four questions from the Diagnostic Interview Schedule for Children (Poulton et al., 2000; Costello, Edelbrook, Kalas, Kessler & Klaric, 1982) and three further questions on visual hallucinations, delusions of control and grandiosity. The 7-item APSS included questions about mind reading, TV/radio, spying, auditory hallucinations, control, visual hallucinations and grandiosity (see Table 2.1). The questionnaire took approximately 20 minutes for each participant to complete. Participants were asked to complete the questionnaire independently and without allowing other participants to see their answers in order to ensure accuracy and confidentiality. They were advised that if there was any question that they did not understand, they could ask one of the research team for clarification. Upon completion

of data collection within the school, participants were then posted information in relation to the next stage of research which involved completion of a clinical interview and neuropsychological testing (see Appendix VI).

Table 2.1: *Questions from the 7-item Adolescent Psychotic-like Symptom Screener.*

Item Abbreviation	Item Question
Mind reading	Some people believe that their thoughts can be read by another person. Have other people ever read your mind?
TV/Radio	Have you ever had messages sent just to you through TV or radio?
Spying	Have you ever thought that people are following or spying on you?
Auditory Hallucinations	Have you ever heard voices or sounds that no one else can hear?
Controlled	Have you ever felt you were under the control of some special power?
Visual Hallucinations	Have you ever seen things that other people could not see?
Grandiosity	Have you ever felt like you had extra special powers?

2.1.3 Clinical Interview

Of the 1131 adolescents who completed the first part of the ABD Study in the classroom, 656 (58%) adolescents and their parents provided information to be contacted about the subsequent stages of the study. In total 212 (32% of those who agreed to be contacted) adolescents and their parents were interviewed. Prior to commencing the clinical interview the participant and their parent/guardian were informed about the nature of the interview, were given time to ask questions about the process and then completed assent and consent forms respectively. The participant and

their parent/guardian were advised that they had the right to withdraw their participation at any time and that both the child and parent/guardian would be interviewed separately and that information discussed in the interviews would remain confidential. However, participants were informed that if information arose in the interview which led the interviewer to believe that the safety of an individual was under threat then the interviewer would be legally bound to break that confidentiality.

The Kiddie – Schedule for Affective Disorders and Schizophrenia for School Aged Children (6-18 Years) – Present and Lifetime Version (K-SADS-PL; Kaufman, Birmaher, Brent, Rao & Ryan, 1996) was used to further assess and confirm the validity of the psychotic-like experiences (PLEs) which participants had reported in the 7-item APSS (Kelleher et al., 2011) previously administered in the school classroom. The K-SADS-PL diagnostic interview is designed to assess current and past episodes of psychopathology in children and adolescents according to DSM-III-R and DSM-IV criteria (Kaufman et al., 1996). The K-SADS-PL is used for the diagnosis of all Axis-1 psychiatric disorders in children and adolescents. If the interviewer was concerned about symptoms which arose during the interview process or if sufficient evidence of an underlying disorder was uncovered in the participant, the parent was informed and a referral letter was provided for the participant's General Practitioner or the Child and Adolescent Mental Health Team.

The K-SADS-PL is a well validated semi-structured interview. Probes are included in the interview document; however these probes do not have to be recited verbatim. Rather, they are provided to illustrate ways to elicit the information necessary to score each item. The interviewer can adjust the probes to the developmental level of the child, and use language supplied by the parent and child when querying about specific symptoms. Interviews were carried out by a group of psychologists and psychiatrists who were fully trained and skilled in the use of the instrument. When

administering the interview to pre-adolescent participants, it is advised that the parent interview is conducted first; when interviewing adolescents, it is advised that the parent interview is conducted second. For the present study the participant was always interviewed first, followed by the parent/guardian interview. Administration of the K-SADS-PL requires the completion of: 1) an Unstructured Introductory Interview; 2) a Diagnostic Screening Interview; 3) the Supplement Completion Checklist; 4) the appropriate Diagnostic Supplements; 5) the Summary Lifetime Diagnoses Checklist; and 6) the Children's Global Assessment Scale (C-GAS; Shaffer et al., 1983) ratings.

The K-SADS-PL was completed with each informant (i.e. the child and parent/guardian) separately initially, and then the Summary Lifetime Diagnoses Checklist and C-GAS ratings were completed after synthesizing all the data and resolving discrepancies in informants' reports. If there was no suggestion of current or past psychopathology, no assessments beyond the Screen Interview were necessary. The psychosis section of the K-SADS-PL was used to enquire about any PLEs reported, both current and past, and positive responses to any of the screening questions were followed by detailed probing. All participants who reported PLEs during the screening section were subsequently assessed using the detailed psychosis supplement of the K-SADS-PL, and extensive notes were taken during the interview.

The Unstructured Introductory Interview of the K-SADS-PL took approximately 10 to 15 minutes to complete. In this section, demographic, health, any presenting complaints and prior psychiatric treatment data were obtained, together with information about the child's school functioning, hobbies, and peer and family relations. Discussion of these latter topics was extremely important, as they provided a context for eliciting mood symptoms (depression and irritability), and obtaining information to evaluate functional impairment. This section of the K-SADS-PL was used to establish rapport with the child and the parent/guardian. A current C-GAS score was assigned to

assess all participants' current level of functioning based on the information obtained during the clinical interview. C-GAS scores range from 1-100 ranging from a score of 1-10 indicating that a child needs constant supervision to 91-100 indicating superior functioning in all areas (see Appendix VII for the full range of C-GAS scores).

2.1.4 Consensus Meeting

Once the interviews were completed a consensus meeting was held between three raters (1 psychologist and 2 psychiatrists) in order to evaluate the results of the interviews. Raters reviewed the psychosis sections of the K-SADS-PL interviews for each participant and were blind to psychiatric diagnoses (see Appendix VIII for a copy of the psychosis section of the K-SADS-PL). Based on the clinical judgement of the raters participants were rated as having no PLEs, strong PLEs or weak PLEs (see Appendix IX for study guidelines on rating strong PLEs and weak PLEs). Strong PLEs were hypothesised as being at increased risk for psychotic disorder. Weak PLEs were deemed to be of little clinical significance and these participants were included as part of the control group. The most commonly reported strong PLEs included both formed and unformed auditory hallucinations. A formed hallucination involves hearing one or more voices saying at least one word whereas an unformed auditory hallucination may involve whispering voices, voices at normal volume or shouting voices where the words cannot clearly be distinguished by the individual (see Table 2.2 and Appendix X for more information on the type of experiences classed as strong PLEs).

2.1.4.1 Reports of PLEs during the clinical interviews.

The analysis of the interview data revealed that 52.8% (N = 112) of participants reported no experience of PLEs, 22.2% (N = 47) reported weak PLEs and 25% (N = 53) reported strong PLEs. Henceforth the groups in the present thesis will be referred to as the control group comprising of those participants who reported no PLEs and those participants who reported weak PLEs and the PLEs group comprising of those participants who reported strong PLEs.

Table 2.2: *Classification of PLEs in the ABD Study.*

Hallucinations	**Delusions**
Auditory Hallucinations:	Being watched by a person or organisation
Formed: Hearing one or more voices saying at least one word	Recurrent, unfounded or exaggerated ideas that others are saying negative things about the individual
Unformed: Hearing voices where the words cannot easily be distinguished	Belief in communication with ghosts
Visual Hallucinations:	Mind reading
Seeing people, faces, ghosts, aliens	
Tactile Hallucinations:	
Classed as strong PLEs if involving delusional attributions	

2.1.5 Neuropsychological Assessment

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB; www.matrics.ucla.edu) was employed as the neuropsychological assessment tool. The MCCB included ten tests

which assess seven cognitive domains. These domains are as follows; speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving and social cognition (see Table 2.3). The social cognition domain was not included in the test battery for the ABD Study.

The list of tests included in the MCCB for each domain was as follows:

Speed of Processing:

1) Brief Assessment of Cognition in Schizophrenia Symbol Coding (BACS SC) – this is a timed paper-and-pencil test in which participants use a key to write digits that correspond to nonsense symbols.
2) Category Fluency – an oral test in which the participant name as many animals as he/she can in one minute.
3) Trail Making Test – a timed paper and pencil test in which the participant draws a line to connect consecutively numbered circles placed irregularly on a sheet of paper in Trail A and a series of consecutively numbered and lettered circles in Trail B.

Attention/Vigilance:

1) Continuous Performance Test – Identical Pairs (CPT-IP) – a computer administered measure of sustained attention in which the participant makes a button press response to two consecutive matching numbers.

Working Memory (verbal and non-verbal):

1) Wechsler Memory Scale – 3rd Ed. (WMS-III): Spatial Span – Using a board on which ten cubes are irregularly spaced, the participant taps cubes in the same or reverse sequence as the test administrator.

2) Letter Number Span (LNS) – an orally administered test in which the participant must mentally reorder strings of numbers and letters and repeat them to the administrator.

Verbal Learning:

1) Hopkins Verbal learning Test – Revised (HVLT-R) – an orally administered test in which a list of twelve words from three taxonomic categories is presented and the participant is asked to recall as many of the words as possible after each of three learning trials.

Visual Learning:

1) Brief Visuospatial Memory Test – Revised (BVMT-R) – a test that involves reproducing six geometric figures from memory.

Reasoning and Problem Solving:

1) Neuropsychological Assessment Battery (NAB): Mazes – seven timed paper-and-pencil mazes of increasing difficulty that measure foresight and planning.

Table 2.3: *Neuropsychological Tests included in the MATRICS Consensus Cognitive Battery.*

Domain	**Speed of Processing**	**Attention/Vigilance**	**Working Memory (Verbal and Non-Verbal)**	**Verbal Learning**	**Visual Learning**	**Reasoning and Problem Solving**
Test	Brief Assessment of Cognition in Schizophrenia Symbol Coding (BACS SC)	Continuous Performance Test – Identical Pairs (CPT-IP)	Wechsler Memory Scale – 3rd edn (WMS-III): Spatial Span (WMS-SS)	Hopkins Verbal learning Test – revised (HVLT-R)	Brief Visuospatial Memory Test – Revised (BVMT-R)	Neuropsychological Assessment Battery (NAB) Mazes
	Category Fluency		Letter Number Span (LNS)			
	Trail Making Test (TMT)					

2.2 Electrophysiology

2.2.1 A Brief History of Electrophysiology and Electroencephalography (EEG)

Richard Caton (1842-1926) first explored electrical phenomena of the exposed cerebral hemispheres of rabbits and monkeys. A detailed report of his findings was published in the British Medical Journal in 1877 outlining experiments on over 40 rabbits, cats and monkeys (Niedermeyer & da Silva, 2005). Caton noted that the external surface of the gray matter was positively charged in relation to deep structures of the cerebrum. He also noted that the electrical currents of the cerebrum appeared to have a relation to underlying function; therefore Caton has been credited with pioneering work on the evoked potential (EP). Adolf Beck (1863-1939) added to the work of Caton by investigating the spontaneous activity of the brain in dogs and rabbits. Beck observed the disappearance of rhythmical oscillations when the eyes were stimulated with light, a finding which later led to Berger's discovery of alpha blocking (Niedermeyer & da Silva, 2005).

Studies of the human EEG began in 1924 when Hans Berger showed oscillations presumably coming from the electrical activity of the underlying brain. In 1929, Berger reported what could be described as the first set of experiments using an electroencephalogram to record the electrical activity of the human brain from the scalp. It was in this publication that Berger first used the term "Elektenkephalogramm". Berger (1929) reported that one could measure the electrical activity of the human brain by placing an electrode on the scalp, amplifying the signal and plotting the changes in voltage over time. This report featured the alpha rhythm and the alpha blocking response, along with a description of the beta waves. Throughout the 1930s, Berger's reports contained studies of fluctuations of consciousness, EEG recordings of sleep the

effect of hypoxia on the brain, diffuse and localised brain disorders and a reference to epileptic discharges (Niedermeyer & da Silva, 2005).

In the years following Berger's (1929) report, other researchers confirmed the details of Berger's observations, including Adrian and Matthews (1934), who also reported the observation of human EEG activity, as well as Jasper and Carmichael (1935) and Gibbs, Davis and Lennox (1935). The first sensory ERP recordings from awake humans were published by Pauline and Hallowell Davis, in which changes in the EEG due to a sensory stimulus were extracted and named the evoked potential (Davis, Davis, Loomis, Harvey & Hobart, 1939; Davis, 1939a; 1939b).

In 1947, the American EEG Society was founded and the First International EEG Congress was held in London. In the late 1940s, the EEG technique became invasive, and deep intra cerebral regions were explored with the use of special depth electrodes. George D. Dawson published a paper entitled *"A summation technique for detecting small signals in a large irregular background"*, which was considered a pioneering study in the field of evoked potential studies (Dawson, 1951). Up until the 1950's no standard map for electrode placement on the scalp existed. The 10-20 system of electrode placement, the most common system for placing and naming electrode sites, was developed in the late 1950s by the International Federation of Clinical Neurophysiology (Jasper, 1958).

The first cognitive ERP component was reported by Walter and colleagues (Walter, Cooper, Aldridge, McCallum & Winter, 1964) and was observed during the period of time that separated a warning signal (e.g. a click) from a target stimulus (e.g. a series of flashes). Walter et al. (1964) observed a large negative voltage at frontal electrode sites during this period and named this voltage contingent negative variation (CNV). The P3 (or P300) component was discovered by Sutton, Braren, Zubin and

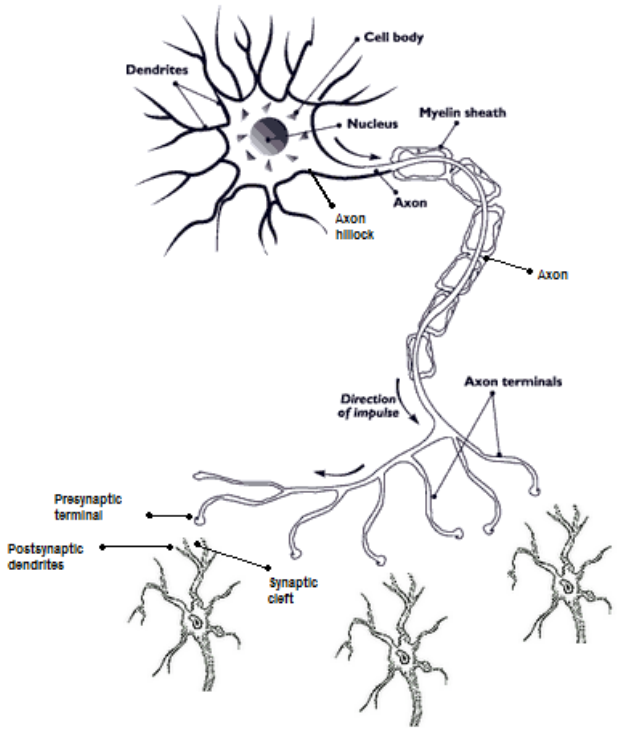
Johns (1965), who reported a large positive component, peaking 300ms post stimulus in response to an unpredictable event i.e. when a stimulus could be either visual or auditory as opposed to visual only or auditory only.

2.2.2 Physiological Basis of Event-Related Potentials (ERPs)

In order to understand the activity recorded at the scalp, it is necessary to first outline how this activity is generated inside the brain. The neuron (nerve cell) is the basic information processing and transmission unit of the nervous system – see Figure 2.2 a and 2.2 b for an outline of the basic structure of a neuron and synaptic transmission. Neurons contain several basic components including the soma or cell body, the dendrites, the axon and the axon terminals or terminal boutons (as outline in Figure 2.2 a).

Neurons have a difference in the electrical charge between the inside and the outside of the cell, the inside of the cell being negatively charged relative to the outside of the cell. This difference in electrical charge is the neuron's *resting potential*. The resting potential of a neuron is typically -70millivolts (mV), i.e. the inside of the cell is approximately 70mV more negatively charged than the outside. The cell membrane of a neuron acts as a barrier which separates electrically-charged particles known as ions on the inside of the cell from ions on the outside of the cell. There are two types of electrical activity associated with neurons; these are action potentials and postsynaptic potentials (Luck, 2005).

(a)



(b)

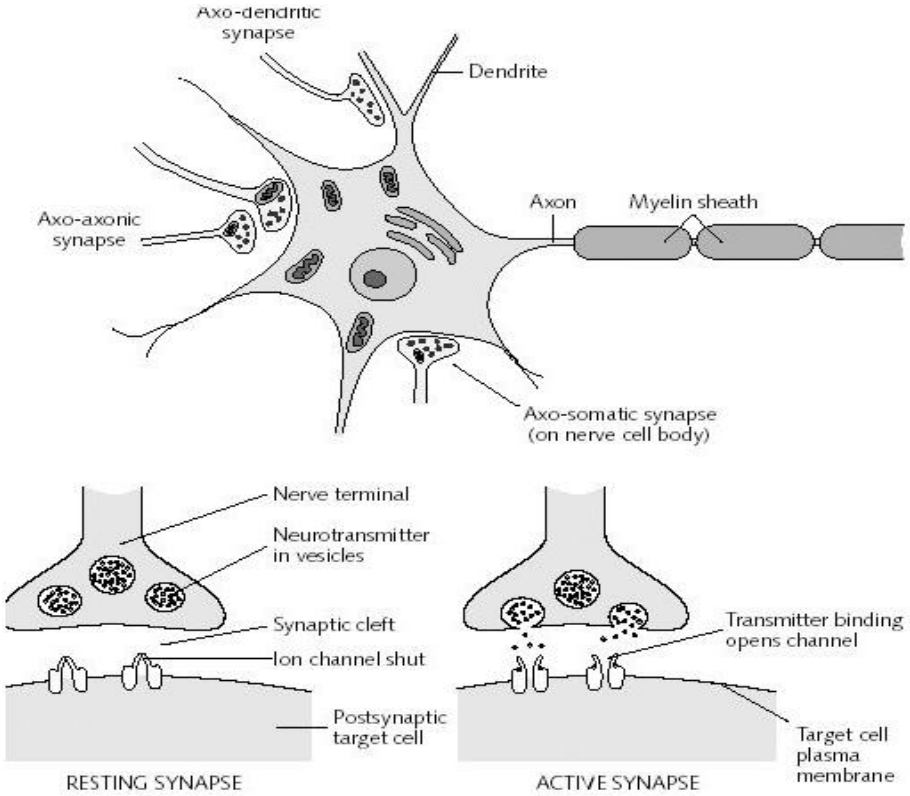
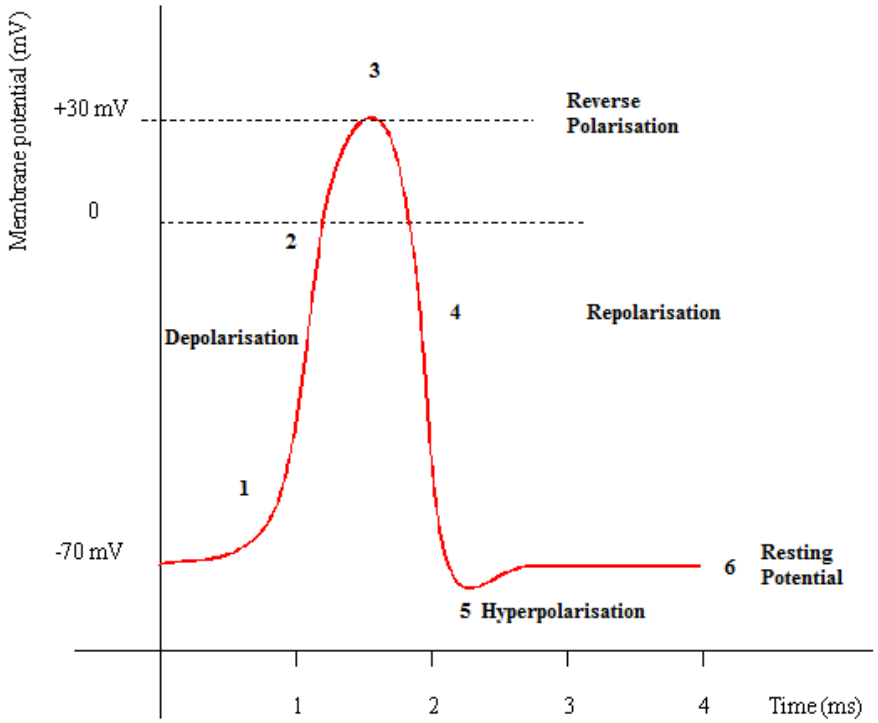


Figure 2.2: *(a) Structure of a typical neuron* – adapted from: http://www.suboxoneassistedtreatment.org/resources/mom_nerve1_fs.gif

(b) Synaptic transmission Source: http://content.answcdn.com/main/content/img/oxford/Oxford_Body/019852403x.synapse.1.jpg

Action potentials (APs) are discrete voltage spikes/brief electrical impulses that travel from the beginning of the axon at the cell body to the axon terminal boutons, where neurotransmitters are released. APs are very brief (~1.5ms) and provide the basis for the conduction of information along the axon. The generation of an AP requires a threshold to be reached; in other words it is an 'all or nothing' occurrence. This threshold (approx -50mV) must be reached in order for the AP to be generated and the cell to fire. The generation of an AP depends on the opening and closing of the voltage-dependent sodium (Na) and potassium (K) ion channels of the cell membrane (see Figure 2.3 for an illustration of the steps involved in the generation of an AP). Once the required voltage is reached, sodium channels open, sodium rushes into the cell causing *depolarisation*; i.e. the membrane potential changes and the inside of the cell becomes more positively charged (~-30mV). This positive shift in potential means the membrane becomes less polarised. As the voltage goes above zero, this opens voltage-dependent potassium channels, which are less sensitive than the sodium channels and thus need more depolarisation before they open. When the action potential reaches its peak +30mV at approximately 1ms, the electrical charge then begins to return to the baseline resting potential, a process known as *repolarisation*. As the membrane potential returns to the normal resting potential it becomes even more negative, to ~-90mV, this is known as *hyperpolarisation*, before returning to the resting potential at ~-70mV (see Figure 2.3).



1 - Once the voltage threshold is reached, sodium channels open

2 - Sodium ions rush into the cell causing depolarisation, the membrane potential changes

3 - As the voltage goes above zero, this opens voltage-gated potassium channels, these are less sensitive than the sodium channels and require more depolarisation before they open, potassium ions leave the cell

4 - This makes the membrane potential start to return to a negative state again (repolarisation)

5 - As the membrane potential starts to return to normal (-70mV) the potassium channels begin to close, no more potassium leaves the cell. The membrane actually overshoots it's resting membrane potential (hyperpolaristion)

6 - Following hyperpolarisation, the neuron gradually returns to the resting potential via the work of the sodium-potassium pump

Figure 2.3: *An Action Potential* – adapted from: http://www.antonine-education.co.uk/physics_a2/options/Module_6/Topic_4/action_potential.gif

Postsynaptic potentials (PSPs) are the voltages that arise when the neurotransmitters released across a synapse by a presynaptic neuron (due to the occurrence of an AP) bind to receptors on the membrane of the postsynaptic cell, causing ion channels to open or close and leading to a graded change in the potential across the cell membrane. Signals that depolarise the postsynaptic cell increase the chance of an AP and are called excitatory postsynaptic potentials (EPSP). On the other hand, signals that hyperpolarise the postsynaptic cell decrease the chance of an AP and are called inhibitory postsynaptic potentials (IPSP). Unlike APs which remain constant in magnitude for the entire duration of their journey, PSPs dissipate the further they travel from their source. In addition, PSPs can be either excitatory or inhibitory, unlike APs which can only be excitatory; in addition PSPs smaller in magnitude (range 0.5 to 5mV) than APs.

The electrical potential recorded at an electrode site on the scalp is the summed signal of the postsynaptic electrical fields of similarly-aligned neuronal dendrites (Banich, 2004). While EPSPs produce local membrane current sinks with corresponding distributed passive sources to preserve current conservation, IPSPs produce local membrane current sources with more distant distributed passive sinks (Nunez & Srinivasan, 2006). It is the summated effects of these sinks (depolarisations, EPSPs) and sources (hyperpolarisations, IPSPs) *rather than action potentials themselves* that are recorded by EEG and ERPs. The co-occurrence of these sinks and sources means that the cell can be viewed as a dipole. The dipole created by a single neuron is so small that it is not possible to record this activity from the scalp. Instead the scalp recorded activity reflects the activity of large numbers of dipoles of the same polarity which fire synchronously. This summation of dipoles is most likely to occur in cortical pyramidal layers.

EEG and ERPs measure the electrical activity produced by the brain through the summated activity of electrical currents produced post-synaptically, via electrodes placed on the scalp. Luck (2005) defines an ERP component as scalp-recorded neural activity that is generated in a given neuroanatomical module when a specific computational operation is performed. ERPs are any changes in the EEG recording (i.e. the ongoing electrical activity of the brain) which are caused by the specific occurrence of a cognitive, motor or perceptual event. That is, any changes in the ongoing EEG which occur in response to a visual, auditory or motor event are amplified, averaged and extracted from the background EEG are stimulus-locked or response-locked ERPs. The resulting component is then plotted as a graph with time in milliseconds displayed on the x-axis and voltage plotted in microvolts on the y-axis (see section 2.2.3).

2.2.3 A Summary of Major Event-Related Potential (ERP) Components

As mentioned in section 2.2.2, ERPs are any change in EEG recording, i.e. the ongoing electrical activity of the brain, which are caused by the specific occurrence of a cognitive, motor or perceptual event. ERPs are generally averaged over a large number of trials in order to reduce the signal to noise ratio. After averaging the data over a large number of trials, the resulting averaged ERP waveform consists of a sequence of positive and negative voltage deflections, which are called peaks, waveforms or components (Luck, 2005).

ERP components are named according to whether their voltage is positive or negative and according to the approximate time within the epoch at which they occur. *P* and *N* are usually used to indicate positive-going or negative-going components, respectively. The number which follows P or N indicates a component's position or latency within the epoch; for example, P3 or P300 indicates a positive component

occurring at approximately 300ms (following the presentation of a stimulus). Components can be either exogenous or endogenous. Exogenous components are linked to the physical characteristics of a stimulus and usually occur early in the waveform (up to 200ms), whereas endogenous components seem to be independent of stimulus characteristics and driven by internal cognitive states (Banich, 2004). Table 2.4 presents an overview of some of the main components elicited in cognitive research.

2.2.3.1 The P300 component.

The P3 or P300 component is one of the most studied components in ERP research. Although there is a lot of disagreement in the literature about what exactly the P300 component measures, it has been proposed that it is related to attention and the updating of memory processes which occurs when a person modifies his or her environment to include incoming information (Donchin, 1981; Donchin & Coles, 1988). Bramon et al. (2004) state that the P300 waveform has been conceptualised as the physiological correlate of a working memory update of changes in the environment or as an index of the allocation of attentional resources. Researchers have further distinguished between the earlier P3a and the later P3b components. Squires, Squires and Hillyard (1975) were the first to make this distinction, stating that the P3a was frontally maximal while the P3b was parietally maximal.

The P300 component occurs in many ERP experiments, however it is commonly observed in oddball paradigms, in particular in auditory oddball paradigms in which a larger P300 is generally elicited by the oddball tone. Typically a P300 is observed when the participant must pay attention (i.e. on the oddball trial) and when that oddball is distinct from the information that is currently being held in memory, thus necessitating the update of memory (Banich, 2004).

Table 2.4: *Basic ERP Components and the Psychological Processes with which they are associated – adapted from Banich (2004).*

ERP Component	Time Period (ms) post-stimulus presentation	Eliciting Conditions	Associated Mental Processes
Sensory Components	0-100	Sensory information	Transmission of sensory information from the periphery to the cortex
MMN	100-240	Elicited by an infrequent stimulus within a stimulus stream when an individual is not paying attention	Pre-attentive processing, sensory memory
N100-P200	100-300	When participants pay attention to the stimulus stream in which the material was presented	Selective attention
N200	200-300	When a stimulus is physically deviant from other recent stimuli; not affected by whether the participant is paying attention to the task or not	Detection of deviance within the stimulus stream
P300	300-800	Elicited by an infrequent stimulus within a stimulus stream when an individual is paying attention	Memory context updating, attention
N400	400-600	When items deviate in meaning from what is expected e.g. semantic incongruity	Detection of semantic deviance

2.2.3.2 EEG frequency bands.

EEG may be separated into a number of different frequency bands for analysis; these include the low-frequency bands (delta: δ – 1.5-3.5Hz; theta: θ – 3.5-7.5Hz), alpha (α – 7.5-12.5Hz) and the higher frequency bands (beta: ϐ – 12.5-22.5Hz; gamma: γ – >22.5Hz) – see Table 2.5.

Table 2.5: *EEG frequency bands and ranges.*

BAND	RANGE
Delta	1.5-3.5 Hz
Theta	3.5-7.5 Hz
Alpha	7.5-12.5 Hz
Beta	12.5-22.5 Hz
Gamma	Roughly >22.5 Hz

Range from Somsen et al. (1997)

These EEG frequency bands can be examined during resting state or while participants complete a task. Nunez and Srinivasan (2006) warn that these qualitative labels should be used carefully as actual EEG is composed of mixtures of multiple frequency components as revealed more clearly by spectral analysis. Phasic (or event-related) changes in the EEG are task or stimulus related. A number of tonic changes occur over the lifecycle in response to circadian rhythms, fatigue, distress and neurological disorders etc (Klimesch, 1999). When a person is relaxed or with eyes closed, alpha

frequencies of 9 to 12 Hz tend to dominate (Banich, 2004). By age 12 years, a strong increase in alpha power and a decrease in theta and delta power can be observed (Somsen, van't Klooster, van der Molen, van Leeuwen & Licht, 1997) – more information on EEG frequency bands will be outlined in Chapter 3, section 3.1.2.

2.2.4 Limitations and the Inverse Problem

When a dipole is present within the brain, current is conducted throughout the brain until it reaches the surface. The current recorded at a given point on the scalp will depend on the position and orientation of the dipoles which generated the current. However, the human head consists of many layers (the brain, skull, meninges and scalp) which electrical current must pass through in order to be recorded by electrodes placed on the scalp. Electricity does not run directly between the two poles of a dipole in a conductive medium, but instead spreads out through the conductor (Luck, 2005). Electrical current follows the path of least resistance and ERPs spread out as they travel through the brain, spreading laterally when they encounter the high resistance of the skull. As a result, ERPs recorded at a given location on the scalp may reflect underlying activity at a distant part of the brain.

If the locations and orientations of a set of dipoles in a volume with a known distribution of conductances are available, then it is possible to use a set of equations to compute the distribution of voltage that would be observed from the dipoles. This is known as the *forward problem*. However, if the observed voltage distribution is available, it is not so easy to determine (or reverse calculate) the locations and orientations of the dipoles. This is called the *inverse problem* (Luck, 2005). In other words, there is no one set of dipoles which can explain the voltage distribution recorded on the scalp; there are in fact many solutions or many sets of dipoles that can account

for this scalp recorded activity i.e. there is *no unique solution* to the inverse problem. As discussed later (in section 2.2.5) spatial resolution is simply not one of the strengths of the ERP technique. Researchers have focused on using complex algorithms and computer models of the head that make simplifying assumptions about the brain in order to localise more precisely the neural generators of scalp recorded potentials.

2.2.5 Advantages and Disadvantages for Research

Each neuroimaging technique has both advantages and disadvantages. The performance of neuroimaging techniques is usually judged on their temporal resolution and spatial resolution. ERPs are very useful due to their temporal resolution. Electrical potentials travel through the bone and the skin of the skull at high speed and as a result the time course of processing in the cortex may be seen to millisecond accuracy. When compared with the temporal resolution of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), ERPs are far superior. Both PET and fMRI operate on the premise that increased cognitive processing in a given area of the brain requires an increase in regional cerebral blood flow (rCBF). When compared with ERPs, which measure electrical impulses from the scalp, rCBF as measured by PET and fMRI is quite slow (in the region of seconds), making it difficult to obtain an accurate real-time record of processing. When comparisons of the spatial resolution of ERPs and other methods are made, ERPs have comparably poor spatial resolution. PET and fMRI allow for excellent spatial resolution as the anatomical structures receiving increased blood flow are represented three dimensionally. PET and fMRI also allow for the examination of activity in deeper sub cortical regions; however, electrical fields are significantly distorted by the skin and bone of the scalp and skull, which means that the pattern of activity recorded with EEG may bear little resemblance to the region of

cortex responsible for the activity. The advantages and disadvantages of ERPs are compiled in Table 2.6 below.

The two methods employed to overcome the deficit in spatial resolution of ERPs are source localisation analysis and co-registration. Source localisation analysis involves the use of source localisation algorithms to attempt to mathematically solve the Inverse Problem. Co-registration involves the employment of more than one brain imaging technique in an attempt to pinpoint more accurately the source of any recorded activity. Using a combination of techniques may prove the most successful way to accurately determine the location and timing of a cognitive event.

Table 2.6: *Advantages and Disadvantages of EEG and ERPs.*

Advantages	Lower cost compared to other imaging techniques such as fMRI and MEG
	Excellent temporal resolutions compared to other techniques
	Greater freedom of movement for participants
	Participation in EEG experiments is not limited by participant age or gender making participant selection and comparison easier
	Participants can still partake in EEG experiments if they have metal implants, braces etc
	Testing cubicles are usually large enough to avoid claustrophobic reactions
	EEG is not invasive and testing results in no major discomfort for participants
	Less demanding statistical analysis (2 dimensional versus 3 dimensional analysis for PET and fMRI)
Disadvantages	Low spatial specificity
	Participant performance fatigue can occur because many trials are needed in order to reduce background noise and artifacts
	Potential problems with comparison across subjects because consistent electrode placement depends on careful identification of bony landmarks that vary across participants

Other limitations of PET and fMRI are as follows: PET scans are limited to between 2 and 5 scans per annum per subject as their administration involves ionising radiation and also PET scans can only be used on a subset of the population as they are not used on women of childbearing age or children. This limits their utility in psychological experiments and obviously hinders participant selection and comparison. PET is compatible with many implants as it is compatible with metallic and magnetic components; fMRI on the other hand is not. Also, while participants should be advised not to move excessively during EEG and ERP recording, EEG still provides greater freedom of movement for participants when compared to fMRI. Even slight head movements, as small as a quarter of an inch, can cause major problems for fMRI recordings, as fMRI records the changes in blood-oxygen-level-dependent (BOLD) response in a given voxel (volumetric pixel) over time. This is only possible if the participant's head stays in the same position within the scanner for the duration of testing. Small movements can cause large changes in signal, and changes in signal due to movement can be much larger than the BOLD activation signal.

2.3 Data Collection and Analyses

What follows in section 2.3 is an overview of data collection and analysis techniques used in the present thesis. The following section will outline the steps which were taken to gain ethical approval for the study as well participant briefing and consent. This section will also summarise the procedure followed during the collection of the behavioural and electroencephalographic data used in chapters 3, 4, 5 and 6.

2.3.1 Ethical Approval, Participant Briefing and Consent

Approval for the study was obtained from the Beaumont Hospital Ethics Board and the National University of Ireland (NUI) Maynooth Ethics Committee. All experiments were carried out in accordance with the ethical standards of the American Psychological Association (American Psychological Association, 2002).

Prior to arriving at the EEG laboratory, information packs were posted to the participant's parent/guardian. These information packs contained information sheets for both the EEG participant and a separate information sheet for the parent/guardian, as well as directions to NUI Maynooth and a campus map (see Appendix XI for a copy of the information leaflets posted to the participant's parent/guardian prior to EEG testing). Of the overall total number of participants who took part in the EEG study (N = 95), 47 (49.5%) reported no PLEs, 15 (15.8%) reported weak PLEs and 33 (34.7%) reported strong PLEs during the clinical interview stage of the ABD Study.

Prior to commencing the EEG data collection, participants were briefed on the purpose, method and requirements of the study. On arrival at the EEG laboratory, participants were brought to the testing cubicle and shown all of the equipment and a full description of the EEG testing process was given. Participants were allowed time to ask questions about the EEG testing process and all questions were answered. Two copies of the informed assent form (see Appendix XII for a copy of the assent form for participants) were signed by the participant, one copy was retained by the experimenter and the second copy was given to the participant for his/her records. As all participants were aged between 11 to 13 years old, informed consent was also obtained from the participant's parent or guardian (see Appendix XIII for a copy of the consent form for parents/guardians). Two copies of the informed consent form were signed by the

participant's parent or guardian, one copy was retained by the experimenter and the second copy was given to the participant for his/her records.

2.3.2 Behavioural Data

E-Prime© logged response times for each participant and sent Transistor-Transistor Logic (TTL) voltage triggers to the EEG acquisition PC to allow stimulus presentations (stimulus type) and responses to be logged in real time on the EEG recording. This was made possible due to the use of a parallel port connection between the E-Prime© stimulus presentation computer and the EEG recording computer. Participants' responses were made via a mouse press. Response times were measured as the time between presentation of the stimulus and the participant's response and were recorded for all trials. Response latencies and accuracy were calculated automatically by E-Prime© and average response times were collated in E-Prime© for each block.

2.3.3 Event-Related Potentials (ERPs) Setup and Data Collection

The electrophysiological recording was performed at the Department of Psychology at NUI Maynooth, Co. Kildare. A 64-channel electrode cap (Easy-Cap©) was used when recording the EEG. Care was taken to ensure that the midline electrodes (Fpz, Fz, FCz, Cz, CPz, Pz, POz and Oz) on the electrode cap were placed along the saggital axis of the head. EEG activity was recorded with Silver/Silver Chloride (Ag/AgCl) electrodes (BrainVision©) mounted in the elastic cap fastened with a chin strap (Easy-Cap©). EEG data were collected from 62 scalp sites, using the extended version of the International 10-20 system for electrode placement (American Encephalographic

Society, 1994; see Figure 2.4). An electrode placed on the nasion was used as a reference.

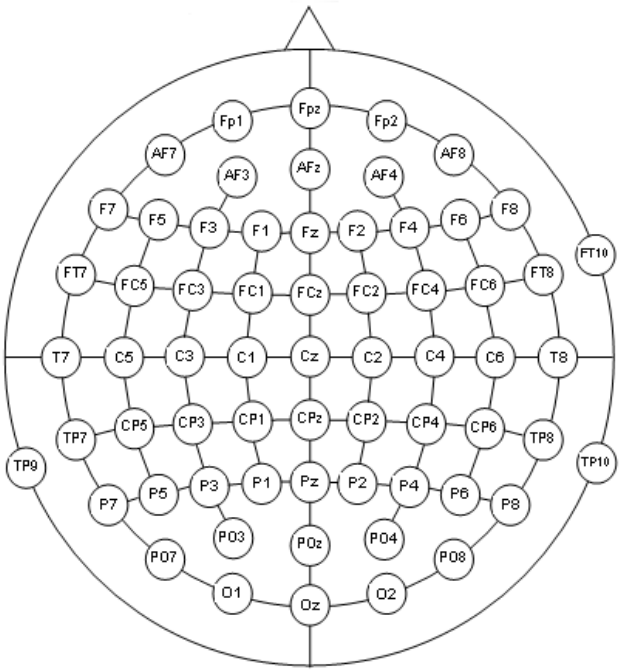


Figure 2.4: *International 10-20 System for Electrode Placement 64 Channels. Electrodes over the left hemisphere are labelled with odd numbers; those over the right hemisphere are labelled with even numbers. The uppercase letter is an abbreviation for the location of each electrode: Fp, frontal pole; A, auricle; F, frontal, C, central; T, temporal, P, parietal, O, occipital.*

Vertical and horizontal eye movements were recorded using electrooculography (EOG). Vertical eye movements (VEOG) were recorded from electrodes located above and below the left eye and horizontal eye movements (HEOG) were recorded from electrodes positioned at the outer canthus of each eye. These electrodes were held in place using either electrode pads or surgical tape, and non-abrasive electro-conductive

electrolyte gel (Signa Gel®) was used to apply the EOG and nasion electrodes. The impedance level was kept to below 10kΩ in all cases and this was monitored in BrainVision©. BrainVision© displays a colour-coded measure of impedance quality for the entire array of electrodes; this ranges from red, signalling poor quality, to green signalling good quality of approximately 5kΩ impedance. In order to reduce the impedance at any electrodes which were displayed at above 10 kΩ, a cotton bud stick was used to move the electro-conductive gel (Abralyte) through the hair in each electrode cup to ensure good contact between electrode and scalp. Where necessary more gel was applied in the electrode cups using a 10ml flat-tipped syringe.

After electrophysiological preparation, participants were seated on their own, in a darkened, copper-plated electrically shielded cubicle (150cm X 180cm) half a metre from the LCD computer monitor and had access to a mouse for responses (see Figure 2.5). Participants were instructed to leave any mobile phones or electrical devices with the experimenter during testing; these were kept in a safe place outside the testing cubicle. Before testing began, all subjects were given verbal instructions to ensure that they fully comprehended the on-screen instructions for each of the tasks and were advised to ask the experimenter any questions that they may have had before commencing the task. All stimuli were presented using the E-Prime© E-Run graphical interface software on an Intel Pentium 4 processor (3.00GHz CPU) and displayed on an LCD monitor measuring 14.5 X 10.5in.

EEG activity was amplified using a band-pass of 0.16-100Hz and a gain of 1000. The conversion rate was 2000Hz per channel and the range was 150mV. The amplifier used was supplied by BrainVision©. Blinks were averaged off-line and a blink reduction algorithm was applied to the data. This algorithm involved automatic artifact correction (Berg & Scherg, 1991; Ille, Berg & Scherg, 2002). Recordings were

notch filtered off line at 50Hz. EEG data were digitized at a sampling rate of 500 and were averaged offline using Brain Electrical Source Analysis software (BESA©). Stimulus-locked average ERPs were obtained by averaging the EEG using stimulus presentation as the trigger. Source waveforms were plotted in BESA©. Topographical voltage maps were generated in BESA© for all electrode sites and sites were chosen for further analysis based on visual inspection.

Figure 2.5: *EEG Setup and Recording Cubicle.*

2.4 Tasks

2.4.1 Active Auditory Oddball Task

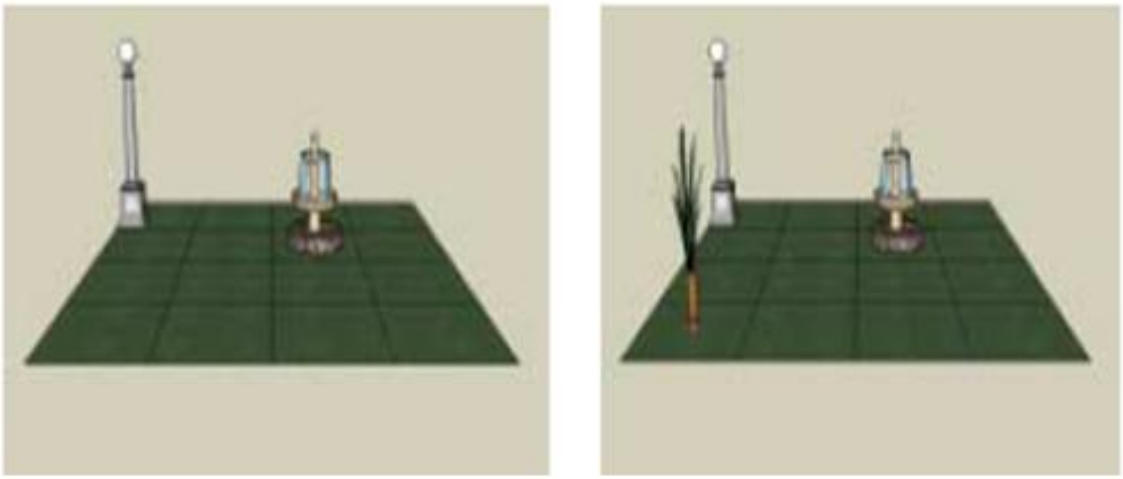
Participants completed a modified Auditory Oddball Task, based on the task used by Bramon et al. (2005) and previously by Frangou et al. (1997). Stimuli were 200 60dB tones with a 3 second inter-stimulus interval. Tones were presented through speakers in the testing cubicle and participants were advised to keep their eyes open and look straight ahead at a blank computer screen while completing the task. 80% of the tones were 'non-target' (160 trials) whereas 20% of the tones were 'targets' (40 trials) presented in a pseudo-randomised order. Tones were generated using Audacity® (http://audacity.sourceforge.net/) audio editor and recorder. Non-target tones were 1000Hz and target oddball tones were 1500Hz. Tone duration was 1000ms for both target and non-target tones. Participants were instructed to press a mouse button with their index finger in response to target tones only (see Appendix XIV for a full list of instructions given to participants). The response window length was 1900ms; however, the overall data window length was 2000ms.

2.4.2 Implicit Spatial Memory Task

Participants completed a version of the Spatial Grid Task developed by Murphy, Wynne, O'Rourke, Commins & Roche (2009) designed to test implicit spatial memory (referred to in the present thesis as the Implicit Spatial Memory Task). Participants were required to memorize the locations of 8 objects within an environmental spatial grid. The particular set of objects presented included a bin, a bucket, a post-box, a road-cone, a fire hydrant, a tree, a tyre and a keg; distractors included a parasol, a microphone stand, a cactus plant, a blender, a fire extinguisher, a stool, a lamp and a cavity/cinder

block. All objects were presented on a grass environmental grid. During the Study Block participants were asked to study the objects that appeared one at a time in the environmental grid with two stationary landmarks (a fountain and a lamppost) and were told that they would need to remember the objects for a subsequent recognition test. No reference was made to the location of the objects, only that the objects themselves had to be learned. The Study Block consisted of 64 trials of object presentations. Each of the 8 objects was presented in isolation 8 times in a pseudo-randomised order so that consecutive presentations of the same object did not coincide. A fixation cross was presented first for 750ms, followed by the spatial grid with landmarks for 1500ms and then the study stimulus was presented on the grid and remained onscreen for 2000ms. This cycle was repeated for the 64 trials (see Figure 2.6 for an example of stimuli used in the Implicit Spatial Memory Task).

Following the 64 trials of study presentations, another set of instructions was provided. Participants were told to respond to previously studied (or 'old') objects that appeared during the test block by pressing the left mouse button with their index finger. If a 'new' object (i.e. not shown in the study phase) was presented, then the right mouse button should be pressed with their middle finger (see Appendix XV for a full list of instructions given to participants). For the test block, the sequence of a single trial was as follows; fixation cross was presented first for 750ms, followed by the spatial grid with landmarks for 1500ms and then the test stimulus was presented on the grid and remained onscreen for 2000ms with the stimulus duration as the response interval, i.e. less than 2000ms. This trial sequence was repeated for 128 trials of object presentations. Three test conditions were constructed using either the 8 'old' (studied) objects or 8 'new' (distractor) objects and were presented in a pseudorandomised order, to test the implicit learning of object locations. The first condition (Study Object- Correct Location condition) involved the presentation of each of the 8 'old' objects in their



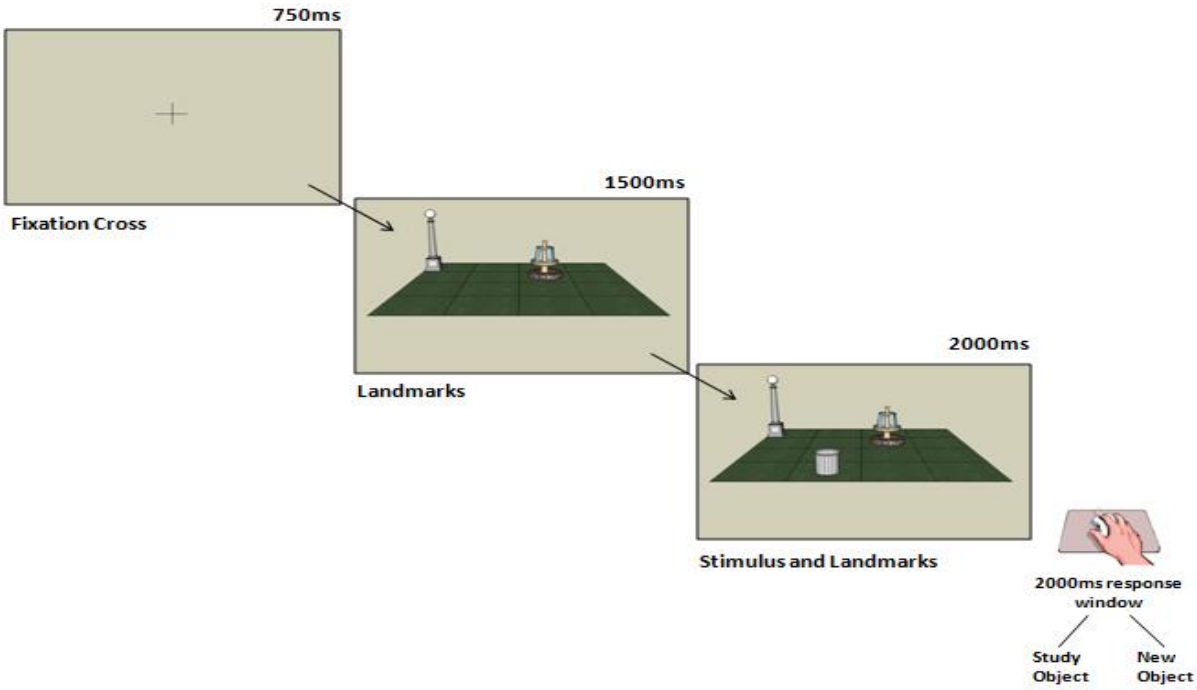


Figure 2.6: *Stimuli used in the Implicit Spatial Memory Task showing the environment with landmarks (top left) and with one of the target objects added (top right) and temporal sequence of a single test trial in the Implicit Spatial Memory Task.*

previously studied or 'correct' location a total of 4 times each, i.e. 32 trials in total. The second condition (Study Object-Incorrect Location condition) involved the presentation of each of the 8 'old' objects in 4 allocated 'incorrect' locations, i.e. 32 trials in total.

The third condition (Distractor Object condition) then presented 8 novel or distractor objects in 4 random locations that were unfamiliar to the participant; these 32 trials were each repeated twice, i.e. 64 trials in total. All objects were presented from a stationary viewpoint during both the Study Block and the Test Block which permitted a person-centred (i.e. egocentric) frame of reference.

2.4.3 Spatial Working Memory Task

Participants completed a computerised Spatial Working Memory Task which was created for use with a young adolescent population based on the Sternberg Working Memory paradigm (Sternberg, 1966). Participants were presented with a study stimulus showing a number of target stimuli in fixed placeholders. The task consisted of 128 trials in total. Each block contained 32 test trials in which participants made a button press response, via a mouse with their index or middle finger, to indicate whether a stimulus was in a correct (positive probe) or incorrect (negative probe) location.

Specifically, participants were initially presented with the blank placeholder array for 1000ms (which displayed the empty placeholders for that block). Participants were then presented with a study array stimulus which displayed a number of target stimuli in a subset of the placeholders. This study array was presented for 3500ms. The presentation of the study array was then followed by another presentation of the blank placeholder array for a further 1000ms. Finally participants were presented with the test stimulus (one target stimulus presented in the placeholder array), which required the

participant to make a button press response using a mouse to indicate whether the test stimulus was in a correct (left button) or incorrect (right button) placeholder.

Stimuli were either fish in fishbowls or birds in bird cages generated in Microsoft Word using ClipArt. For each block, participants were instructed to try to remember which placeholders (i.e. fishbowls or bird cages) contained target stimuli (i.e. fish or birds) and that later a target stimulus would appear in one of the placeholders and they would have to remember whether they had seen a target stimulus in that placeholder or not (see Appendix XVI for a full list of instructions given to participants). Following 16 test trials using the fish/fishbowl stimuli, the second half of each block contained a further 16 trials which followed the same format using bird/birdcage stimuli (see Figure 2.7 for an example of the study stimuli used in the Spatial Working Memory Task).

The task included 4 blocks (2 x low memory load and 2 x high memory load). Blocks 1 and 2 were classed as low memory load, while Blocks 3 and 4 were classed as high memory load. In Block 1, 4 out of 9 placeholders in the study array contained a target stimulus. In Block 2, 5 out of 12 placeholders in the study array contained a target stimulus. In Block 3, 6 out of 15 placeholders in the study array contained a target stimulus, while in Block 4, 7 out of 18 placeholders in the study array contained a target stimulus.

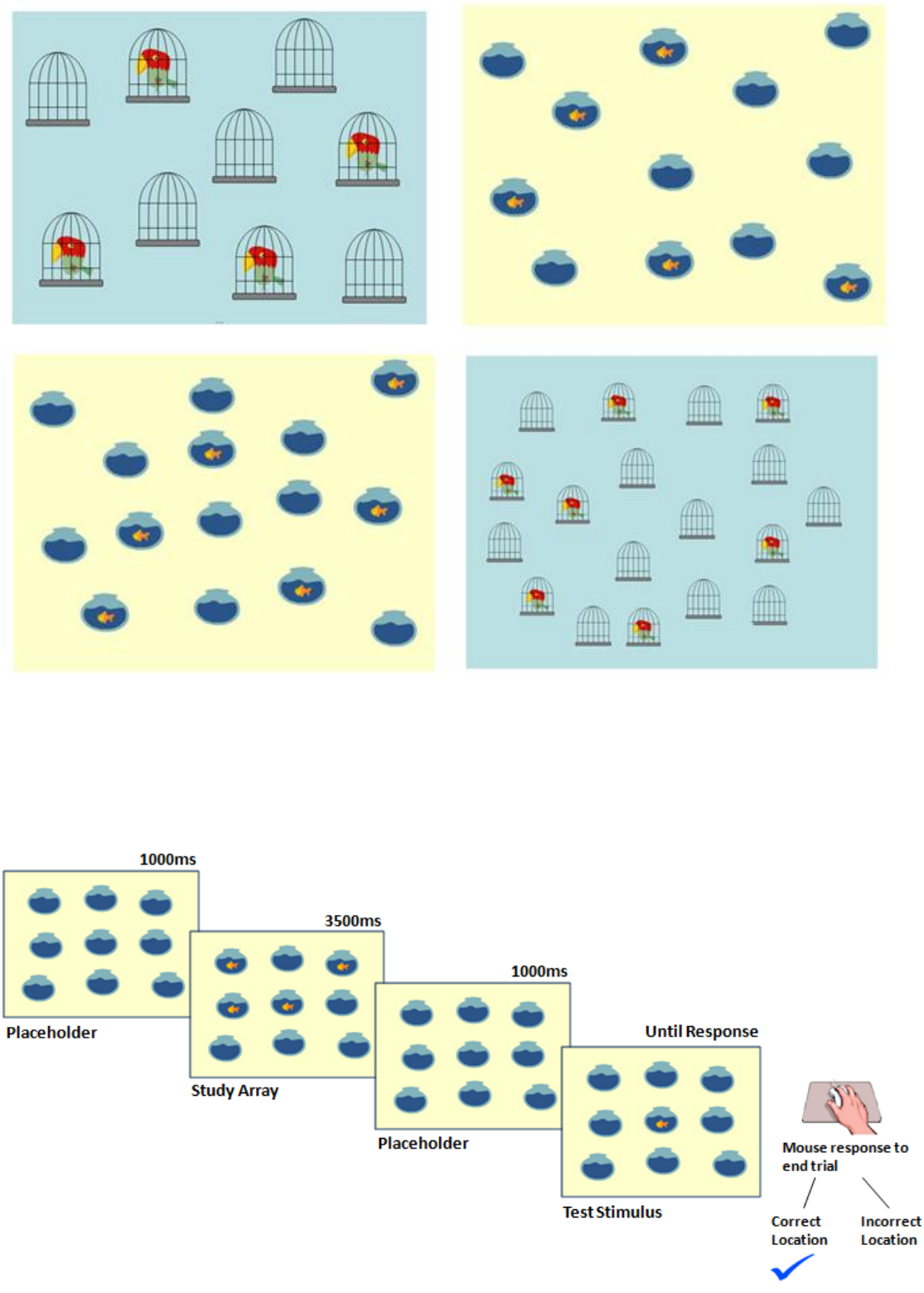


Figure 2.7: *Study stimuli used in the Spatial Working Memory Task (top) and an example from Block 1 of the Spatial Working Memory Task displaying a fish bowl placeholder array, followed by the study array, followed by another placeholder array and a test stimulus in a correct location (bottom).*

2.5 Summary

The current chapter provided an overview of the methods used in the ABD Study and the present thesis. In section 2.1 the participant recruitment process for the ABD Study was outlined as well as details of the screening process carried out within the schools, the clinical interviews which participants completed and the neuropsychological assessments which were administered during Years 1, 2 and 3 of the ABD Study.

Section 2.2 provided an outline of the method used in the present thesis, including an overview of the history of electroencephalography, a description of the physiological basis of ERPs, as well as an overview of the advantages and disadvantages of using EEG and ERPs for research. In section 2.3, the participant recruitment and data collection processes were outlined for the present thesis. Reports of PLEs at the interview stage of the ABD Study were presented. This section also included a summary of the electrophysiological recording process and the settings used during data collection as well as information relating to the data analysis techniques employed. Finally, section 2.4 provided a brief description of each of the three tasks used during EEG testing; the Active Auditory Oddball Task, the Implicit Spatial Memory Task and the Spatial Working Memory Task. Chapter 3, which follows, will examine resting state EEG power in the delta, theta and alpha EEG frequency bands during eyes open and eyes closed recordings. In addition, neuropsychological tests from the MCCB will be employed to test group difference in speed of processing, attention, working memory, verbal learning, visual learning, reasoning and problem solving.

Chapter 3

Neuropsychological Comparison and Spectral Analysis of EEG Resting State in Adolescents Reporting Psychotic-Like Experiences and Controls

Abstract

Psychotic disorders are characterised by poorer neuropsychological functioning in a number of areas. In addition, augmented low-frequency resting state activity has also been reported in schizophrenia and at-risk groups. The following chapter examines neuropsychological functioning in an adolescent sample with reported psychotic-like experiences (PLEs) and a control group. The following chapter also explores EEG activity in 3 spectral frequency bands (delta, theta and alpha) acquired during resting state. The MATRICS Consensus Cognitive Battery (MCCB) was employed in order to test group differences in areas usually impaired in schizophrenia, including speed of processing, working memory, verbal learning, visual learning, reasoning and problem solving. Twenty-nine participants were divided into those who reported PLEs (N = 11) and those who reported no PLEs (N = 18), i.e. the control group. All participants completed the MCCB and quantitative EEG spectral power in the low frequency bands (*delta* 1.5-3.5Hz; *theta* 3.5-7.5Hz; *alpha* 7.5-12.5Hz) was examined during resting state recordings in which participants had their eyes open for two minutes and eyes closed for an additional two minutes. Group differences were observed on non-verbal speed of processing measures. No group differences were observed in the resting state data for the delta, theta or alpha frequency bands at anterior, posterior or fronto-temporal recording sites. These findings are discussed in relation to the current literature on schizophrenia and risk for psychotic disorders.

3.1 Introduction

3.1.1 Neuropsychological Functioning

Schizophrenia is characterised by poor neuropsychological functioning in a number of areas. Working memory deficits have been hypothesised as a core deficit in schizophrenia (Goldman-Rakic, 1994). Working memory deficits have also been reported in first-episode psychosis (FEP; Zanello et al., 2009) and groups at clinical high-risk for psychosis (Smith et al., 2006; Pflueger et al., 2007; Frommann et al., 2011). Visuospatial working memory deficits have also been reported in adolescent-onset schizophrenia (Vance et al., 2006; Vance, Hall, Casey, Karsz & Bellgrove, 2007). In addition, speed of processing deficits have been reported in schizophrenia patients (Dickinson et al., 2007; 2008), FEP (Mesholam-Gately et al., 2009) and those at clinical high-risk for developing a psychotic disorder (Seidman et al., 2010).

Deficits in working memory, in particular spatial working memory, have been associated with abnormal brain activity in the prefrontal and parietal cortices in schizophrenia patients (Brahmbhatt et al., 2006), FEP (Broome et al., 2009) and prodromal groups including at-risk mental state for psychosis (ARMS) groups (Broome et al., 2010). In contrast, it has been suggested that speed of processing differences may result from aberrant connectivity between distributed brain networks, rather than discrete networks, in line with the dysconnection hypothesis of schizophrenia (Friston & Frith, 1995).

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery (MCCB) comprises a number of neuropsychological tests across domains which have been shown to be impaired in schizophrenia. These domains include speed of processing, attention, working memory, verbal learning, visual learning, reasoning and problem solving (Nuechterlein et al., 2008). The MCCB

was compiled in order to address some of the limitations in current research in the area of psychosis, and to provide a standard set of neuropsychological assessments which can be employed across different studies, thus making comparisons between studies and neuropsychological domains easier – see Chapter 2, section 2.1.5 for more information on the MCCB.

3.1.2 Resting State EEG

The resting state electrical activity of the brain is generally believed to be both stable and heritable (Iacono, 1982). Resting state EEG may be separated into a number of different frequency bands for analysis, including the low-frequency bands (delta: δ – 1.5-3.5Hz; theta: θ – 3.5-7.5Hz), alpha (α – 7.5-12.5Hz) and the higher frequency bands (beta: β – 12.5-22.5Hz; gamma: γ – > 22.5Hz). Alpha is the dominant frequency in the adult human brain and EEG power within the alpha frequency range is positively related to cognitive performance and brain maturity and has been observed to increase from childhood to adulthood and then decline with ageing (Klimesch, 1999). Alpha waves occur primarily during wakefulness over posterior scalp regions and are observed best when participants close their eyes and relax, i.e. during periods of mental inactivity. The frequency of alpha waves is faster at posterior and slower at anterior recording sites (Niedermeyer, 1993). By age 12 years, a strong increase in alpha power and a decrease in theta power can be observed (Somsen et al., 1997). When participants engage in a task with increased task demands alpha desynchronises, whereas theta synchronises (Klimesch, 1999).

Increased low-frequency activity in individuals with schizophrenia has been reported during resting state recordings (Itil, 1977; Sponheim, Celementz, Iacono & Beiser, 2000; Venables, Bernat & Sponheim, 2009). Resting state abnormalities have

also been uncovered in FEP and participants at genetic risk such as unaffected relatives of schizophrenia patients (Clementz, Sponheim, Iacono & Beiser, 1994). EEG power within the theta frequency range is negatively related to cognitive performance and brain maturity (Klimesch, 1999). EEG studies have reported augmented theta activity in schizophrenia (Harris, Melkonian, Williams & Gordon, 2006). Higher beta activity over frontal brain regions specific to the relatives of schizophrenia patients has been reported by Venables et al. (2009) who propose that high frequency EEG abnormalities may serve as an endophenotype for schizophrenia.

In a review and meta-analysis of spectral EEG abnormalities in schizophrenia Boutros et al. (2008) predicted increased delta, increased theta, decreased alpha and increased beta power across studies. A number of studies included in their report noted that increases in slow wave activity is seen considerably more in schizophrenia. For theta, of the 13 studies included in the meta-analysis 11 of them reported statistically significant theta increases. For delta, of the 13 studies included in the meta-analysis 10 were also statistically significant. Studies suggest that slow wave abnormalities, in particular increases in the delta band, are localised to frontal regions (Winterer et al., 2000). Boutros et al. (2008) reported that from the studies included in their review, frontal abnormalities were more commonly reported than abnormalities over posterior regions of the scalp. They propose that due to the strong evidence that delta and theta abnormalities exist in schizophrenia, these aberrations in slow wave EEG activity could be considered as biological markers of schizophrenia. Venables et al. (2009) reported that augmented low EEG frequencies may be specific to the pathophysiology to schizophrenia as they failed to find similar delta and theta frequency abnormalities in a group of bipolar disorder patients.

Increases in alpha activity over frontal and temporal regions have been reported in schizophrenia patients during resting state with eyes closed (Kahn, Weiner, Coppola,

Kundler & Schlutz, 1993; Venables et al., 2009). Similar abnormalities were also noted with eyes open by Venables et al. (2009); however, augmented alpha activity was observed over frontal regions in this condition. A study by John et al. (2009) reported that higher alpha 1 (defined as 8.5-10Hz in their study) power was observed in a positive symptoms subgroup in their study than a group of healthy controls or a negative symptoms subgroup.

Altered resting-state networks have been observed in ultra high-risk (UHR) groups using fMRI (Shim et al., 2010). Resting state data in the delta, theta and beta frequency bands in the presence of negative symptoms have been shown to predict transition to psychosis in ARMS groups (Zimmermann et al., 2010). A study which investigated EEG in an ARMS group, as well as a FEP psychosis group and controls, reported that pathological signs are more prevalent in the EEGs of FEP patients and ARMS than that of healthy controls (Gschwandtner et al., 2009). These EEG differences were mostly located over the temporal and fronto-temporal scalp. When EEG was considered in addition to measures of psychopathology, the specificity of prediction of transition to psychosis in the ARMS group increased from 59 to 73 percent in their study, i.e. ARMS participants who would have been incorrectly classified as transitioning to psychosis were reclassified when EEG findings were considered in addition to measures of psychopathology, reducing false positives. Results of this study were based on visual inspection of a clinical EEG recordings however, thus eliminating the ability to test for group differences in the frequency bands.

3.1.3 Aims and Objectives

The present chapter investigates between-group differences on a number of neuropsychological tests from the MCCB. In addition, differences in EEG activity in 3 EEG frequency bands (delta, theta and alpha) will be explored in data acquired during resting state (eyes open and eyes closed). The meta-analysis carried out by Boutros et al. (2008) also highlighted the issue of inconsistency in frequency band definition in spectral EEG analysis. The delta, theta and alpha EEG frequency bands are defined as 1.5-3.5Hz, 3.5-7.5Hz and 7.5-12.5Hz respectively in the present chapter, in line with settings previously reported by Somsen et al. (1997).

The hypotheses are as follows:

- It is anticipated that the PLEs group will perform more poorly on measures of speed of processing and working memory than will the control group.
- Resting state alpha will be examined over anterior, fronto-temporal and posterior scalp sites and it is anticipated that resting state alpha may be increased in the PLEs group relative to the control group.
- Resting state delta and theta will be examined over anterior, fronto-temporal and posterior scalp sites and it is anticipated that, if a group difference exists, then resting state theta and/or delta will be increased in the PLEs group.

3.2 Methods

3.2.1 Participants

Neuropsychological tests were administered and resting state data were recorded from twenty-nine participants (17 male; age range 11-13 years; mean age = 11.52 years) after participants had completed a clinical interview (see Chapter 2, section 2.1.3 for details of the clinical interview process). Eleven participants reported PLEs (6 male; age range 11-13 years; mean age = 11.64 years). Eighteen participants did not report PLEs and were included as a control group (11 males; age range 11-13 years, mean age = 11.44 years) for EEG analysis. In addition all participants completed the MCCB. Participants gave written informed assent and parental consent was obtained before participation in the study (see Chapter 2, section 2.3.1 for further details). All participants had normal or corrected-to-normal vision and no previous neurological disorders or brain injuries.

3.2.2 Neuropsychological Assessment

The MCCB (www.matrics.ucla.edu) was employed as the neuropsychological assessment tool. The MCCB assesses seven cognitive domains. These domains are as follows; speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving (see Table 3.1 for a summary of the tests analysed in the present chapter and see Chapter 2, section 2.1.5 for further details of the neuropsychological assessment employed).

Table 3.1: *Neuropsychological tests from the MCCB*

Domain	Test
Speed of Processing	**TMTA –** Trail Making Test A
	TMTB – Trail Making Test B
	BACS SC - Brief Assessment of Cognition in Schizophrenia Symbol Coding
	Fluency – Category Fluency (Animal Naming)
Working Memory (non-verbal and verbal)	**WMS-III SS -** Wechsler Memory Scale Spatial Span
	LNS - Letter Number Span
Reasoning and Problem Solving	**NAB Mazes -** Neuropsychological Assessment Battery Mazes
Visual Learning	**BVMT-R -** Brief Visuospatial Memory Test – Revised
Verbal Learning	**HVLT-R -** Hopkins Verbal learning Test – Revised

3.2.3 Instructions for Resting State EEG Data Recording

Approximately four minutes of EEG resting state data were collected from each participant. Two minutes of EEG resting state data were collected while participants had their eyes open. Participants were instructed to look ahead at a fixation cross displayed onscreen during this time. After two minutes of EEG recording with eyes open, participants were given instructions onscreen to close their eyes. A further two minutes of resting state data were collected from each participant while their eyes were shut. A minimum of one minute recording time has previously been suggested by Boutros et al. (2008).

3.2.4 Procedure and Data Analysis

3.2.4.1 Procedure.

A detailed explanation of the electrophysiological setup and data recording procedure is provided in Chapter 2 (section 2.3.3). EEG data were recorded in μV from 62 scalp sites. EEG activity was amplified using a band-pass of 0.16-100Hz and a gain of 1000. The conversion rate was 2000Hz per channel and the range was 150mV. The amplifier used was supplied by BrainVision©. The nasion was used as a reference. Vertical eye movements (VEOG) were recorded from electrodes located above and below the left eye and horizontal eye movements (HEOG) were recorded from the electrodes positioned at the outer canthus of each eye. EEG data were digitized at a sampling rate of 500 and were averaged offline using BrainVision Analyzer Version 1 (Brain Products©).

A low cut-off filter of 0.5Hz and a high cut-off filter of 100Hz were applied to the data off line with a slope of 24dB/oct. Recordings were notch filtered off line at 50Hz. Blinks were averaged offline using the Gratton and Coles blink detection algorithm. Resting state EEG data were then divided into 1 second segments for both eyes open and eyes closed data separately. Artifact correction was then carried out across all EEG channels using a semiautomatic segment selection. The gradient criterion was set at 50μV (maximum allowed voltage step/sampling point). The difference criterion was set at 300μV. The minimum allowed amplitude was set at -200μV while the maximum allowed amplitude was set at 200μV. The low activity criterion was set at 0.5μV with an interval of 100ms. Segments violating the set criteria were then highlighted in BrainVision Analyzer. Following visual inspection these segments could be excluded from further analysis. Fast Fourier Transformations (FFT) were then performed with resolution set to maximum (0.977Hz) and a hanning window

(window length 20%). FFT were displayed as power in each spectral band per segment (defined as 1 second) over each channel. Data were then exported for each channel for the delta (1.5-3.5Hz), theta (3.5-7.5Hz) and alpha bands (7.5-12.5Hz) with figures expressed as mean activity (μV^2). Log transformations were applied to the EEG data in order to normalise the distributions.

3.2.4.2 Data analysis.

Statistical analyses were carried out using SPSS Statistics version 20 for Windows. Data were tested for normality using Kolmogorov-Smirnov tests. Demographic variables were compared using independent-samples t-tests and chi-square analyses.

3.2.4.2.1 Neuropsychological Assessment.

Raw scores on the neuropsychological subtests of the MCCB were examined for normality and outliers, and then converted to z-scores. A one-way between-groups MANOVA was carried out to investigate between-group differences in scores on the MCCB. Nine dependent variables were used: score on Trail Making Test A (TMTA), scores on Trail Making Test B (TMTB), Brief Assessment of Cognition in Schizophrenia: Symbol Coding (BACS SC), Hopkins Verbal Learning Test –Revised ™ (HVLT-R), Wechsler Memory Scale –III (WMS-III): Spatial Span (WMS-III SS), Letter-Number Span (LNS), Neuropsychological Assessment Battery ® (NAB): Mazes, Brief Visuospatial Memory Test – Revised™ (BVMT-R) and Category Fluency: Animal Naming (Fluency). A second one-way between-groups MANOVA was carried out to investigate group differences on non-verbal speed of processing (SOP) measures.

3.2.4.2.2 Resting State EEG Data.

As outlined in section 3.2.4.1 the continuous EEG recordings for eyes open and eyes shut data were divided into 1 second segments for spectral analysis. Data were averaged for each participant and grand averages for eyes open and eyes shut were compiled. Data for anterior (AF3, AF4, F1, Fz, F2, FC1, FCz, FC2), fronto-temporal (FT7, T7, FT8, T8) and posterior (CP1, CPz, CP2, P1, Pz, P2, PO3, POz, PO4) electrode sites were averaged for analysis. Separate 2x2x2 mixed factorial ANOVAs were employed to examine group differences for each of the frequency bands (delta, theta, alpha) with Location (anterior, posterior) and State (eyes open, eyes closed) as the within-subjects variables and Group (control, PLEs) as the between-subjects variable. Separate 2x2 mixed factorial ANOVAs were employed to examine group differences across each frequency band for fronto-temporal electrodes with State (eyes open, eyes closed) as the within-subjects variable and Group (control, PLEs) as the between-subjects variable. For each ANOVA, an alpha value of 0.05 was used for main and interaction effects. Levene's tests were employed to examine homogeneity of variances and Greenhouse-Geisser correction was employed where the assumption of sphericity was violated.

3.3 Results

3.3.1 Demographic and General Functioning Comparisons

Groups were compared on the following variables; age, gender, handedness, parental socioeconomic status (SES), scores on the Strengths and Difficulties Questionnaire (SDQ; Goodman 1997; Goodman et al., 1998) and overall current Children's Global Assessment Scale from the K-SADS-PL interview schedule (C-GAS; Shaffer et al., 1983) – see Table 3.2.

No differences in mean age [$t(27) = -0.723$, $p = 0.476$], gender [$\chi^2(1) = 0.001$, $p = 1.000$], handedness [$\chi^2(1) = 0.001$, $p = 1.000$] or SDQ scores [$t(27) = -1.03$, $p = 0.314$] were observed between the control and PLEs groups. A between groups difference in C-GAS scores was observed [$t(25) = 3.04$, $p = 0.006$] with the PLEs group [$M = 59.3$, $SEM = 6.57$] receiving a lower mean score on this measure than the control group [$M = 79.76$, $SEM = 3.46$]. Groups were also found to differ on parental SES [$\chi^2(1) = 6.47$, $p = 0.011$] with more control parents in professional and managerial employment.

3.3.2 Neuropsychological Test Data

A one-way between-groups MANOVA was performed to investigate results on a number of neuropsychological tests in the group reporting PLEs and the control group. Nine dependent variables from the MCCB were used. Preliminary assumption testing was conducted to check for normality, linearity, univariate and multivariate outliers, homogeneity of variance-covariance matrices and multicollinearity, with no serious violations noted.

Table 3.2: *Demographic and general functioning details for the control and PLEs groups from whom resting state data were recorded.*

Variable	**Overall (*N*=29)**	**Control (*N*=18)**	**PLEs (*N*=11)**	**Result**
Mean Age (SEM)	11.52 (0.13)	11.44 (0.15)	11.64 (0.23)	$t(27) = -0.723$, $p = 0.476$
Gender	17 males (58.62%)	11 males (61.11%)	6 males (54.55%)	$\chi^2(1) = 0.001$, $p = 1.000$
Handedness	3 left (10.34%)	2 left (11.11%)	1 left (9.09%)	$\chi^2(1) = 0.001$, $p = 1.000$
SES 1	22 (75.86%)	17 (94.44%)	5 (45.45%)	**$\chi^2(1) = 6.47$, $p = 0.011$**
SDQ scores* **(SEM)**	12.24 (0.99)	11.44 (1.17)	13.55 (1.8)	$t(27) = -1.03$, $p = 0.314$
C-GAS scores (SEM)	72.19 (3.73)	79.76 (3.46)	59.3 (6.57)	**$t(25) = 3.04$, $p = 0.006$**

*Higher scores reveal greater impairment.
Significant differences are highlighted in bold.
SES 1 – professional and managerial, SES2 – other.

No significant difference was observed between the PLEs group and the control group on the combined dependent variables: $F(19) = 0.93$, $p = 0.524$, Wilk's Lambda = 0.695, partial eta squared = 0.305. An inspection of the mean scores indicated that the PLEs group reported lower scores on symbol coding task ($M = 44.45$, $SEM = 1.96$) than

the control group (*M* =50.83, *SEM* =1.75). Higher scores on the TMTB were noted for the PLEs group (*M* = 85.17, *SEM* = 12.12) compared to the control group (*M* = 68.11, *SEM* = 5.88) – see Table 3.3.

Table 3.3: *Raw scores on the neuropsychological tests from the MCCB.*

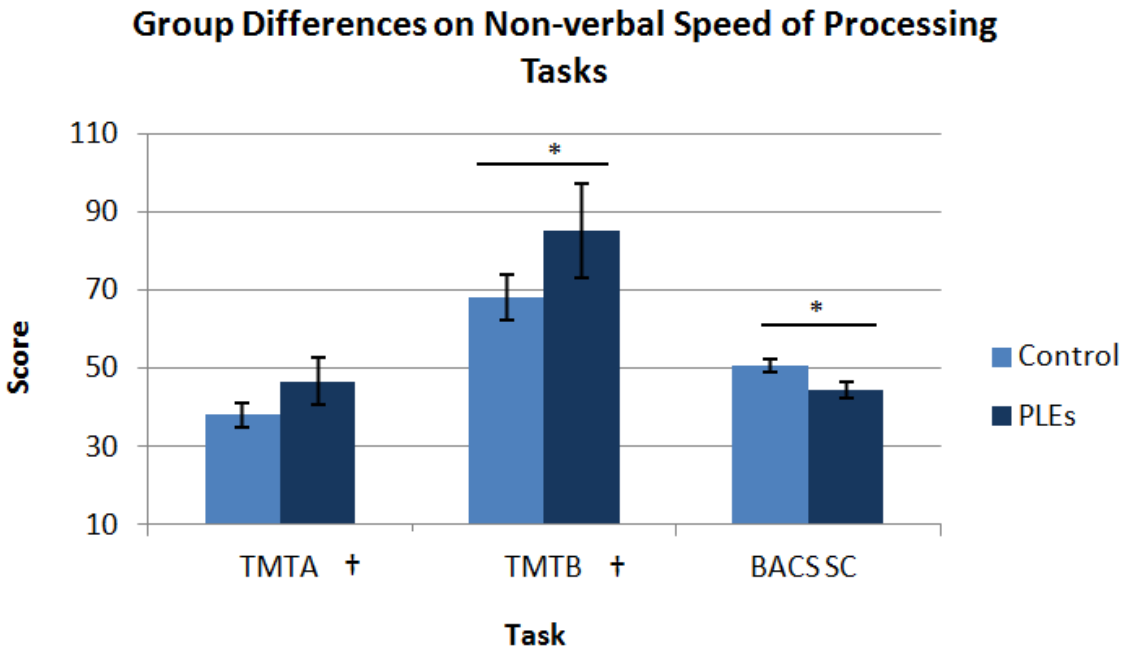
Neuropsychological Test Variable	**Control (*N*=18) Mean (SEM)**	**PLEs (*N*=11) Mean (SEM)**	**Result *p* value****
Test:			
TMTA*	38.17 (3.19)	46.45 (5.98)	0.055
TMTB*	**68.11 (5.88)**	**85.18 (12.12)**	**0.050**
BACS SC	**50.83 (1.75)**	**44.45 (1.96)**	**0.020**
HVLT-R	25.05 (1.23)	21.64 (2.15)	0.416
WMS-III SS	16.22 (0.48)	14.73 (0.9)	0.085
LNS	14.56 (0.68)	13.55 (0.81)	0.517
NAB Mazes	17.33 (1.12)	15.18 (1.49)	0.408
BVMT-R	26.28 (1.43)	28.73 (1.2)	0.192
Fluency	21.00 (1.29)	18.81 (1.1)	0.406

*Higher scores reveal greater impairment; ** p values calculated using z-scores. Significant differences are highlighted in bold.

A second one-way between-groups MANOVA was carried out to further investigate group differences on non-verbal speed of processing (TMTA, TMTB, BACS SC). A significant difference was observed between the PLEs group and the control group on the combined dependent variables: $F(25) = 3.01$, $p = 0.049$, Wilk's Lambda = 0.735, partial eta squared = 0.265. Significant differences were observed on TMTB scores [$F(1, 27) = 4.23$, Bonferroni corrected $p = 0.05$, partial eta squared = 0.135] and

BACS SC scores [$F(1, 27) = 6.16$, Bonferroni corrected $p = 0.02$, partial eta squared = 0.186] – see Table 3.3 and Figure 3.1.

Figure 3.1: *Group differences on measures of non-verbal speed of processing from the MCCB.*



* p < 0.05 † Higher scores reveal greater impairment.

3.3.3 Electrophysiological Data

3.3.3.1 Overall group.

3.3.3.1.1 Delta.

At anterior and posterior electrode sites, main effects of Location [$F(1, 27) = 18.6$, $p < 0.0005$, partial eta squared = 0.408] and State [$F(1, 27) = 17.11$, $p < 0.0005$, partial eta

squared = 0.388] were observed in the delta frequency band and a Location*State interaction effect was observed [$F(1, 27) = 32.56$, $p < 0.0005$, partial eta squared = 0.547]. For the overall group resting state EEG activity in the delta frequency band was greater for eyes closed than eyes open conditions at posterior electrode sites [eyes open: $M = 0.98$, $SEM = 0.04$; eyes closed: $M = 1.15$, $SEM = 0.05$; $t(28) = -5.00$, $p < 0.0005$]. Activity was also observed to be greater at posterior regions than anterior regions for eyes closed [anterior: $M = 1.01$, $SEM = 0.03$; posterior: $M = 1.15$, $SEM = 0.05$; $t(28) = -5.06$, $p < 0.0005$] – see Table 3.4. Both observations remained significant when a Bonferroni corrected p value of 0.01 was applied. A main effect of State was observed for the delta frequency band at fronto-temporal scalp sites [eyes open: $M = 0.91$, $SEM = 0.03$; eyes closed: $M = 0.99$, $SEM = 0.03$; $F(1, 27) = 10.59$, $p = 0.003$, partial eta squared = 0.282].

3.3.3.1.2 Theta.

A main effect of State [$F(1, 27) = 26.87$, $p < 0.0005$, partial eta squared = 0.499] in the theta frequency band and a Location*State interaction effect was observed [$F(1, 27) = 59.42$; $p < 0.0005$, partial eta squared = 0.688] for anterior and posterior electrode sites. No main effect of Location was observed [$F(1, 27) = 1.27$, $p = 0.271$, partial eta squared = 0.045]. Activity was greater at anterior [$M = 0.69$, $SEM = 0.03$] than posterior [$M = 0.62$, $SEM = 0.04$] regions for the eyes open condition [$t(28) = 3.21$, $p = 0.003$] and activity was greater at posterior [$M = 0.87$, $SEM = 0.06$] than anterior [$M = 0.77$, $SEM = 0.04$] regions with eyes closed [$t(28) = -3.01$, $p = 0.004$]. Activity increased with eyes closed at both anterior [$t(28) = -3.48$, $p = 0.002$] and posterior recording sites [$t(28) = -6.28$, $p < 0.0005$] – see Table 3.4. All observations remained significant when a Bonferroni corrected p value of 0.01 was applied. A main effect of State was observed

for the theta frequency band at fronto-temporal scalp sites with lower power observed for eyes open [*M* = 0.61, *SEM* = 0.02] than eyes closed [*M* = 0.72, *SEM* = 0.03; *F* (1, 27) = 16.43, *p* < 0.0005, partial eta squared = 0.378].

3.3.3.1.3 Alpha.

At anterior and posterior electrode sites, main effects of Location [*F*(1, 27) = 126.81, *p* < 0.0005, partial eta squared = 0.824] and State [*F*(1, 27) = 184.86, *p* < 0.0005, partial eta squared = 0.873] were observed in the alpha frequency band and a Location*State interaction effect was observed [*F*(1, 27) = 14.02, *p* < 0.0005, partial eta squared = 0.0].– see Table 3.4. Activity was greater at posterior than anterior regions for the eyes open condition [anterior: *M* = 0.38, *SEM* = 0.05; posterior: *M* = 0.61, *SEM* = 0.06; *t*(28) =-5.83 , *p* <0.0005] and eyes closed conditions [anterior: *M* =0.77 , *SEM* = 0.06; posterior: *M* = 1.15, *SEM* = 0.06; *t*(28) = -15.03, *p* <0.0005]. Activity increased with eyes closed at both anterior [*t*(28) = -12.89, *p* < 0.0005] and posterior recording sites [*t*(28) = -12.24, *p* < 0.0005] – see Table 3.4. All observations remained significant when a Bonferroni corrected p value of 0.01 was applied. A main effect of State was observed for the alpha frequency band at fronto-temporal scalp sites with lower power observed for eyes open [*M* = 0.39, *SEM* = 0.05] than eyes closed [*M* = 0.69, *SEM* = 0.05; *F* (1, 27) = 95.27, *p* < 0.0005, partial eta squared = 0.779].

Table 3.4: *Mean activity in each frequency band for the overall group and the control and PLEs groups.*

Frequency Band	**Mean Activity * (SEM)**		
	Overall Group (*N* = 29)	**Control (*N* = 18)**	**PLEs (*N*=11)**
Delta (1.5-3.5Hz):			
Anterior (EO)	0.96 (0.03)	0.97 (0.04)	0.93 (0.05)
Posterior (EO)	0.98 (0.04)	0.99 (0.05)	0.98 (0.06)
Fronto-temporal (EO)	0.91 (0.02)	0.91 (0.04)	0.9 (0.03)
Anterior (EC)	1.01 (0.03)	1.04 (0.04)	0.97 (0.06)
Posterior (EC)	1.15 (0.05)	1.15 (0.07)	1.14 (0.08)
Fronto-temporal (EC)	0.99 (0.03)	1.00 (0.04)	0.96 (0.04)
Theta (3.5-7.5Hz):			
Anterior (EO)	0.69 (0.03)	0.72 (0.03)	0.63 (0.05)
Posterior (EO)	0.62 (0.04)	0.64 (0.05)	0.6 (0.07)
Fronto-temporal (EO)	0.61 (0.02)	0.64 (0.03)	0.57 (0.04)
Anterior (EC)	0.77 (0.04)	0.8 (0.05)	0.71 (0.07)
Posterior (EC)	0.87 (0.06)	0.88 (0.07)	0.86 (0.12)
Fronto-temporal (EC)	0.72 (0.03)	0.74 (0.04)	0.68 (0.07)
Alpha (7.5-12.5Hz):			
Anterior (EO)	0.38 (0.05)	0.41 (0.05)	0.33 (0.09)
Posterior (EO)	0.61 (0.06)	0.59 (0.08)	0.64 (0.11)
Fronto- temporal (EO)	0.39 (0.05)	0.42 (0.06)	0.34 (0.08)
Anterior (EC)	0.77 (0.06)	0.76 (0.06)	0.78 (0.11)
Posterior (EC)	1.15 (0.06)	1.14 (0.07)	1.17 (0.12)
Fronto-temporal (EC)	0.69 (0.05)	0.71 (0.06)	0.66 (0.11)

*power – $\log10(\mu V^2)$; EO – Eyes open; EC –Eyes closed

3.3.3.2 Group analyses.

3.3.3.2.1 Delta.

No between-group effect was observed when resting state activity in the delta frequency band was examined at anterior and posterior scalp locations across both States [$F(1, 27) = 0.16$, $p = 0.693$, partial eta squared = 0.006] – see Figure 3.2. No between-group differences were observed at fronto-temporal sites across States [$F(1, 27) = 0.25$, $p = 0.622$, partial eta squared = 0.009].

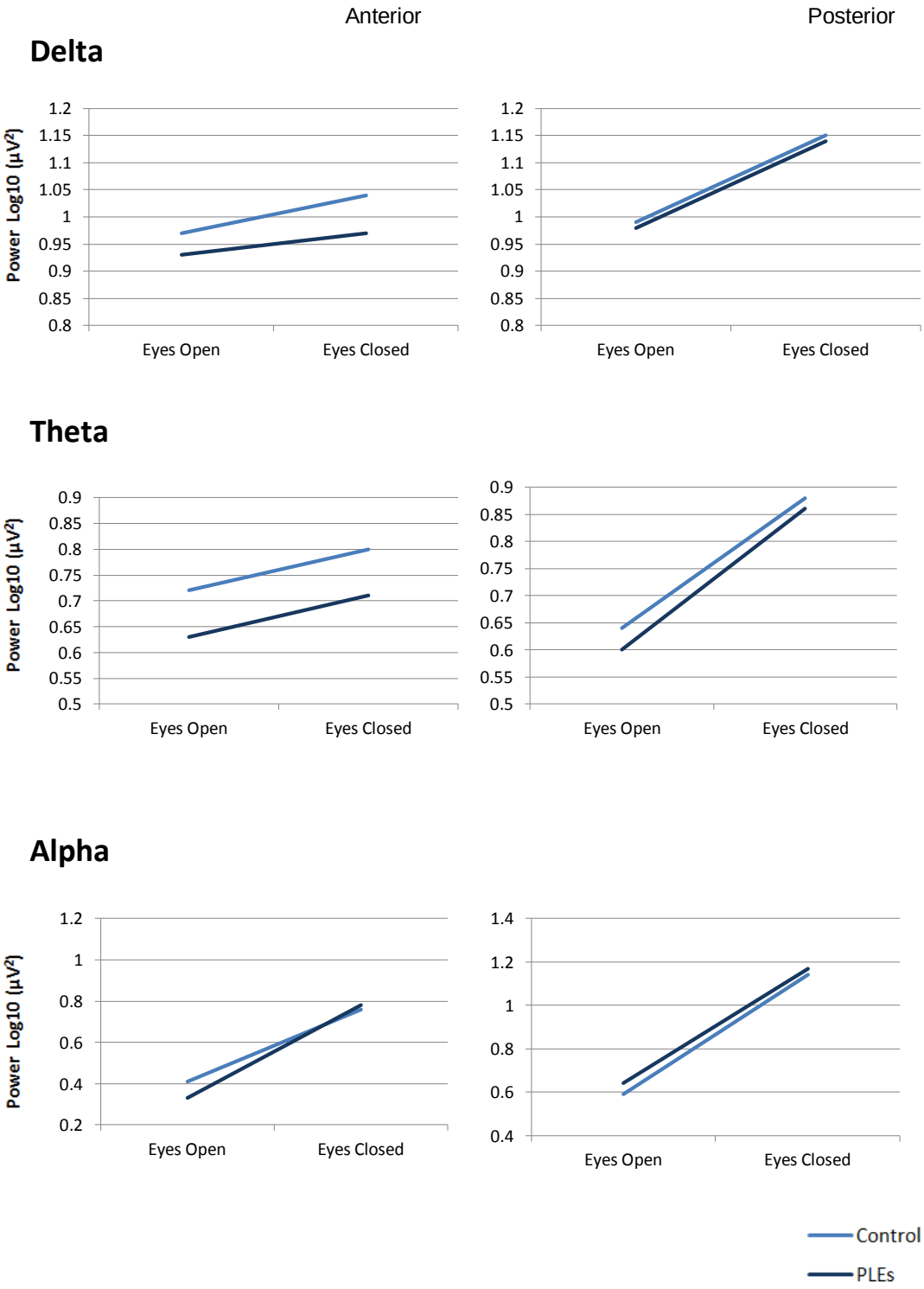
3.3.3.2.2 Theta.

No between-group effect was observed when resting state activity in the theta frequency band was examined at anterior and posterior scalp locations across both States [$F(1, 27) = 0.55$, $p = 0.467$, partial eta squared = 0.02] – see Figure 3.2. No between-group differences were observed at fronto-temporal sites across States [$F(1, 27) = 1.42$, $p = 0.243$, partial eta squared = 0.05].

3.3.3.2.3 Alpha.

No between-group effect was observed when resting state activity in the alpha frequency band was examined at anterior and posterior scalp locations across both States [$F(1, 27) = 0.002$, $p = 0.962$, partial eta squared = 0.001] – see Figure 3.2. No between-group differences were observed at fronto-temporal sites across States [$F(1, 27) = 0.43$, $p = 0.515$, partial eta squared = 0.016].

Figure 3.2: *Mean activity in each frequency band for the control and PLEs groups at anterior and posterior recording sites.*



3.3.4 Summary of Results

In summary, no between-group differences were observed for the demographic variables age and gender. In terms of general psychopathology group scores on the SDQ did not differ. In terms of general functioning, the PLEs group obtained lower C-GAS scores than the control group. A between-groups difference was observed in parental SES with more control parents in the professional and managerial employment categories. Group differences were observed on two measures of non-verbal speed of processing. A significant difference in TMTB scores was observed with the PLEs group scoring higher on this measure (with higher scores indicating poorer performance). A significant difference in BAC SC was also observed with the PLEs group scoring lower on this measure (with lower scores indicating poorer performance). No group differences were observed on measures of verbal or spatial working memory or in the domains of verbal learning, visual learning or reasoning and problem solving. No between-group differences were observed in the resting state data for the delta, theta or alpha EEG frequency bands at either anterior or posterior scalp recording sites. No differences were observed in the resting state data from the delta EEG frequency band at fronto-temporal sites.

3.4 Discussion

The present chapter reports speed of processing deficits in a group of adolescents reporting PLEs on two neuropsychological tests (TMTB and BACS SC). These results reflect the findings of the overall Adolescent Brain Development Study (ABD Study) by Blanchard et al. (2010) and Kelleher et al. (2012c; 2012d) which previously reported

speed of processing deficits in adolescents reporting PLEs. No group differences were observed on measures of verbal or spatial working memory in the present sample. In contrast, findings from the overall ABD Study reported deficits in nonverbal working memory as measured by the Wechsler Memory Scale – spatial span (WMS-III SS; Kelleher et al., 2012c; 2012d) in addition to speed of processing differences between groups. Resting state EEG was examined during eyes open and eyes closed recordings and resting state power in the delta, theta and alpha frequency bands were explored. No group differences were uncovered in the EEG resting state data indicating that resting state power in the delta, theta and alpha frequency bands is normal and unaffected by reports of subclinical psychotic symptoms in adolescent reporting PLEs.

Speed of processing may be one of the key neuropsychological deficits associated with self-reports of PLEs from community-based samples of adolescents (Kelleher et al., 2012c; 2012d). Speed of processing has been reported to be impaired in schizophrenia (Dickinson et al., 2007; 2008), FEP (Mesholam-Gately et al., 2009) and those at clinical high-risk for developing a psychotic disorder (Seidman et al., 2010). Some researchers have proposed that speed of processing deficits may in fact be one of the core deficits in schizophrenia (Dickinson et al., 2007; 2008). In contrast to other neuropsychological task which might be attributed to specific anatomical regions or neural networks, it has been argued that speed of processing tasks reflect integration and coordination between distributed brain networks and measure a systems-based process (Dickinson et al., 2008; Kelleher et al., 2012c).

Kelleher et al. (2012d) note the difficulty in comparing findings across studies in relation to the Trail Making Test and suggest the use of scores for individual tests rather than domain scores. While some studies include the Trail Making Test in the processing speed domain, other groups include the Trail Making Test in the executive function or working memory domains. Trail Making Tests have been hypothesised to reflect a

number of cognitive processes including attention, sequencing and shifting, psychomotor speed and flexibility (Salthouse, 2011). It has been suggested however, that speed of processing, as measured by symbol coding tasks, may reflect the core neurocognitive impairment in schizophrenia (Dickinson et al, 2007; 2008). Reported speed of processing deficits may also reflect or contribute to difficulties in other higher-order cognitive functions such as working memory. The ability to reason and solve problems requires information to be held in working memory. This information is subject to loss due to decay or interference; as a result faster processing is more likely to permit reasoning and problem solving to be completed before the necessary information is lost (Miller & Vernon, 1996; Fry & Hale, 2000). It is possible that processing speed is related to working memory capacity as faster rehearsal allows for more information to be held in working memory (Baddeley, 1981; 1986).

Although the present chapter does not report working memory deficits in adolescents reporting PLEs, results from the overall ABD Study which included 212 participants in total indicated that participants who reported psychotic symptoms in the general population were impaired on spatial working memory (Kelleher et al., 2012c). Furthermore, the subsample from this group who fulfilled criteria for a prodromal syndrome (8% of the population sample) were also impaired on measures of speed of processing and spatial working memory (Kelleher et al., 2012d). This finding highlights the continuity of deficits between adolescents who report PLEs in the general population and do not meet criteria for a prodromal disorder and those who could potentially meet the necessary criteria to meet a diagnosis of a prodromal syndrome on neuropsychological measures. As a result of these findings and given the evidence for working memory as a trait marker for schizophrenia, spatial processing and spatial working memory will be explored using both behavioural and EEG techniques in further detail in Chapters 5 and 6, respectively.

Augmentation of resting state activity in the low-frequency bands (delta and theta) have been reported in schizophrenia patients (Itil, 1977; Sponheim et al., 2000; Venables et al., 2009), FEP and groups at genetic risk for schizophrenia (Clementz et al., 1994). This has led researchers such as Boutros et al. (2008) to suggest that aberrations in slow wave EEG activity could be considered as biological markers of schizophrenia. In addition, Gschwandtner et al. (2009) reported that pathological signs are more prevalent in the EEGs of FEP patients and ARMS than that of healthy controls over temporal and fronto-temporal regions. Despite these findings from clinical groups, the present chapter found no evidence of disrupted resting state activity in adolescents reporting PLEs, i.e. the non-clinical psychosis phenotype. However, the study carried out by Gschwandtner et al. (2009) was based on visual inspection of clinical EEG recordings and not spectral analysis of frequency bands and analysed EEG recordings based on spikes, sharp waves, pathologic rhythmic patterns and delta and theta activity. This makes it difficult to compare findings across studies in an accurate manner as group differences in alpha or increases in delta or theta could not have been observed accurately enough by visual inspection alone to differentiate between groups or uncover group differences.

While the ABD Study focused on positive symptoms such as self-reported hallucinations and delusions in order to classify participants as at-risk or not, previous studies have focused on negative symptoms of psychosis and their association with EEG resting state anomalies in at-risk groups. Zimmermann et al. (2010) found positive correlations between EEG power in the delta, theta and beta frequency bands and negative symptoms of psychosis in an ARMS group who later transitioned to psychosis. The results of these correlations were similar to those previously reported by Gschwandtner et al. (2009) in an FEP group and opposite to the ARMS group who did not later transition to psychosis.

Thus far, adolescents reporting PLEs have been characterised by impaired speed of processing and spatial working memory on tests of neuropsychological functioning (Blanchard et al., 2010; Kelleher et al., 2012c; 2012d). The present chapter did not find group differences on measures of resting state EEG in the delta, theta or alpha frequencies despite speed of processing differences between the groups. Speed of processing has been proposed as a key neurocognitive deficit in schizophrenia and has been associated with aberrant functional connectivity in the brain, in line with the dysconnection hypothesis of schizophrenia (Friston & Frith, 1995). It is possible that differences in EEG power may only become evident during task based recordings examining both absolute frequency power and the level of synchronisation/ desynchronisation between frequency bands during task performance.

It is possible that underlying differences may not have been uncovered by quantitative EEG (qEEG) methods in the present study due to the age of the participant sample. All participants in the present study were aged between 11 and 13 years when the data were collected. While it has been reported that by age 12 years a strong increase in alpha power and decrease in theta power can be observed (Somsen et al., 1997), it has also been noted that EEG power (particularly within the alpha frequency range) is positively related to brain maturity and increases from childhood to adulthood (Kilmesch, 1999). It is possible that abnormalities in brain development may not be uncovered using qEEG techniques until a later stage in development and other imaging techniques may be more useful in the attempt to uncover changes in resting state brain activity. Previous research by Jacobson et al. (2010) investigated the structural brain correlates of psychotic symptoms in a similar group of 11 to 13 year olds and, using diffusion tensor imaging (DTI), found decreased fractional anisotropy (FA) values in fibre tracts including the inferior fronto-occipital fasiculus and the inferior longitudinal

fasiculus. Results from Jacobson et al. (2010) indicate altered fronto-temporal connectivity in the psychotic symptoms group.

There are a number of other possible reasons why between-group differences may not have been observed in the present chapter. The issue of differences in EEG recording techniques and settings has been highlighted recently in a meta-analysis of spectral EEG studies in schizophrenia carried out Boutros et al. (2008). EEG band settings are different across different studies. While some studies report absolute power measures others report relative measures of EEG band power. These different methods may contribute to differences in findings across studies. The settings for each frequency band also differ across studies. Differences in spectral frequency may also be better observed during a cognitive task as opposed to during resting state in this group, for example on cognitive tasks assessing speed of processing.

3.4.1 Chapter Summary

In summary, the present chapter reports reduced speed of processing in a group of adolescents reporting PLEs compared to a control group. No differences were uncovered in the absolute power of the delta, theta or alpha EEG frequency bands during resting state between groups during eyes open or eyes closed recordings. Chapter 4 which follows will investigate the P300 event-related potential (ERP) component elicited to target tones using an Active Auditory Oddball Task based on a task previously used by Bramon et al. (2005) and Frangou et al. (1997) and adapted for use with an adolescent population. A reduction of the P300 to target tones on auditory oddball tasks has been proposed as a possible trait marker for schizophrenia (Özgürdal et al., 2008). The N100 auditory evoked potential (AEP) component to non-target tones will also be investigated using the Active Auditory Oddball Task.

Chapter 4

Event-Related Potentials Elicited Using an Active Auditory Oddball Paradigm in Adolescents Reporting Psychotic-Like Experiences and Controls

Abstract

The following chapter explores event-related potentials (ERPs) elicited using a two-tone active auditory oddball paradigm in an adolescent sample with reported psychotic-like experiences (PLEs) and a control group. A reduction of the amplitude of the P300 component is widely reported in schizophrenia, first episode psychosis (FEP) and those at high genetic risk for psychosis, as well as most recently in those at clinical high risk for a psychotic disorder. Most commonly these results are elicited in response to target tones during active auditory oddball experiments. Recently a reduction of the amplitude of the N100 auditory evoked potential (AEP) component in response to non-target stimuli has also been reported in a group at high genetic risk for schizophrenia. Twenty-eight participants were divided into those who reported PLEs (N = 11) and those who reported no PLEs (N = 17), i.e. the control group. Behavioural differences in accuracy and reaction time were explored between these groups using an Active Auditory Oddball Task developed for use with an adolescent population. In addition to the behavioural data, electrophysiological correlates of 'target' (oddball) versus 'non-target' tones elicited during the Active Auditory Oddball Task were also explored between groups. Specifically, between-group differences in mean amplitude of the P300 and N100 AEP components were explored. No between-group behavioural differences in accuracy or reaction times were observed. An increase in the amplitude of the N100 AEP component to non-target tones was observed in the PLEs group. No between-group-differences in mean amplitude of the P300 component to target tones were observed; however, mean amplitude to target tones at FCz was found to be significantly greater than mean amplitude to non-target tones in the control group but not in the PLEs group at fronto-central locations. The findings are discussed in relation to the current literature on schizophrenia and risk for psychotic disorders.

4.1 Introduction

Electroencephalographic (EEG) methods may prove to be a particularly useful tool in the search for antecedents to the development of psychotic disorders. In particular the P300 ERP component has been highlighted as a potential biological marker for schizophrenia. In a summary of previous research, Frangou et al. (1997) report that the P300 wave is a post-identification phenomenon related to either context updating of the working model of the environment (Donchin, 1979), termination of stimulus evaluation (Desmedt, Kornhubek & Deecke, 1980), or a third possibility is that it reflects allocation of attentional resources (Posner, 1975). Reductions in the amplitude and increases in the latency of the P300 waveform have also been observed in working memory tasks (Marchand et al., 2006; Galletly, MacFarlane & Clark, 2007) and the P300 has also been conceptualised as the physiological correlate of a working memory update of changes in the environment (Donchin & Coles, 1988).

In relation to auditory tasks, deviations in the amplitude of the Mismatch Negativity (MMN) waveform have been reported in chronic schizophrenia (Umbricht & Krljes, 2005), FEP (Atkinson et al., 2012) and genetically at-risk groups, in particular in relation to duration MMN (Jessen et al., 2001). MMN is an auditory ERP component that occurs in response to any violation of the regularity of the recent auditory past, and is usually observed in a passive auditory oddball task. MMN is observed when a stimulus which deviates in frequency, duration, intensity or location is presented among a set of non-deviant stimuli. MMN is thought to be a measure of preattentive information processing or sensory memory and is usually best observed as a difference waveform between standard and deviant tones which usually peaks between 100 and 240ms after the presentation of the deviant stimulus (Näätänen, 1995). The generation of MMN is thought to be completely independent of the participant's attention

(Näätänen, 1992; Näätänen, Schröger, Karakas, Tervaniemi & Paavilainen, 1993). Reduced MMN has most recently been reported in prodromal populations (Shin et al., 2009; Atkinson et al., 2012). Brockhaus-Dumke et al. (2005) also reported a trend towards MMN amplitude in a putatively prodromal group being intermediate between schizophrenia patients and controls; however, their result did not reach statistical significance. A study by Bodatsch et al. (2011) reported that duration MMN was significantly reduced in at-risk subjects who converted to first-episode psychosis compared to those subjects who did not convert. Reduced MMN has recently been found in adolescents reporting PLEs (Murphy et al., 2013). The earlier part of the P300 component, the P3a, has been studied in schizophrenia, with reports of a reduced P3a in response to novel irrelevant stimuli in an active oddball task (Turetsky et al., 2009). P3a/P3b disturbances were associated with avolition, attentional disturbances and delusions in this study.

While reduced MMN is commonly reported in *passive* auditory oddball tasks, the majority of papers reporting reductions in amplitude and increases in the latency of the P300 component have employed two-tone *active* auditory oddball tasks. That is, the P300 wave is measured during a continuous performance task in which participants respond to target stimuli embedded in a set of standard stimuli. The P300 to target stimuli is commonly used as an electrophysiological marker of cognitive disturbances specific to schizophrenia (Higashima et al., 1998; Higashima et al., 2004). A meta-analysis carried out by Jeon and Polich (2001) reported reduced P300 amplitude in patients with schizophrenia and reported the greatest effect size at the midline electrode site Pz. Bramon et al. (2004) carried out a further meta-analysis of 46 studies on the P300 waveform. These studies included data from a total of 1443 patients with schizophrenia and 1251 controls collected while participants completed a standard two-

tone auditory oddball task. They reported that patients with schizophrenia had significantly smaller amplitudes than the healthy unrelated comparison group for the P300 waveform. Furthermore, the latency of the P300 waveform was also significantly delayed in the patient group, albeit with a reduced effect size.

The P300 waveform has been proposed as a possible endophenotype for schizophrenia. Bramon et al. (2005) define endophenotypes as anatomical, physiological or biochemical variables that correlate with a trait of interest but have a more straightforward genetic basis than clinical syndromes. The overwhelming majority of the literature has examined the P300 wave at specific midline or temporal electrodes (Bramon et al., 2005). The P300 at the midline electrode site Fz as well as other measures of frontal cognition have been put forward as endophenotypes for schizophrenia (Gallinat et al., 2003). Reduced P300 amplitude and increased latency have been consistently reported in schizophrenia (Frangou et al., 1997; Bramon et al., 2004). Qualitatively similar, but less severe, deviance in amplitude and latency are evident in the non-psychotic relatives of patients with schizophrenia (Blackwood et al., 1991; Frangou et al., 1997; Bramon et al., 2005) strengthening the case for the P300 waveform as an endophenotype for schizophrenia.

P300 amplitude reduction and latency increases may be risk markers of vulnerability for psychosis (Bramon et al., 2008), however so far only amplitude reductions have been reported in prodromal groups and high-risk individuals with schizotypal personality trait. Van der Stelt, Lieberman and Belger (2005) were the first to report P300 amplitude reductions in prodromal cases which were of similar severity to those found in patients with recent onset, as well as chronic schizophrenia. High-risk cases showed poor bilateral P300 amplitudes, whereas first episode psychosis and chronic patients showed asymmetrical P300 abnormalities compared to controls.

Özgürdal et al. (2008) have also reported reduced amplitude of the P300 waveform in participants with at-risk mental state (ARMS) for schizophrenia. They state that their finding of reduced P300 amplitude in prodromal participants is in line with other studies that investigated the trait aspect of P300 amplitude in healthy siblings or biological relatives of schizophrenia patients, as well as high-risk individuals with schizotypal personality trait where reductions of P300 amplitude were also found (Blackwood et al., 1999; Mannan, Hiramatsu, Hokama & Ohta, 2001).

Using a P300 task with fMRI, Morey et al. (2005) reported that participants with ARMS showed less activation in the temporal cortex than controls, but more activation than patients with schizophrenia. It has been suggested that positive symptoms are related to abnormalities in temporal regions which are the main generators of P300 amplitude at electrode site Pz (Mc Carley et al., 1993). A study by Pantelis et al. (2003) of ultra high-risk (UHR) participants supports the theory that progressive changes in temporal regions could be found to predate the onset of psychosis. Özgürdal et al. (2008) state that the P300 at electrode site Pz could be a trait-marker which the authors suggest may reflect structural abnormalities in this region. P300 amplitude at Pz could also serve as a state-marker reflecting possible progression of alterations in temporal regions. Trait effects are assessed by comparing patients and control subjects, and state effects are assessed by correlating P300 amplitude with symptom ratings. Evidence for P300 amplitude as a trait marker for schizophrenia has been provided by a number of studies which have reported P300 reductions in patients and FEP (Salisbury, Shenton, Sherwood, Fischer, Yurgelun-Todd, Tohen et al., 1998; Frangou et al., 2007). In contrast, evidence for P300 amplitude as a state marker of disorder comes from studies which report that patients with more severe negative symptoms have smaller auditory P300s and observations that P300 amplitude is inversely correlated with positive

symptoms (see Mathalon, Ford & Pfefferbaum, 2000 for a review). Variations in P300 amplitude may reflect both trait and state influences (Mathalon et al., 2000).

Foxe et al. (2010) suggested that the N100 component of the AEP may also represent a candidate endophenotype for schizophrenia. The AEP is thought to arise from generators in the frontal and parietal cortices, as well as sources in the primary auditory cortex (Giard et al., 1994; Molholm et al., 2006). The AEP is best observed over fronto-central scalp sites and marks a crucial auditory sensory processing period (Foxe et al., 2010). Reduced amplitude of the N100 component of the AEP to non-target tones has been reported in schizophrenia patients, FEP and unaffected first-degree relatives of the schizophrenia probands relative to controls by Foxe et al. (2010). This decrease in the N100 component was observed over fronto-central scalp sites with a peak latency of 106ms. Other studies have also reported similar diminution of this component in schizophrenia patients, FEP and groups defined as genetically at-risk for schizophrenia (O'Donnell, Vohs, Hetrick, Carroll & Shekhar, 2004; Ahveninen et al., 2006; Salisbury, Collins & McCarley, 2010). The usefulness of the auditory N100 component as a potential endophenotype for schizophrenia has also been challenged by authors such as Rosburg, Boutros and Ford (2008).

4.1.1 Aims and Objectives

As amplitude reductions of the P300 and N100 AEP have been reported in the early stages of schizophrenia and in clinically at-risk and genetically at-risk groups, respectively, the present chapter focuses on the amplitude of the P300 ERP and N100 AEP components. The present chapter investigates whether amplitude differences in the P300 ERP and the N100 AEP exist between a group of young adolescents reporting

PLEs and a group of healthy controls using an active auditory oddball paradigm. To date, no EEG studies have been carried out using active auditory oddball paradigms with community-based samples of adolescents who report PLEs in an attempt to uncover possible markers of the developmental trajectory to psychosis and schizophrenia. The present chapter investigates ERPs elicited during a two-tone Active Auditory Oddball Task in a group of young adolescents considered symptomatically at-risk of developing psychosis compared to a matched group of healthy controls. This is achieved using a task developed for use with an adolescent population based on a task previously used by Bramon et al. (2005) and Frangou et al. (1997). In this task, participants make a button press response to infrequent 'target' (oddball) tone embedded in a series of frequent 'non-target' (standard) tones. The present study employs both behavioural and EEG measures while participants complete the task. Due to the simplicity of the task, no between-group differences in accuracy or reaction times are anticipated. Mean amplitude is expected to be greater for target tones compared to non-target tones during the P300 timeframe across midline (FCz, Cz, CPz, Pz) and central (Cz, C1, C2) electrode sites. It is also anticipated that the task will elicit an N100 AEP over fronto-central sites.

The hypotheses are as follows:

- It is hypothesised that the group of adolescents who report PLEs will show reductions in the amplitude of the P300 component to target tones compared to the healthy control participants. These differences in amplitude are expected at midline and central electrode sites.

- It is expected that the group of adolescents who report PLEs will show reductions in the amplitude of the N100 AEP component to non-target tones compared to the healthy control participants. These differences in amplitude are anticipated over fronto-central electrode sites.

4.2 Methods

4.2.1 Participants

Thirty-one participants (20 male; age range 11-13 years; mean age = 11.53 years) completed the Active Auditory Oddball Task after completing a clinical interview (see Chapter 2, section 2.1.3 for details of the clinical interview process). One participant was removed from the PLEs group due to a current diagnosis of Attention Deficit Disorder (ADD). Eleven participants reported PLEs (6 male; age range 11-13 years; mean age = 11.64 years). Data from two participants from the control group were removed due to excessive artifacts in the EEG recording leaving a control group of seventeen (11 males; age range 11-13 years, mean age = 11.41 years) for EEG analysis. Participants gave written informed assent and parental consent was obtained before participation in the study (see Chapter 2, section 2.3.1 for further details). All participants had normal or corrected-to-normal vision and no previous neurological disorders or brain injuries.

4.2.2 Stimuli

Participants completed a modified two-tone Active Auditory Oddball Task, based on the task used by Bramon et al. (2005) and previously by Frangou et al. (1997). The task was written and presented in E-Prime© - see Figure 4.1. Stimuli were 200 60dB tones with a 3 second inter-stimulus interval. Tones were presented through speakers in the testing cubicle and participants were advised to keep their eyes open and look straight ahead at a blank computer screen while completing the task.

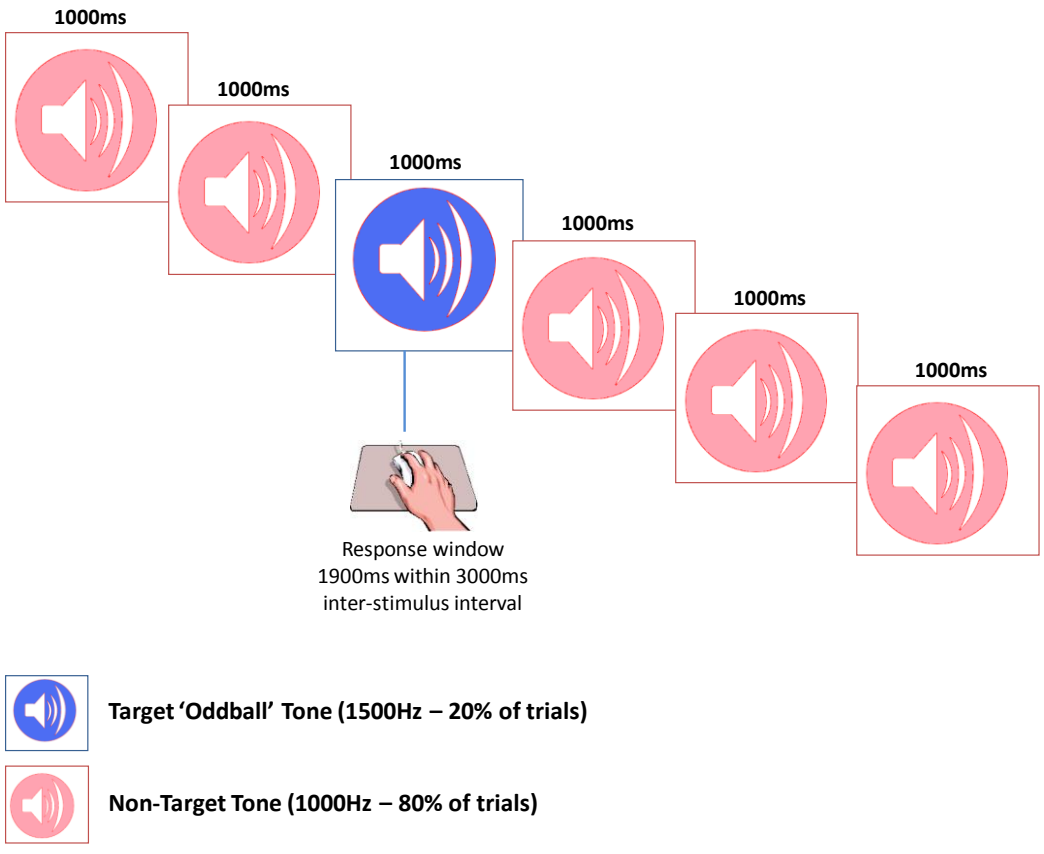


Figure 4.1: *Temporal sequence of trials in the Active Auditory Oddball Task.*

80 percent of the tones were ‘non-target’ (160 trials) whereas 20 percent of the tones were ‘targets’ (40 trials) presented in a pseudo-randomised order. Tones were generated using Audacity® (http://audacity.sourceforge.net/) audio editor and recorder. Non-target tones were 1000Hz and target oddball tones were 1500Hz. Tone duration was 1000ms for both target and non-target tones. Participants were instructed to press a mouse button with their index finger in response to target tones only (see Appendix XIV for a full list of instructions given to participants). The response window length was 1900ms; however, the overall data window length was 2000ms.

4.2.3 Procedure and Data Analysis

4.2.3.1 Procedure.

Details of the electrophysiological setup and recording are reported in Chapter 2 (section 2.3.3). E-Prime© logged response times for each participant and sent Transistor-Transistor Logic (TTL) triggers to the electroencephalography (EEG) acquisition PC to allow stimulus presentations (stimulus type) and responses to be logged in real time on the EEG recording. Response times were measured as the time between presentation of the stimulus and the response, and were recorded for all trials. Response latencies and accuracy were calculated automatically by E-Prime© and average response times to target stimuli were collated in E-Prime© for each block.

EEG data were recorded in μV from 62 scalp sites. The nasion was used as a reference. Vertical eye movements (VEOG) were recorded from electrodes located above and below the left eye and horizontal eye movements (HEOG) were recorded from the electrodes positioned at the outer canthus of each eye. Blinks were averaged off-line and a blink reduction algorithm was applied to the data. This algorithm

involved automatic artifact correction (Berg & Scherg, 1991; Ille et al., 2002). Stimulus-locked average ERPs were obtained by averaging the EEG using the test stimulus presentation as the trigger. ERP component time windows were chosen based on previous literature and visual inspection of grand averaged waveforms.

4.2.3.2 Data analysis.

Stimulus-locked epochs were defined as -100ms pre-stimulus presentation until 1000ms after stimulus presentation. Data were averaged for each participant and grand averages for each block were compiled. Only epochs in which participants made correct responses were included for group comparisons of ERP mean amplitude analysis. Statistical analyses were carried out using SPSS Statistics version 20 for Windows. Data were tested for normality using Kolmogorov-Smirnov tests. Demographic variables were compared using independent-samples t-tests and chi-square analyses.

Independent-samples t-tests were used to explore between-group differences in accuracy to target and non-target tones in addition to differences in reaction times (defined in milliseconds – ms) to target tones. Following visual inspection the central and midline electrode sites FCz, Cz, C1, C2, CPz and Pz were chosen to explore differences in the P300 waveform and the frontal and fronto-central scalp sites FCz, FC1, FC2, Fz, F1 and F2 were chosen to explore differences in the N100 AEP component. The P300 timeframe was defined from visual inspection and based on activity at fronto-central sites as 270ms to 430ms post-stimulus. A 2x3x2 mixed factorial ANOVA was used to assess differences in mean amplitude across central electrode sites with Tone (target, non-target) and Electrode (Cz, C1, C2) as the within-subjects variables and Group (control, PLEs) as the between-subjects variable. A second

2x4x2 mixed factorial ANOVA was used to assess differences in mean amplitude across midline electrode sites with Tone (target, non-target) and Electrode (FCz, Cz, CPz, Pz) as within-subjects variables and Group (control, PLEs) as the between-subjects variable.

The timeframe for the N100 AEP component was defined as 90ms to 170ms post-stimulus. Separate 2x3x2 mixed factorial ANOVAs were utilised to explore group differences in mean amplitude of the N100 AEP at frontal and fronto-central electrode sites with Tone (target, non-target) and electrode (FCz, FC1, FC2/Fz, F1, F2) as within-subjects variables and Group (control, PLEs) as the between-subjects factor. Bonferroni corrected paired-samples t-tests were used to further explore interaction effects observed in the ANOVAs.

Pearson's product-moment correlations were carried out to assess the relationship between mean amplitude of the P300 and measures of spatial working memory and non-verbal speed of processing from the MCCB. For each ANOVA, an alpha value of 0.05 was used for main and interaction effects. Levene's tests were employed to examine homogeneity of variances and Greenhouse-Geisser correction was employed where the assumption of sphericity was violated.

4.3 Results

4.3.1 Demographic and General Functioning Comparisons

Groups were compared on the following variables; age, gender, handedness, socioeconomic status (SES), scores on the Strengths and Difficulties Questionnaire (SDQ; Goodman 1997; Goodman et al., 1998) and overall current Children's Global Assessment Scale from the K-SADS-PL interview schedule (C-GAS; Shaffer et al., 1983) – see Table 4.1.

No differences in mean age, [$t(26) = -0.832$, $p = 0.413$] gender [$\chi^2(1) = 0.02$, $p = 0.887$], handedness [$\chi^2(1) = 0.001$, $p = 1.000$] or SDQ scores [$t(26) = -0.96$, $p = 0.347$] were observed between the control and PLEs groups. A between groups difference in C-GAS scores was observed [$t(24) = 2.99$, $p = 0.006$] with the PLEs group [$M = 59.3$, $SEM = 6.57$] receiving a lower mean score on this measure than the control group [$M = 80.06$, $SEM = 3.67$]. Groups were also found to differ on parental SES with more control parents in the professional and managerial employment categories [$\chi^2(1) = 6.04$, $p = 0.014$].

Table 4.1: *Demographic and general functioning details for the control and PLEs groups for the Active Auditory Oddball Task.*

Variable	**Overall (*N*=28)**	**Control (*N*=17)**	**PLEs (*N*=11)**	**Result**
Mean Age (SEM)	11.50 (0.13)	11.41 (0.15)	11.64 (0.24)	$t(26) = -0.832$, $p = 0.413$
Gender	17 males (60.71%)	11 males (64.71%)	6 males (54.55%)	$\chi^2(1) = 0.02$, $p = 0.887$
Handedness	3 left (10.71%)	2 left (11.76%)	1 left (9.09%)	$\chi^2(1) = 0.001$, $p = 1.000$
SES 1	21 (75%)	16 (94.12%)	5 (45.45%)	**$\chi^2(1) = 6.04$, $p = 0.014$**
SDQ scores* **(SEM)**	12.32 (1.03)	11.53 (1.24)	13.55 (1.8)	$t(26) = -0.96$, $p = 0.347$
C-GAS scores (SEM)	72.08 (3.88)	80.06 (3.67)	59.3 (6.57)	**$t(24) = 2.99$, $p = 0.006$**

*Higher scores reveal greater impairment.
Significant differences are highlighted in bold.
SES 1 – professional and managerial, SES2 – other.

4.3.2 Behavioural Data

For the overall group, mean accuracy scores for both target (*M* = 39.14, *SEM* = 0.4) and non-target tones (*M* = 157.86, *SEM* = 0.77) were high. No between-group differences in mean accuracy to target tones ($t(26) = 0.64$, $p = 0.53$) or non-target tones ($t(26) = -0.05$, $p = 0.96$) were observed. No between-group difference in mean reaction times to target tones was observed ($t(23.42) = 1.95$, $p = 0.06$) – see Table 4.2.

Table 4.2: *Accuracy scores and reaction times for the Active Auditory Oddball Task.*

Condition	**Group (*N*)**	**Mean**	**SEM**
Target Accuracy	Control (17)	39.35	0.34
	PLEs (11)	38.82	0.9
Non-Target Accuracy	Control (17)	157.82	1.11
	PLEs (11)	157.91	0.99
Target Reaction Times	Control (17)	890.2	70.39
	PLEs (11)	734.62	37.71

4.3.3 Electrophysiological Data

4.3.3.1 Overall group.

4.3.3.1.1 Mean amplitude of the P300 component.

For the overall group a significant difference in mean amplitude (μV) between target and non-target tones was observed along central [$F(1, 27) = 34.93$, $p < 0.0005$, partial eta squared = 0.564] and midline [$F(1, 27) = 36.52$, $p < 0.0005$, partial eta squared = 0.575] electrode sites for the P300 timeframe of 270ms to 430ms – see Figure 4.2. Paired-samples t-tests confirmed that mean amplitude to non-target tones was reduced compared to target tones at all 6 electrode sites and these results remained significant after a Bonferroni corrected p value of 0.008 was applied – see Table 4.3.

Table 4.3: *Mean amplitude for target and non-target tones at central and midline electrode sites for the P300 ERP component (Note: SEM indicated in brackets).*

Electrode	Target	Non-Target	Result
FCz	0.68 (0.65)	-1.83 (0.39)	$t(27) = 3.7$, $p = 0.001$
Cz	2.91 (0.62)	-0.72 (0.4)	$t(27) = 5.52$, $p < 0.0005$
C1	3.48 (0.63)	-0.77 (0.35)	$t(27) = 7.37$, $p < 0.0005$
C2	1.84 (0.49)	-0.43 (0.36)	$t(27) = 4.12$, $p < 0.0005$
CPz	4.42 (0.55)	0.61 (0.39)	$t(27) = 6.46$, $p < 0.0005$
Pz	4.1 (0.5)	0.97 (0.35)	$t(27) = 5.62$, $p < 0.0005$

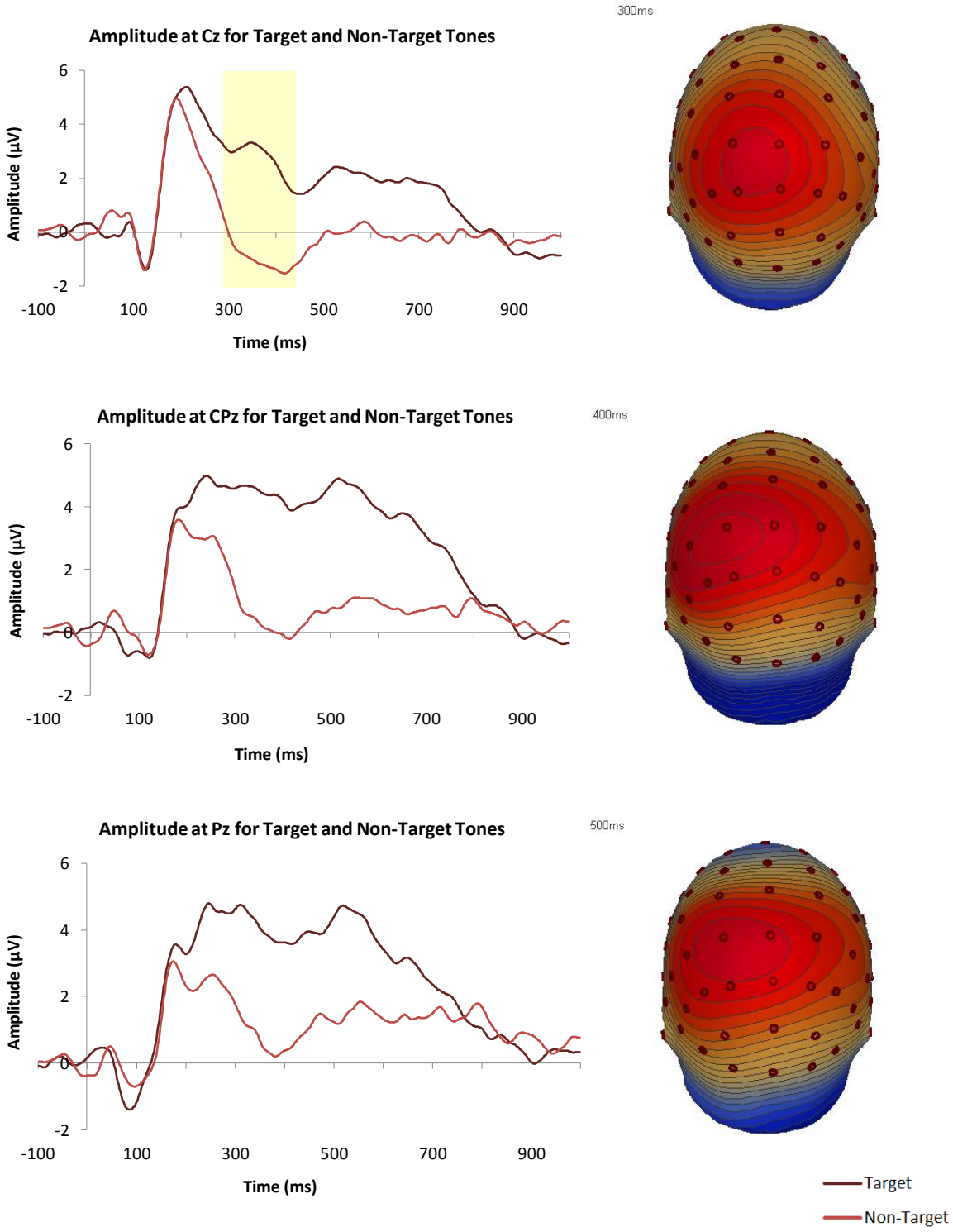


Figure 4.2: *ERP waveforms showing differences in mean amplitude to target and non-target tones at midline electrode sites Cz, CPz and Pz and scalp topographies for target tones at 300ms, 400ms and 500ms post-stimulus.*

4.3.3.1.2 Mean amplitude of the N100 AEP component.

No main effect of Tone was observed when mean amplitude was assessed at fronto-central electrode sites FCz, FC1 and FC2 for the timeframe 90ms to 170ms post-stimulus [$F(1, 26) = 0.01$, $p = 0.939$, partial eta squared = 0.001]. A main effect of Electrode was observed [$F(2, 54) = 7.14$, $p = 0.005$, partial eta squared = 0.209]. No main effects of Tone [$F(1, 26) = 0.31$, $p = 0.584$, partial eta squared = 0.011] or Electrode [$F(2, 54) = 0.55$, $p = 0.51$, partial eta squared = 0.02] were observed at frontal electrode sites Fz, F1 and F2 for the N100 AEP timeframe.

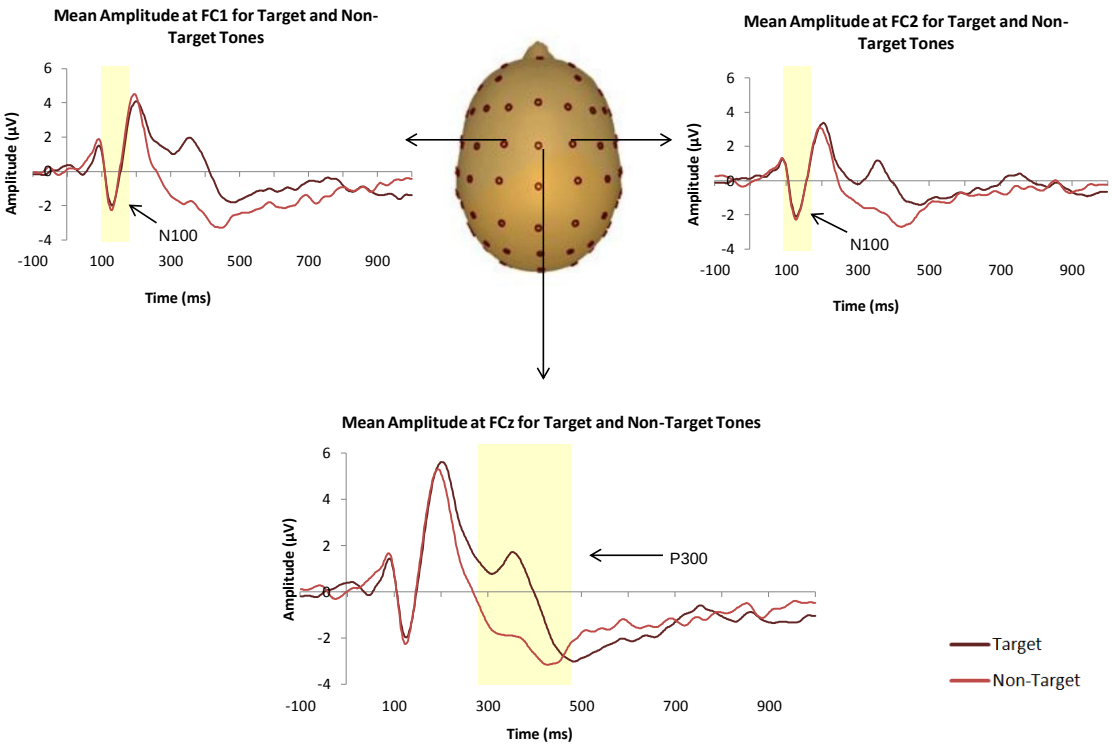


Figure 4.3: *ERP waveforms showing differences in mean amplitude to target and non-target tones at FC1, FCz and FC2.*

4.3.3.2 Group analyses.

4.3.3.2.1 Mean amplitude of the P300 component.

No between-groups effect was observed along midline electrode sites FCz, Cz, CPz and Pz for the timeframe 270ms to 430ms [$F(1, 26) = 0.16$, $p = 0.689$, partial eta squared = 0.006]. Main effects of Tone [$F(1, 26) = 33.92$, $p < 0.0005$, partial eta squared = 0.566] and Electrode [$F(3, 78) = 29.22$, $p < 0.0005$, partial eta squared = 0.529] were observed. No interaction effects of Tone*Group [$F(1, 26) = 0.02$, $p = 0.893$, partial eta squared = 0.001] or Electrode*Group [$F(3, 78) = 0.82$, $p = 0.421$, partial eta squared = 0.03] were observed. Tone*Electrode [$F(3, 78) = 4.66$, $p = 0.025$, partial eta squared = 0.152] and Tone*Electrode*Group [$F(3, 78) = 5.84$, $p = 0.012$, partial eta squared = 0.182] interaction effects were observed.

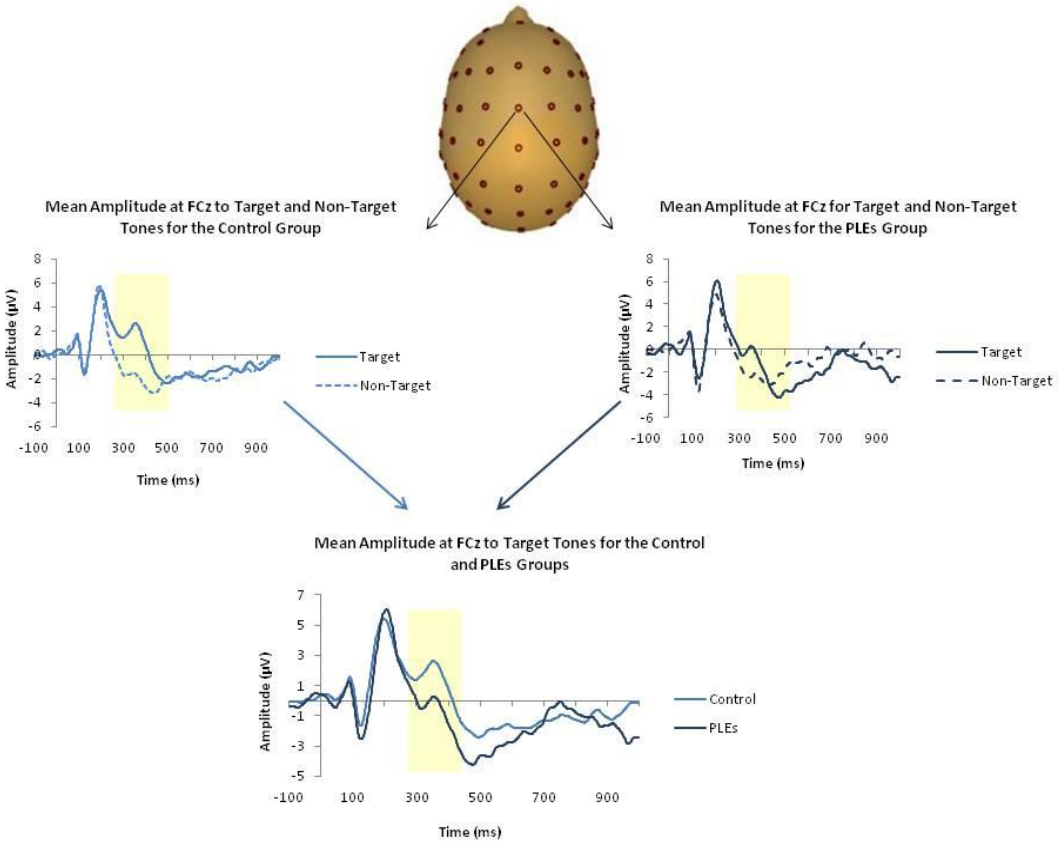


Figure 4.4: *ERP waveforms for the P300 component at FCz.*

Paired-samples t-tests revealed that for the control group a significant increase in mean amplitude was observed for target tones (M = 1.46, *S.E.M.* = 0.74) compared to non-target tones (M = -1.94, *S.E.M.* = 0.48) at FCz [$t(16) = 4.65$, $p < 0.0005$] and this result remained significant after a Bonferroni adjusted p value of 0.012 was applied. This effect was not observed in the PLEs group [target tones: M = -0.5, *S.E.M.* = 1.16; non-target tones: M = -1.67, *S.E.M.* = 0.67; $t(10) = 0.93$, $p = 0.373$] – see Figure 4.4. For all other electrode sites mean amplitude to target tones was greater than mean amplitude to non-target tones within both groups – see Table 4.4.

Table 4.4: *Mean amplitude for target and non-target tones at central and midline electrode sites for the P300 ERP component for each group (Note: SEM indicated in brackets).*

Electrode	Group	Target	Non-Target	Result (*p* value)
FCz	Control	1.46 (0.74)	-1.94 (0.48)	< 0.0005*
	PLEs	-0.5 (1.16)	-1.67 (0.67)	0.373
Cz	Control	3.01 (0.7)	-0.46 (0.47)	< 0.0005*
	PLEs	2.75 (1.23)	-1.13 (0.72)	0.016*
C1	Control	3.92 (0.67)	-0.49 (0.41)	< 0.0005*
	PLEs	2.78 (1.26)	-1.2 (0.62)	0.006*
C2	Control	1.57 (0.59)	-0.17 (0.5)	0.022*
	PLEs	2.26 (0.89)	-0.84 (0.51)	0.006*
CPz	Control	4.21 (0.52)	0.85 (0.42)	< 0.0005*
	PLEs	4.74 (1.18)	0.23 (0.78)	0.002*
Pz	Control	3.72 (0.38)	1.09 (0.44)	< 0.0005*
	PLEs	4.69 (1.15)	0.79 (0.59)	0.008*

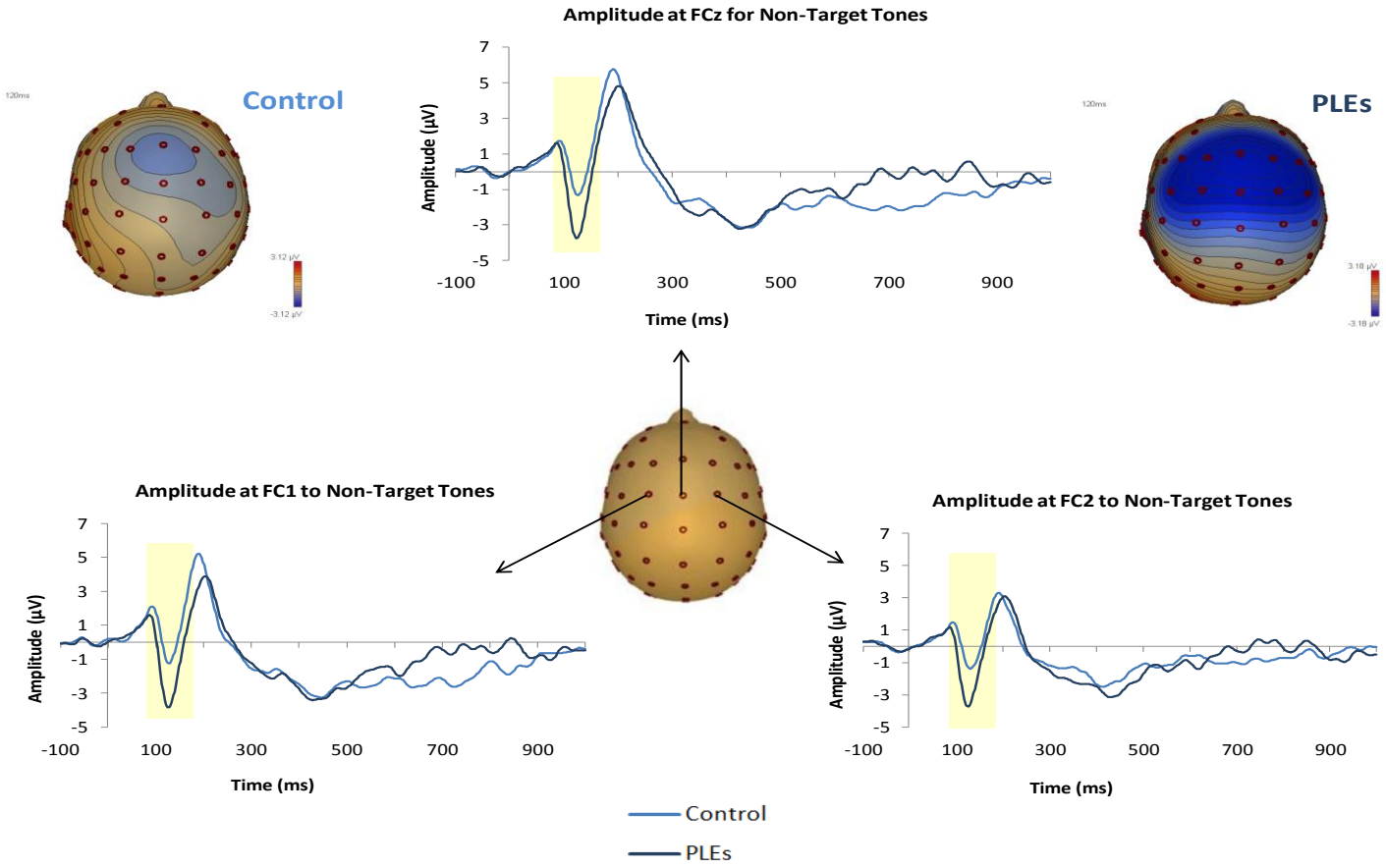
* Significant after Bonferroni correction.

No between-groups effect was observed along central electrode sites Cz, C1 and C2 for the timeframe 270ms to 430ms [$F(1, 26) = 0.36$, $p = 0.554$, partial eta squared = 0.014]. Main effects of Tone [$F(1, 26) = 33.2$, $p < 0.0005$, partial eta squared = 0.561] and Electrode were observed [$F(2, 52) = 3.09$, $p = 0.078$, partial eta squared = 0.106] Interaction effects were observed for Tone*Electrode [$F(2, 52) = 20.79$, $p < 0.0005$, partial eta squared = 0.444] and Tone*Electrode*Group [$F(2, 52) = 4.91$, $p = 0.018$, partial eta squared = 0.159]. No interaction effects were observed for Tone*Group [$F(1, 26) = 0.14$, $p = 0.709$, partial eta squared = 0.005] or Electrode*Group [$F(2, 52) = 2.25$, $p = 0.137$, partial eta squared = 0.08]. Paired-samples t-tests revealed that for both groups a significant increase in mean amplitude was observed for target tones compared to non-target tones at central electrode sites – see Table 4.4.

4.3.3.2.2 Mean amplitude of the N100 AEP component.

A between-groups effect was observed when mean amplitude at electrode sites FCz, FC1 and FC2 were explored [$F(1, 26) = 5.21$, $p = 0.031$, partial eta squared = 0.167] for the timeframe 90ms to 170ms post-stimulus. A main effect of Electrode was observed [$F(2, 52) = 6.29$, $p = 0.009$, partial eta squared = 0195]. A between-groups effect was also observed when mean amplitude was explored at frontal sites Fz, F1 and F2 [$F(1, 26) = 5.59$, $p = 0.026$, partial eta squared = 0.177]. A Tone*Electrode*Group effect was also observed [$F(2, 52) = 3.75$, $p = 0.047$, partial eta squared = 0.126].

Figure 4.5: *Group differences in ERP waveforms for the N100 AEP component to non-target tones at fronto-central sites.*



Independent-samples t-test revealed that N100 AEP mean amplitude elicited to non-target tones was greater in amplitude in the PLEs group than the control group at frontal [Fz: $t(26) = 2.29$, $p = 0.03$; F1: $t(26) = 2.09$, $p = 0.046$; F2: $t(26) = 2.62$, $p = 0.015$] and fronto-central electrodes [FC1: $t(26) = 2.64$, $p = 0.014$; FC2: $t(26) = 2.13$, p 0.043] – see Table 4.5 and Figure 4.5. N100 AEP mean amplitude to target tones was also greater in the PLEs group than the control group at FC1 [$t(26) = 2.27$, p 0.031] and F1 [$t(26) = 2.09$, $p = 0.046$] – see Figure 4.5 and Table 4.5.

Table 4.5: *Mean amplitude for target and non-target tones at frontal and fronto-central electrode sites for the N100 AEP component for each group (Note: SEM indicated in brackets).*

Electrode	Group	Target	Non-Target
FCz	Control	0.47 (0.52)	0.72 (0.56)
	PLEs	-0.65 (0.59)	-0.94 (0.61)
FC1	Control	0.42 (0.5)	0.7 (0.55)
	PLEs	-1.19 (0.4)	-1.35 (0.45)
FC2	Control	-0.29 (0.4)	0.02 (0.45)
	PLEs	-0.87 (0.61)	-1.52 (0.57)
Fz	Control	0.07 (0.6)	0.05 (0.62)
	PLEs	-1.41 (0.48)	-1.94 (0.5)
F1	Control	0.08 (0.52)	-0.002 (0.62)
	PLEs	-1.5 (0.48)	-1.81 (0.47)
F2	Control	-0.26 (0.57)	0.01 (0.59)
	PLEs	-1.26 (0.46)	-2.23 (0.54)

4.3.3.3 Correlation analyses.

Pearson's product-moment correlations were carried out to assess the relationship between mean amplitude at fronto-central electrode sites and scores on the MCCB.

Table 4.6: *Relationship between mean amplitude to target tones at FCz, FC1 and FC2 for the P300 and measures of spatial working memory and speed of processing.*

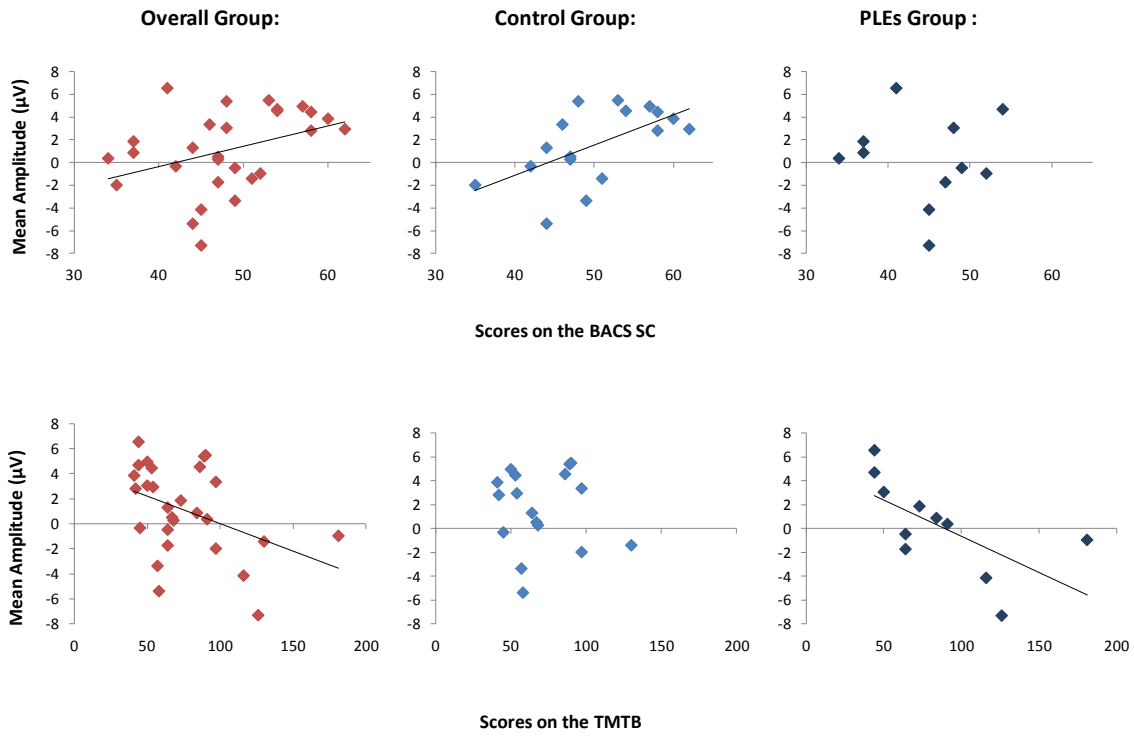
Neuropsychological Test and Electrode	Overall (*N*=28)	Control (*N*=17)	PLEs (*N*=11)
WMS-III SS			
FCz	0.410*	0.204	0.496
FC1	0.288	0.028	0.453
FC2	0.216	0.032	0.374
TMTA†			
FCz	-0.412*	-0.449	-0.307
FC1	-0.518**	-0.503*	-0.494
FC2	-0.312	-0.287	-0.342
TMTB†			
FCz	-0.373	-0.041	-0.550
FC1	-0.408*	-0.051	-0.651*
FC2	-0.206	0.113	-0.436
BACS SC			
FCz	0.377*	0.618**	-0.135
FC1	0.377*	0.593*	-0.045
FC2	0.257	0.536*	-0.071

†Higher scores reveal greater impairment.

*Correlation is significant at the 0.05 level (2-tailed) and **at the 0.01 level (2-tailed).

Mean amplitudes at FCz, FC1 and FC2 for the P300 timeframe (270ms to 430ms) were correlated with measures of spatial working memory and non-verbal speed of processing from the MCCB for each of the groups – see Table 4.6.

Figure 4.6: *Scatterplots indicating the relationship between scores on the TMTB and BASC SC and mean amplitude of the P300 ERP component at FC1.*



The correlation between TMTB scores and mean amplitude at FC1 was mainly influenced by the PLEs group [r = -0.651, n = 11, p = 0.03]. A group differences was previously observed on this measure and reported in Chapter 3, section 3.3.2 with the PLEs group performing more poorly on this test. In addition higher scores on the BACS

SC were found to correlate with higher mean amplitudes for the P300 in the control group across all 3 fronto-central electrode sites [FCz: $r = 0.618$, $n = 17$, $p = 0.008$; FC1: $r = 0.593$, $n = 17$, $p = 0.012$; FC2: $r = 0.536$, $n = 17$, $p = 0.026$] – see Figure 4.6. A significant group difference was also observed on this measure with the control group performing better on this task (see Chapter 3, section 3.3.2).

4.3.4 Summary of Results

In summary, no between-group differences were observed for the demographic variables age and gender. The control and PLEs groups were found to differ in terms of parental SES but did not differ in terms of handedness. In terms of general psychopathology group scores on the SDQ did not differ, however in terms of general functioning the PLEs group obtained lower C-GAS scores than the control group.

The groups did not differ behaviourally on accuracy scores to target and non-target tones or reaction times to target tones. For the overall group mean amplitude of the P300 component was greater for target than non-target tones across central and midline electrode sites FCz, Cz, CPz, Pz, C1 and C2. No between-group differences in the amplitude of the P300 were observed at either central or midline electrode sites. However when a within-groups analysis was carried out mean amplitude to target tones was found to be significantly greater than mean amplitude to non-target tones in the control group at electrode site FCz. This result was not observed within the PLEs group. The amplitude of the P300 ERP to target tones was found to correlate positively with BACS SC scores in the control group and negatively with TMTB scores in the PLEs group, indicating that better scores on speed of processing tasks were associated with greater amplitude of the P300 component at fronto-central locations. Between-group

differences were observed in the amplitude of the N100 AEP to non-target tones across frontal and fronto-central sites.

4.4 Discussion

The present chapter reports alterations in the ERPs elicited during a two-tone Active Auditory Oddball Task in a group of adolescents reporting PLEs compared to a control group. A between-groups difference in the amplitude of the N100 AEP component was revealed, with greater amplitude of the N100 AEP to non-target tones observed in the PLEs group. No between-groups difference in the mean amplitude of the P300 component was observed. When further analysis was undertaken it was noted that the greater P300 elicited to target tones relative to non-target tones in the control group at FCz was absent in the PLEs group. This result did not however reach statistical significance in a between-groups analysis.

No between-group differences in accuracy to target tones and non-target tones or reaction time to target tones were observed. This was expected due to the simplicity of the task. Accuracy scores for target and non-target tones were high for both groups and reaction times to target tones were low for both groups. Based on previous research it was predicted that the mean amplitude of the P300 component would be greater for target tones than non-target tones (Frangou et al., 1997; Bramon et al., 2008) and this effect was observed across midline and central electrode sites for the P300 waveform as predicted, with increased amplitude to target tones relative to non-target tones visible across all midline electrode sites. While sustained parietal positivity was observed for

the target tone compared to the non-target tone condition, the P300 component was most clearly observed over fronto-central sites in the present study, in contrast to previous studies (Jeon & Polich, 2001; Bramon et al., 2004). The majority of papers reporting amplitude reductions of the P300 waveform in schizophrenia have reported data from midline or temporal electrodes, with a large proportion of papers reporting data from central and parietal midline sites such as Cz and Pz (Bramon et al., 2005). The P300 at the frontal electrode site Fz (as well as other measures of frontal cognition) have been suggested as endophenotypes for schizophrenia (Gallinat et al., 2003). The task used in the present chapter was adapted for use with an adolescent population from a task previously reported by Bramon et al. (2005). The number of trials in the task was reduced and this may have contributed to the absence of a clearly defined P300 ERP component at posterior electrode sites. Alternatively, age-related factors may also influence the topography of the P300. Previous studies reporting amplitude reductions of the P300 waveform in 11 to 13 year old adolescents reporting PLEs have also reported a more anterior P300 component (Murphy et al., 2012).

Mean amplitude to target tones was found to be reduced relative to non-target tones in the control group but not in the PLEs group for the P300 ERP component at electrode site FCz. Previous research has reported reduced amplitude of the P300 component to target tones at central and parietal midline electrode sites using active auditory oddball paradigms in schizophrenia patients (Frangou et al., 1997; Bramon et al., 2004). In addition, similar results have been reported in prodromal and ARMS groups (van der Stelt et al., 2005; Bramon et al., 2008; Özgürdal et al., 2008), non-psychotic relatives of patients (Frangou et al., 1997) and in groups scoring high on measures of schizotypal personality (Gassab et al., 2006). The present chapter did not find evidence of reduced P300 to target tones in a group of adolescents reporting PLEs

relative to the control group when between-group differences were explored, however the absence of a relative increase in mean amplitude to target tones compared to non-target tones in the PLEs group indicates that the way in which the two groups process target and non-target tones may differ. This may indicate the early stages of processing differences in this group which could later manifest as a reduced P300. These differences may become more pronounced with the persistence of PLEs.

Amplitude of the P300 component to target tones at fronto-central sites was found to correlate positively with scores on symbol coding (BACS SC) in the control group, indicating that those participants who had higher amplitudes also performed better on this measure of speed of processing. In addition, amplitude of the P300 component to target tones at fronto-central sites was found to correlate negatively with trail making scores (TMTB) in the PLEs group, indicating that those participants who had lower amplitudes performed more poorly (i.e. were slower) on this measure of speed of processing. The control and PLEs groups who completed the Active Auditory Oddball Task were found to differ on these measures of speed of processing in Chapter 3. As speed of processing deficits have been reported in schizophrenia (Dickinson et al., 2007; 2008), FEP (Mesholam-Gately et al., 2009) and clinical high-risk groups (Seidman et al., 2010), this relationship between the amplitude of the P300 component at FCz and measures of speed of processing is important.

Amplitude of the P300 ERP component has been proposed as a reliable trait marker for schizophrenia. The current study adds limited support to the proposal of P300 amplitude as a trait marker for risk of a psychotic disorder. While there is some evidence from the within-groups analysis that the PLEs group differed from the control group and did not elicit a higher P300 to target relative to non-target tones, the present study did not find a reduced P300 between the groups across midline electrode sites. It

is possible that the P300 waveform observed during auditory discrimination on active auditory oddball tasks may reflect both trait and state influences of psychotic disorder (Mathalon et al., 2000). Reductions in the P300 ERP component have been reported in prodromal and ARMS groups (van der Stelt et al., 2005; Bramon et al., 2008, Özgürdal et al., 2008); however, as these groups are help-seeking (in contrast to the participants in the present study) it is possible that the reduced P300 amplitudes observed in these groups may be as a result of symptoms of a clinical disorder which have already commenced e.g. positive symptoms such as hallucinations and delusions which are of a strong enough nature to cause distress.

While the present chapter did not find between-group evidence of reduced amplitude of the P300 component in adolescents who report PLEs using an *active* auditory oddball task, Murphy et al. (2013) have recently reported reduced MMN in a similar group of adolescents reporting PLEs from the general population using a *passive* auditory oddball task. Murphy et al. (2013) employed a duration deviant passive auditory oddball task and reported reduced amplitude of the MMN component at frontal and temporo-parietal areas in line with previous reports of reduced MMN amplitude in schizophrenia patients (Umbricht & Krljes, 2005), FEP (Atkinson et al., 2012) and groups defined as clinically at-risk for psychotic disorders (Shin et al., 2009; Atkinson et al., 2012). While the P300 elicited by active auditory oddball tasks is likely to reflect context updating, stimulus evaluation or allocation of attention resources to stimuli which are actively attended to (Donchin, 1979; Desmedt et al., 1980; Posner, 1975), the MMN waveform is thought to be a measure of preattentive information processing or sensory memory (Näätänen, 1995). Due to evidence that the P300 elicited during active oddball paradigms may reflect state as well as trait influences while the MMN has been suggested as a reliable and robust trait marker for schizophrenia, it is likely that

differences in the MMN waveform may be better suited for detecting risk for psychosis in the non-clinical psychosis phenotype.

A between-group difference in the N100 AEP to non-target tones over fronto-central scalp sites was observed in the present study. This result is in contrast to results previously reported in schizophrenia patients and genetically at-risk groups. Foxe et al. (2010), for example, reported reduced mean amplitude of the N100 component to non-target tones in schizophrenia patients and first-degree relatives of the schizophrenia probands relative to controls. They suggested that the N100 AEP may be a potentially useful endophenotype for schizophrenia. Other studies have also reported similar reductions of this component in schizophrenia patients, FEP and groups defined as genetically at-risk for psychosis (O'Donnell et al., 2004; Ahveninen et al., 2006; Salisbury et al., 2010).

The N100 is thought to be generated by activity in the primary auditory cortex, with the frontal and parietal cortices also contributing to its production (Giard et al., 1994; Molholm et al., 2006). Studies have reported that progressive changes in temporal regions could predate the onset of psychosis (Pantelis et al., 2003). This gives rise to the possibility of alterations in normal development within these areas in the PLEs group in the present study. Although the observation of increased N100 AEP amplitude to non-target tones in the present chapter is in contrast to findings previously reported in the ERP literature on schizophrenia, it nonetheless indicates a difference in early sensory processing of auditory information between the PLEs and control groups. Previous imaging research has reported disrupted prefrontal-temporal connectivity in adolescents reporting PLEs and increased grey matter within the middle and superior temporal gyri, angular gyrus and orbitofrontal gyrus and decreased grey matter in the inferior temporal gyrus (Jacobson et al., 2010).

The N100 is thought to be modulated by selective attention and amplitude increases may stem from increased activity of N100 generators (Hillyard, Hink, Schwent & Picton, 1973; Hillyard, Mangun, Woldorff & Luck, 1995). Selective attention deficits have been linked to positive symptoms and reality monitoring failure in schizophrenia (Brébion, Smith, Gorman & Amador, 1996). The increased N100 to non-target stimuli in the PLEs group observed in the present chapter may indicate increased attention to irrelevant stimuli. While this did not impair the behavioural performance of the PLEs group on the present task, the persistence of attention to task irrelevant stimuli may prove detrimental if task complexity was increased and if this continues throughout development. Morris, Griffiths, Le Pelley & Weickert (2013) suggest that deficits in selective attention results in learning irrelevant causal associations and may be the basis of positive symptoms in schizophrenia.

4.4.1 Chapter Summary

This chapter used electrophysiological measures to investigate the ERPs elicited during a two-tone Active Auditory Oddball Task in an adolescent sample with self-reported PLEs. This chapter is to our knowledge the first study to use an Active Auditory Oddball Task alongside EEG measures in a community-based sample of adolescents reporting PLEs. The present chapter therefore adds to the current literature by exploring P300 amplitude in the treatment-naïve extended psychosis phenotype. A within-groups effect was observed for the P300 component elicited in the present chapter; while an increase in the amplitude of the P300 component to target relative to non-target tones was observed in the control group this effect was absent in the PLEs group. While this indicates that the PLEs group may have processed the tones differently, in the absence

of a between-groups difference in amplitude this indicates the P300 component elicited by the active auditory oddball task employed in the present study may not serve as a useful trait marker of risk for psychotic disorders. Further research is needed in order to uncover the usefulness of reduced amplitude of the P300 component in active auditory oddball paradigms and risk for psychotic disorder.

State influences may play too strong a role in the reduction of the amplitude of the P300 ERP component elicited by active oddball tasks which is reported in schizophrenia, FEP and clinical high-risk groups, thus limiting its usefulness as a trait marker for disorder. In contrast, earlier components such as the N100 AEP in active oddball tasks and the MMN waveform elicited by passive oddball tasks may prove to be more useful trait markers for disorder. The P300 observed during cognitive tasks such as receptive language (previously by Murphy et al., 2012) and memory tasks may prove to be a more useful trait marker for psychotic disorders. Chapters 5 and 6 which follow will explore between-group differences in the P300 ERP component during spatial memory tasks. Chapter 5 will explore spatial processing during encoding and retrieval and implicit spatial memory for object location using the Implicit Spatial Memory Task, a variation of the Spatial Grid Task developed by Murphy et al. (2009). Chapter 6 will further explore the P300 during retrieval on a Spatial Working Memory Task based on the Sternberg paradigm (Sternberg, 1966).

Chapter 5

Electrophysiological Correlates of Spatial Processing and Implicit Spatial Memory in Adolescents Reporting Psychotic-Like Experiences and Controls

Abstract

The following chapter explores spatial processing and implicit spatial memory in a group of adolescents reporting psychotic-like experiences (PLEs) in comparison to a healthy control group. Reduced activity in the hippocampus as well as other areas implicated in spatial navigation has been reported in schizophrenia. The present chapter aims to explore memory processes in participants who report PLEs and controls using an Implicit Spatial Memory Task. This task incorporates testing of an old/new paradigm as well as examining implicit memory for location of objects. Participants were divided into those who reported PLEs (N = 13) and the control group (N = 24). Behavioural differences in accuracy and reaction time were explored using a Spatial Grid Task designed to test implicit object-location memory. Within-group differences were observed for the overall group in the reaction time data, supporting previous work by Murphy et al. (2009). No between-group differences were observed in the behavioural data. In addition to the behavioural data, a within-group difference was observed for the overall group with earlier peak latency of the P300 event-related potential (ERP) component for the study object correct location test condition compared to other test conditions indicating participants classified objects faster using implicit spatial memory. Larger mean amplitude was observed within the overall group with larger mean amplitude for the test conditions compared to the study stimuli. No between-group differences were observed in the peak latency or mean amplitude data for the P300 component. The findings are discussed in relation to the current literature on schizophrenia, risk for psychotic disorders and spatial memory.

5.1 Introduction

Learning and memory impairments are present in schizophrenia and in particular spatial memory deficits have been reported throughout the course of psychotic illness. Object-location memory refers to knowledge of the exact location of objects and their relative position to each other and depends on a variety of component processes such as object processing, spatial-location processing or memory for the locations of individual items and memory for occupied locations (Puglisi, Park, Smith & Hill, 1985; Kessels, de Haan, Kappelle, & Postma, 2001). Results from animal and human studies suggest the involvement of medial temporal lobe structures such as the hippocampus and parahippocampal gyrus, as well as the parietal cortex in spatial representation (Roche, Mangaoang, Commins & O'Mara, 2005). However dissociation in hippocampal and parahippocampal structures for spatial and non-spatial processing has been noted (Murphy et al., 2009). Specifically, hippocampal-lesioned animals fail to increase their reactivity following a spatial change of objects already present in an environment (Save, Poucet, Foreman & Buhot, 1992). Subregions of the dorsal hippocampus have been shown to play a role in detecting novel spatial information but not information about individual objects (Lee, Hunsaker & Kesner, 2005). In humans, extensive damage to the right medial temporal lobe area including the hippocampus impairs spatial memory (Bohbot et al., 1998).

Changes in the structure and volume of the hippocampus have been widely reported in schizophrenia. Reduced hippocampal volume is one of the most robust brain abnormalities noted in the schizophrenia literature (Nelson, Saykin, Flashman & Riordan, 1998; McCarley et al., 1999) with decreases in hippocampal volume noted in the early stages of the illness (Koolschijn et al., 2010). A systematic review and meta-analysis of Magnetic Resonance Imaging (MRI) studies carried out by Steen and

colleagues reported that whole brain and hippocampal volume are reduced in patients with a first psychotic episode (Steen, Mull, McClure, Hamer & Lieberman, 2006).

Genetic studies have reported reduced volume of the hippocampus in non-psychotic relatives of schizophrenia patients (Seidman et al., 2002). In addition, Wood et al. (2005) reported reduced hippocampal volume in an ultra high-risk (UHR) group. Conflicting results have been reported by other authors, however, who argue that hippocampal volume reduction is not seen until the later stages of illness progression (Velakoulis et al., 2006). Velakoulis et al. (2006) found that patients with chronic schizophrenia had bilaterally smaller hippocampi and that left-sided hippocampal volume reduction is seen in first-episode patients with schizophrenia. They examined two UHR groups and found that neither the UHR group who converted to psychosis, nor the UHR group who did *not* convert to psychosis, exhibited hippocampal volume changes.

Functional neuroimaging studies have reported decreased metabolism and increased blood flow in the hippocampus in schizophrenia, and abnormalities of hippocampal function have been linked to the expression of positive symptoms and to activity during memory retrieval (Heckers, 2001). Verbal auditory hallucinations have been linked to activity in a number of areas including the left hippocampus and parahippocampal gyrus (Shergill, Brammer, Williams, Murray & McGuire, 2000; Jardri, Pouchet, Pins & Thomas, 2011; van Lutterveld et al., 2012). Spieker, Astur, West, Griego and Rowland (2012) used a virtual reality eight-arm radial maze to explore reference and working memory in schizophrenia. Participants with schizophrenia displayed impaired spatial learning on the task compared to healthy control participants. Impaired performance on the task was characterised by increased

trial completion time and distance travelled as well as more reference and working memory errors.

The Implicit Spatial Grid Task was designed by Murphy et al. (2009) and based on the Milner paradigm (Johnsrude, Owen, Crane, Milner & Evans, 1999; Milner, Johnsrude & Crane, 1997). In the study block participants are instructed to remember a set of objects presented one at a time alongside two landmark objects on an environmental spatial grid without any references in the instructions to the location of the objects. These "study" objects are then presented one at a time in the test block with new "distractor" objects. Participants must simply indicate whether they have seen the object before or whether it is a new object. Study objects are presented in correct locations (i.e. that object's same location on the spatial grid as seen in the study block) or in incorrect locations (i.e. a new location on the spatial grid). This allows implicit memory for object location to be tested. All objects are encoded and retrieved from a stationary viewpoint which permits a person-centred (i.e. egocentric) frame of reference. The Implicit Spatial Grid Task allows for both the encoding and retrieval stages of spatial memory to be explored.

Using data from a group of adult participants Murphy et al. (2009) reported that accuracy scores differed significantly across conditions in the Implicit Spatial Grid Task (study object correct location, study object incorrect location, distractor objects) when an overall analysis of variance was performed; however, non-significant follow-up t-tests provided no further clarification. Study objects in a correct location were found to be identified fastest. Study stimuli (i.e. encoding) in the task elicited a P300 ERP waveform over parietal scalp electrodes with source analysis revealing a distributed network of frontal, parietal, temporal and medial temporal sources contributing to this component. Differences in the latency of the P300 waveform were observed between

test conditions (i.e. retrieval) with earlier latency for the study object correct location stimuli compared to the other two test stimuli conditions, providing physiological evidence that participants implicitly classified objects more quickly when presented in study locations. Source analysis revealed that the same (or similar) areas were involved in the retrieval of test objects regardless of stimulus-type. Frontal areas (BA 10, 32), the temporal gyri (BA 21, 22), the precuneus (BA 31) and parahippocampus (BA 28) were all found to be contributing sources for the generation of the P300 waveform observed in both the study and test blocks.

5.1.1 Aims and Objectives

To date, no electroencephalography (EEG) studies of spatial processing and spatial memory have been carried out with community-based samples of adolescents who report PLEs in an attempt to uncover possible behavioural and EEG markers associated with these experiences. The present chapter will explore mean amplitude of the P300 component, and in addition the latency of the P300 component will be compared across a group of adolescents reporting PLEs and a control group. The present chapter employs the implicit version of the Spatial Grid Task (Murphy et al., 2009) and uses both behavioural and electrophysiological methods. The Implicit Spatial Grid Task allows for both behavioural and ERP data to be collected in relation to both an old/new memory task as well as implicitly testing memory for the location of objects. This task has previously shown behavioural and physiological differences across conditions which reflect implicit memory processes. The task has been shown to elicit a P300 component and to engage a network of areas involved in spatial memory with parietal, temporal and medial temporal sources engaged in the production of the P300.

For the overall group it is anticipated that reaction time will be faster for study objects presented in a correct location compared to study objects presented in an incorrect location, as observed by Murphy et al. (2009). It is anticipated that peak latency for the study object correct location condition will be earlier than for the other test stimulus conditions for the overall group, as observed in the original study by Murphy et al. (2009). It is anticipated that a late P300 component will only be present in the test stimulus conditions, as observed by Murphy et al. (2009).

The hypotheses are as follows:

- Differences in accuracy scores and reaction times will be explored across all conditions of the task and between the groups.

- Mean amplitude of the P300 component will be explored between-groups for study and test stimuli conditions and it is anticipated that the amplitude of the P300 component will be reduced in the PLEs group relative to the controls, in particular for test stimulus conditions (i.e. retrieval; study object correct location, study object incorrect location, distractor objects).

- Hemispheric differences in the mean amplitude of the P300 component will be explored for both the overall group and between the groups with greater amplitude expected over the right hemisphere (as previously reported by Müller & Knight, 2002).

- Peak latency of the P300 component will also be explored between groups.

5.2 Methods

5.2.1 Participants

Forty-four participants (21 male; age range 11-13 years; mean age = 12.14 years) completed the Implicit Spatial Memory Task after completing a clinical interview (see Chapter 2, section 2.1.3 for details of the clinical interview process). Fifteen participants reported PLEs (7 male; age range 11-13 years; mean age = 12.07 years). The control group consisted of twenty-nine participants (14 male; age range 11-13 years; mean age = 12.07 years). One participant was excluded from the data set due to errors in behavioural responses and a further six participants were excluded due to excessive EEG artifacts. This left a control group comprising data from twenty-four participants (14 males; age range 11-13 years; mean age = 12.13 years) and a PLEs group comprising data from thirteen participants (7 males; age range 11-13 years; mean age = 12 years). Participants gave written informed assent, and parental consent was obtained before participation in the study (see Chapter 2, section 2.3.1 for further details). All participants had normal or corrected-to-normal vision and no previous neurological disorders or brain injuries.

5.2.2 Stimuli

Participants completed a version of the Spatial Grid Task developed by Murphy, et al. (2009; referred to in this chapter as the Implicit Spatial Memory Task) designed to test implicit spatial memory. Participants were required to memorise 8 objects within an environmental spatial grid. The particular set of objects presented included a bin, a bucket, a post-box, a road-cone, a fire hydrant, a tree, a tyre and a keg; distractors

included a parasol, a microphone stand, a cactus plant, a blender, a fire extinguisher, a stool, a lamp and a cavity/cinder block. All objects were presented on a grass environmental grid. During the Study Block participants, were asked to study the objects that appeared one at a time in the environmental grid with two stationary landmarks (a fountain and a lamppost) and were told that they would need to remember the objects for a subsequent recognition test. No reference was made to the location of the objects, only that the objects themselves had to be learned.

The Study Block consisted of 64 trials of object presentations. Each of the 8 objects was presented in isolation 8 times in a pseudo-randomised order so that consecutive presentations of the same object did not coincide. A fixation cross was presented first for 750ms, followed by the spatial grid with landmarks for 1500ms and then the study stimulus was presented on the grid and remained onscreen for 2000ms. This cycle was repeated for the 64 trials.

Following the 64 trials of study presentations, another set of instructions was provided. Participants were told to respond to previously studied (or 'old') objects that appeared during the test block by pressing the left mouse button with their index finger. If a 'new' object (i.e. not shown in the study phase) was presented, then the right mouse button should be pressed with their middle finger (see Appendix XV for a full list of instructions given to participants). For the Test Block, the sequence of a single trial was as follows; a fixation cross was presented first for 750ms, followed by the spatial grid with landmarks for 1500ms and then the test stimulus was presented on the grid and remained onscreen for 2000ms with the stimulus duration as the response interval, i.e. less than 2000ms. This trial sequence was repeated for 128 trials of object presentations (see Figure 5.1 for an example of the temporal sequence of stimuli of a trial in the Test Block of the Implicit Spatial Memory Task).

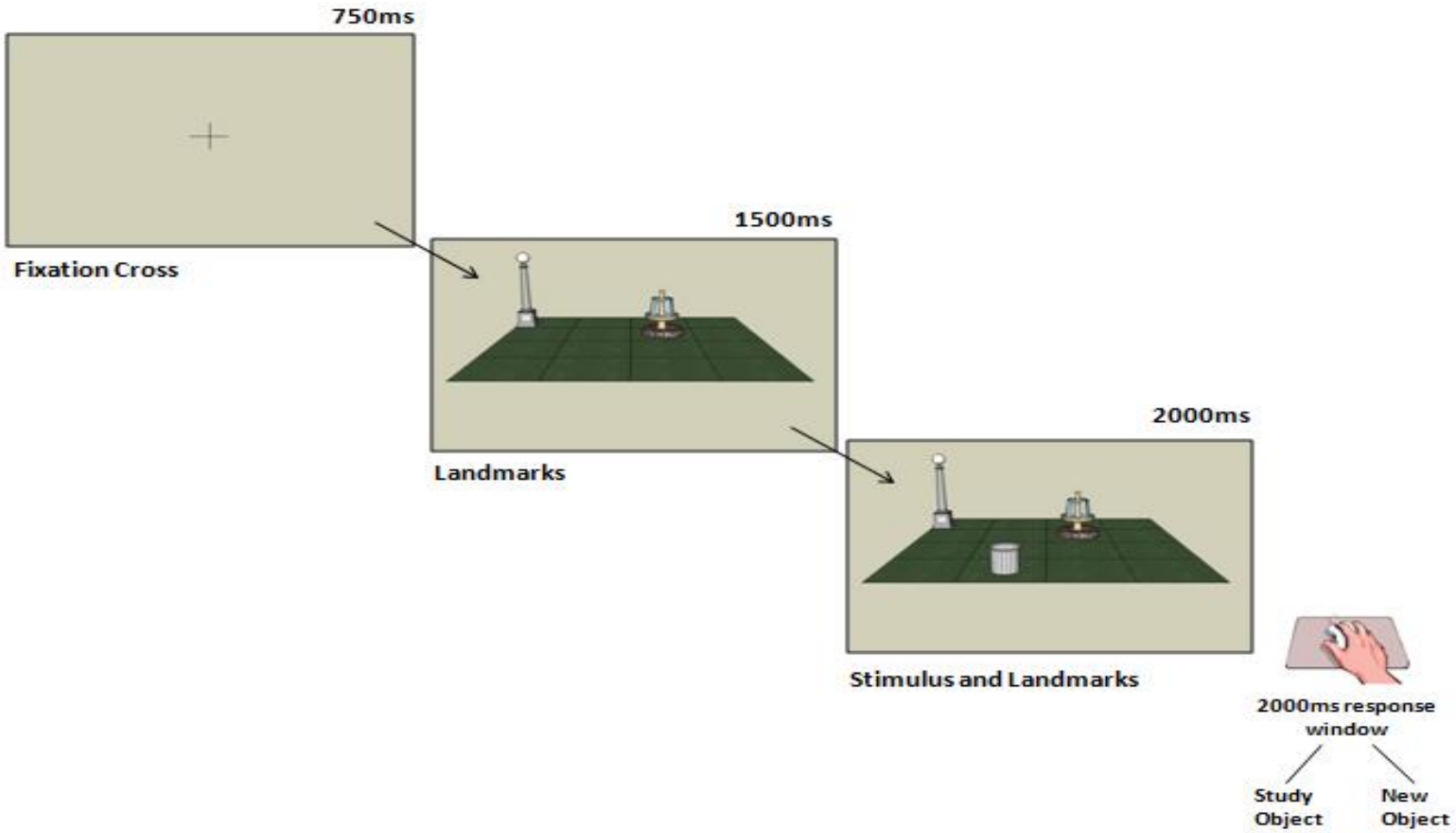


Figure 5.1: *Temporal sequence of a single test trial in the Implicit Spatial Memory Task.*

Three test conditions were constructed using either the 8 ‘old’ (studied) objects or 8 ‘new’ (distractor) objects and were presented in a pseudorandomised order, to test the implicit learning of object locations. The first condition (Study Object Correct Location) involved the presentation of each of the 8 ‘old’ objects in their previously studied or ‘correct’ location a total of 4 times each, i.e. 32 trials in total. The second condition (Study Object Incorrect Location) involved the presentation of each of the 8 ‘old’ objects in 4 allocated ‘incorrect’ locations, i.e. 32 trials in total. The third condition (Distractor Objects) then presented 8 novel or distractor objects in 4 random locations that were unfamiliar to the participant; these 32 trials were each repeated twice, i.e. 64 trials in total. All objects were presented from a stationary viewpoint during both the Study Block and the Test Block which permitted a person-centred (i.e. egocentric) frame of reference.

5.2.3 Procedure and Data Analysis

5.2.3.1 Procedure.

Details of the electrophysiological setup and recording are reported in Chapter 2 (section 2.3.3). E-Prime© logged response times for each participant and sent Transistor-Transistor Logic (TTL) triggers to the EEG acquisition PC to allow stimulus presentations (stimulus type) and responses to be logged in real time on the EEG recording. Response times were measured as the time between presentation of the stimulus and the response, and were recorded for all trials. Response latencies and accuracy were calculated automatically by E-Prime© and average response times were collated in E-Prime© for each block.

EEG data were recorded in μV from 62 scalp sites. The nasion was used as a reference. Vertical eye movements (VEOG) were recorded from electrodes located above and below the left eye and horizontal eye movements (HEOG) were recorded from the electrodes positioned at the outer canthus of each eye. Blinks were averaged off-line and a blink reduction algorithm was applied to the data. This algorithm involved automatic artifact correction (Berg & Scherg, 1991; Ille et al., 2002). Stimulus-locked average ERPs were obtained by averaging the EEG data using stimulus presentation as the trigger. ERP component time windows were chosen based on previous literature and visual inspection of grand averaged waveforms.

5.2.3.2 Data analysis.

Stimulus-locked epochs were defined as -100ms before stimulus presentation until 1500ms after stimulus presentation. Data were averaged for each participant and grand averages for each stimulus type were compiled. Only epochs in which participants made correct responses were included for group comparisons of ERP mean amplitudes and latencies. Groups were compared on the following stimulus type conditions: Study Object Correct Location, Study Object Incorrect Location and Distractor Objects. In some cases a combined Study Object Correct Location and Study Object Incorrect Location condition referred to as the Study Objects condition was used for comparisons.

Statistical analyses were carried out using SPSS Statistics version 20 for Windows. Data was tested for normality using Kolmogorov-Smirnov tests. Demographic variables were compared using independent-samples t-tests and chi-square analyses. Paired-samples t-tests were used to explore differences in accuracy scores and reaction times (defined in milliseconds – ms) between conditions (Study

Object Correct Location versus Study Object Incorrect Location and Study Objects condition versus Distractor Objects conditions) for the overall group. 2x2 repeated measures ANOVAs were used to explore between-group differences in accuracy scores and reaction times for the Study Object Correct Location and Study Object Incorrect Location conditions. A separate 2x2 repeated measures ANOVA was performed to explore between-group differences in accuracy and reaction times for the combined Study Objects condition compared to the Distractor Objects condition.

Following visual inspection of the EEG data the parietal electrode site Pz was chosen for further analysis of the ERP peak latency and mean amplitude data. The ERP waveforms across all parietal sites resembled those recorded at Pz for each of the conditions of interest: Study Stimuli, Study Object Correct Location, Study Object Incorrect Location and Distractor Objects. Electrode sites P3, P1, P2 and P4 were also used in analysis. The P300 timeframe was defined from visual inspection of the data as 250ms to 800ms post-stimulus. This was then divided into an early (250ms to 460ms) and a late (460ms to 800ms) component for further analysis. The timeframe 0ms to 1000ms was used for peak latency analysis.

For the EEG data a repeated measures ANOVA was used to explore differences in peak latency across test conditions (Study Object Correct Location, Study Object Incorrect Location, Distractor Objects) and paired-samples t-tests were employed to further investigate differences across conditions. A 2x3 mixed factorial ANOVA was used to explore differences in peak latency at Pz with Condition (Study Object Correct Location, Study Object Incorrect Location, Distractor Objects) as the within-subjects variable and Group (control, PLEs) as the between-subjects variable. A repeated measures ANOVA was used to explore differences in mean amplitude across study and test conditions (Study Stimulus, Study Object Correct Location, Study Object Incorrect

Location, Distractor Objects) and paired-samples t-tests were employed to further investigate differences across conditions. A 2x4 mixed factorial ANOVA was used to explore differences in mean amplitude at Pz with Condition (Study Stimulus, Study Object Correct Location, Study Object Incorrect Location, Distractor Objects) as the within-subjects variable and Group (control, PLEs) as the between-subjects variable. These steps were repeated for the early (250ms to 460ms) and late (460ms to 800ms) timeframes of the P300 component.

Additional 2x2x4 ANOVAs was carried out to test for hemispheric differences across conditions for the overall early and late P300 timeframes with Condition (Study Stimulus, Study Object Correct Location, Study Object Incorrect Location and Distractor Object) and Hemisphere (left, right) as the within-subjects variable and Group (control, PLEs) as the between-subjects variable. The average mean amplitude at electrode sites P1 and P3 were used for left hemisphere and the average mean amplitude at P2 and P4 was used for right hemisphere. For each ANOVA, an alpha value of 0.05 was used for main and interaction effects. Levene's tests were employed to test for homogeneity of variance and Greenhouse-Geisser correction was employed where the assumption of sphericity was violated.

5.3 Results

5.3.1 Demographic and General Functioning Comparisons

Groups were compared for differences in age, gender, handedness and parental socioeconomic status (SES). Groups were also compared for general functioning on scores on the Strengths and Difficulties Questionnaire (SDQ; Goodman 1997; Goodman et al., 1998) and overall current Children's Global Assessment Scale from the K-SADS-PL interview schedule (C-GAS; Shaffer et al., 1983). The Wide Range Achievement Test 4 was employed as a measure of scholastic ability (WRAT-4; Wilkinson and Robertson, 2005) – see Table 5.1.

No between-group differences in mean age [$t(35) = 0.45$; $p = 0.654$], gender [$\chi^2(1) = 0.001$, $p = 1.000$], handedness[$\chi^2(1) = 0.001$, $p = 1.000$], parental SES [$\chi^2(1) = 0.24$, $p = 0.622$] or WRAT scores [$t(30) = 1.2$, $p = 0.239$] were observed. A between-group difference in scores on the SDQ [$t(35) = -3.4$, $p = 0.002$] was observed with the control group scoring lower on this measure than the PLEs group. A between-groups difference was also observed in current C-GAS scores [$t\ (32) = 3.26$, $p = 0.007$] with the control group achieving a higher mean score on this measure than the PLEs group.

Table 5.1: *Demographic and general functioning details for the control and PLEs groups for the Implicit Spatial Memory Task.*

Variable	**Overall (*N*=37)**	**Control (*N*=24)**	**PLEs (*N*=13)**	**Result**
Mean Age (SEM)	12.08 (0.13)	12.13 (0.16)	12.00 (0.23)	t (35) = 0.45, p = 0.654
Gender	21 males (56.76%)	14 males (58.33%)	7 males (53.85%)	$\chi^2(1) = 0.001$, p = 1.000
Handedness	2 left (5.41%)	1 left (4.17%)	1 left (7.69%)	$\chi^2(1) = 0.001$, p = 1.000
SES 1	17 (45.95%)	12 (50%)	5 (38.46%)	$\chi^2(1) = 0.24$, p = 0.622
SDQ scores* (SEM)	10.41 (0.88)	8.46 (0.86)	14.00 (1.54)	**t (35) = -3.4, p = 0.002**
C-GAS scores (SEM)	81.71 (2.3)	87.13 (1.53)	70.36 (4.91)	**t(32) = 3.26, p = 0.007**
WRAT scores (SEM)	43.09 (1.9)	44.85 (2.32)	40.17 (3.23)	t(30) = 1.2, p = 0.239

*Higher scores reveal greater impairment.
Significant differences are highlighted in bold.
SES 1 – professional and managerial, SES2 – other.

5.3.2 Behavioural Data

5.3.2.1 Overall group.

For the overall group no differences in accuracy scores were observed when Study Object Correct Location and Study Object Incorrect Location conditions were compared [$t(36) = 1.33$; $p = 0.192$]. No differences were observed when accuracy for the Study Objects condition was compared with accuracy scores for Distractor Objects condition for the overall group [$t(34) = 0.64$, $p = 0.526$] – see Figure 5.2 and Table 5.2.

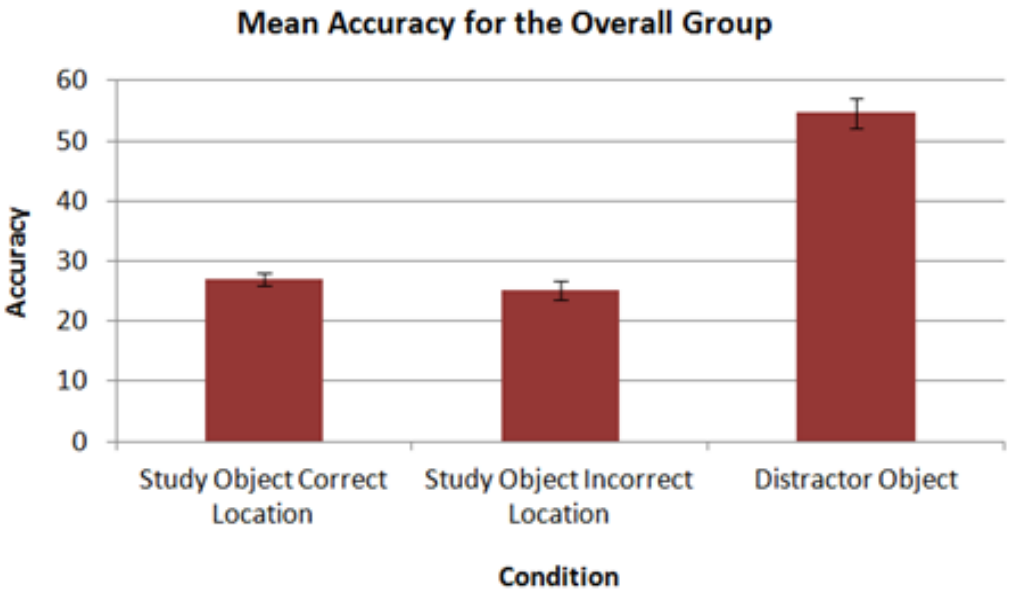


Figure 5.2: *Mean accuracy for each of the stimulus-type conditions for the overall group (Note: Maximum possible accuracy score for Study Object Correct and Incorrect Location conditions is 32 and for the Distractor Objects condition is 64; Error bars indicated SEM).*

For the overall group reaction times were faster for the Study Object Correct Location condition than the Study Object Incorrect Location condition [$t(36) = -2.5$, $p = 0.017$]. Reaction times were slower for the Study Objects condition than for the Distractor Objects condition [$t(34) = -2.39$, $p = 0.022$]; however this result was influenced mainly by the Study Object Incorrect Location condition, with slower responses to study objects in an incorrect location than to distractor objects [$t(34) = 2.97$, $p = 0.005$] – see Figure 5.3 and Table 5.2.

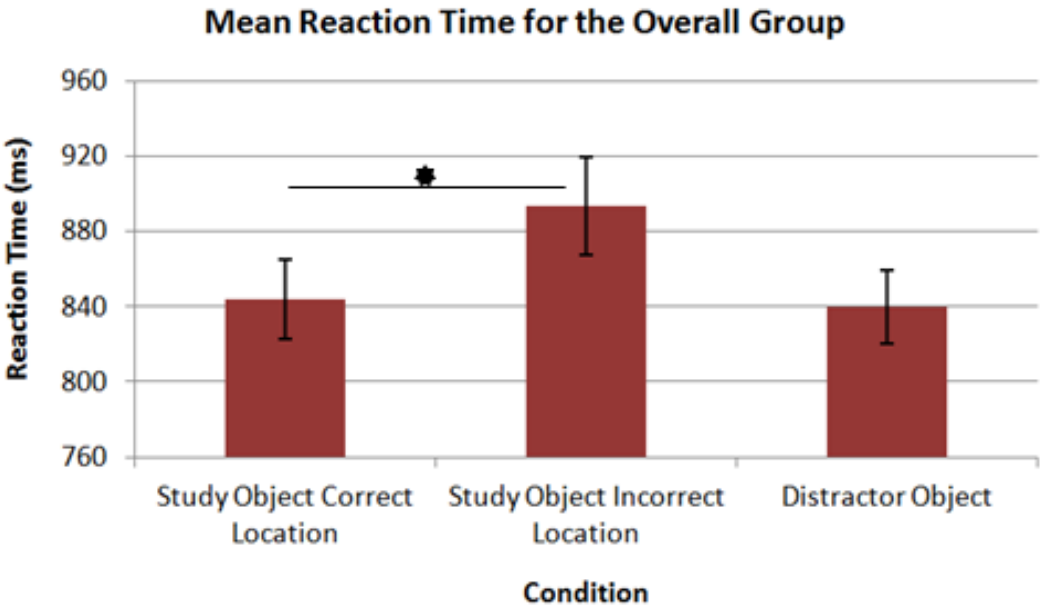


Figure 5.3: *Mean reaction times (SEM) for each of the stimulus-type conditions for the overall group (Note: *indicates p = 0.02; Error bars indicate SEM).*

5.3.2.2 Group analyses.

No between-group difference in accuracy scores was observed when the Study Object Correct Location and Study Object Incorrect Location conditions were compared [$F(1, 35) = 0.93$, $p = 0.342$, partial eta squared = 0.026] and no Condition*Group interaction effect was observed [$F(1, 35) = 0.02$, $p = 0.895$, partial eta squared = 0.001]. No between-group difference was observed when the combined Study Objects and the Distractor Object conditions were compared [$F(1, 33) = 1.71$, $p = 0.201$, partial eta squared = 0.049] and no Condition*Group interaction was observed [$F(1, 33) = 1.21$, $p = 0.279$, partial eta squared = 0.035] –see Figure 5.4 and Table 5.2.

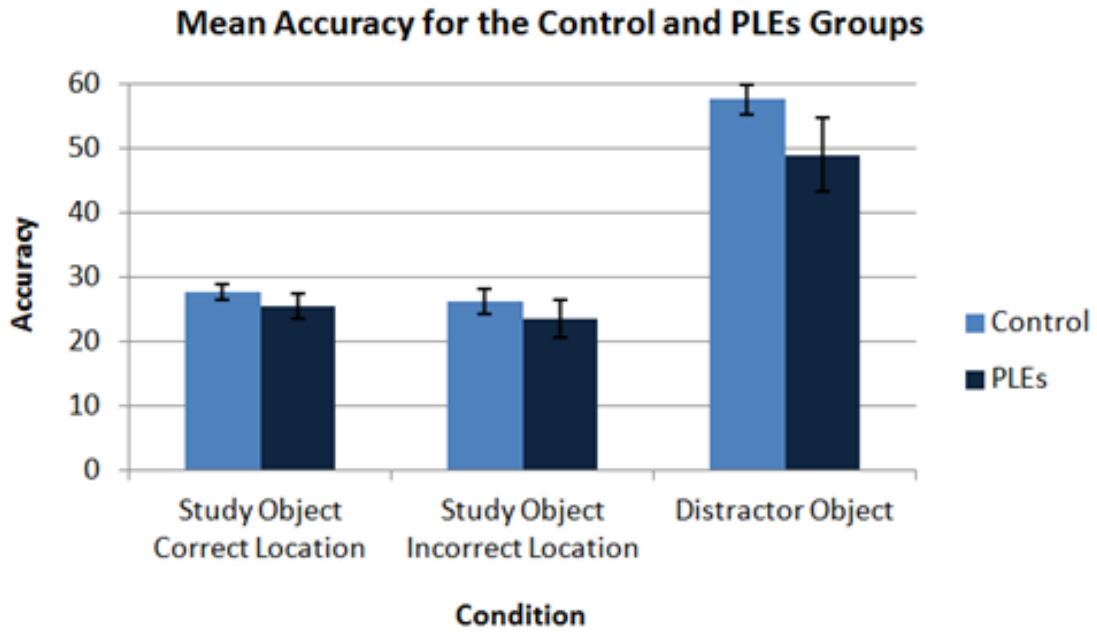


Figure 5.4: *Mean accuracy for the control and PLEs groups for each of the stimulus-type conditions (Note: Maximum possible accuracy score for Study Object Correct and Incorrect Location conditions is 32 and for the Distractor Objects Condition is 64; Error bars indicate SEM).*

No between-group differences were observed in the reaction time data when the Study Object Correct Location and Study Object Incorrect Location conditions were compared [$F(1, 35) = 0.07$, $p = 0.787$, partial eta squared = 0.002] and no Condition*Group interaction was observed [$F(1, 35) = 0.8$, $p = 0.377$, partial eta squared = 0.022]. In addition, no between-group differences were observed when the combined Study Objects and the Distractor Object conditions were compared [$F(1, 33) = 0.29$, $p = 0.589$, partial eta squared = 0.009] and no Condition*Group interaction was observed [$F(1, 33) = 0.14$, $p = 0.715$, partial eta squared = 0.004] – see Figure 5.5 and Table 5.2.

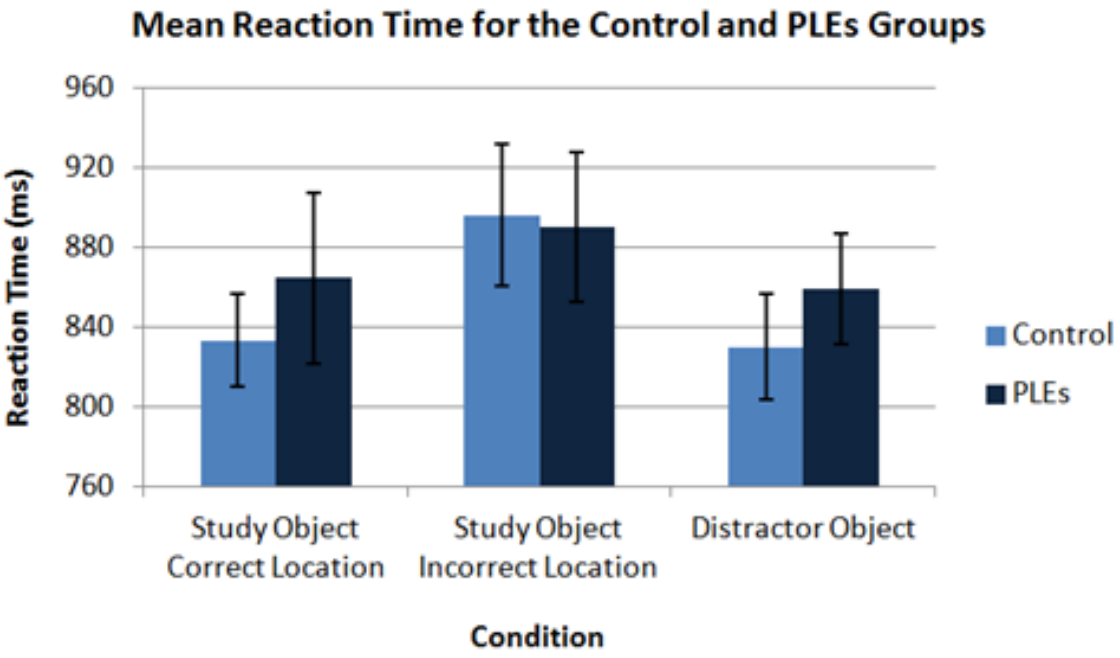


Figure 5.5: *Mean reaction times for the control and PLEs groups for each of the stimulus-type conditions (Note: Error bars indicate SEM).*

Table 5.2: *Mean accuracy (top line) and reaction time (bottom line) scores for the control and PLEs groups for the Implicit Spatial Memory Task.*

Condition	**Overall (*N*=37)**	**Control (*N*=24)**	**PLEs (*N*=13)**
Correct Location	26.92 (1.06)	27.71 (1.25)	25.46 (1.94)
	844.23 (21.16)	833.3 (23.39)	864.41 (42.81)
Incorrect Location	25.16 (1.63)	26.08 (1.93)	23.46 (3.01)
	893.82 (26.16)	895.98 (35.44)	889.83 (37.36)
Distractor	54.69 (2.52)	57.65 (2.31)	49 (5.69)
	839.84 (19.8)	829.94 (26.66)	858.81 (27.55)

5.3.3 Electrophysiological Data

5.3.3.1 Overall group.

5.3.3.1.1 Peak latency analyses.

For the overall group a significant difference in peak latency (ms) at Pz was observed between Study Object Correct Location, Study Object Incorrect Location and Distractor Object conditions [$F(2, 68) = 8.08$, $p = 0.001$, partial eta squared = 0.192]. Peak latency was 460.27ms for the Study Object Correct Location condition, 535.89ms for the Study Object Incorrect Location condition and 498.22ms for the Distractor Object condition – see Figure 5.6.

Subsequent paired-samples t-tests showed that differences existed between the Study Object Correct Location condition and the Study Object Incorrect Location conditions [$t(36) = -4.37$, $p < 0.0005$] with earlier peak latency in the Study Object

Correct Location condition [*M* = 460.27, *SEM* = 16.17] than the Study Object Incorrect Location condition [*M* = 535.89, *SEM* = 16.62]. A significant difference in peak latency was also observed between the Study Object Incorrect Location and Distractor Objects conditions [*t*(34) = 2.21, *p* = 0.034] with later peak latency in the Study Object Incorrect Location condition [*M* = 535.89, *SEM* = 16.62] compared to the Distractor Objects condition [*M* = 498.11, *SEM* = 14.6].

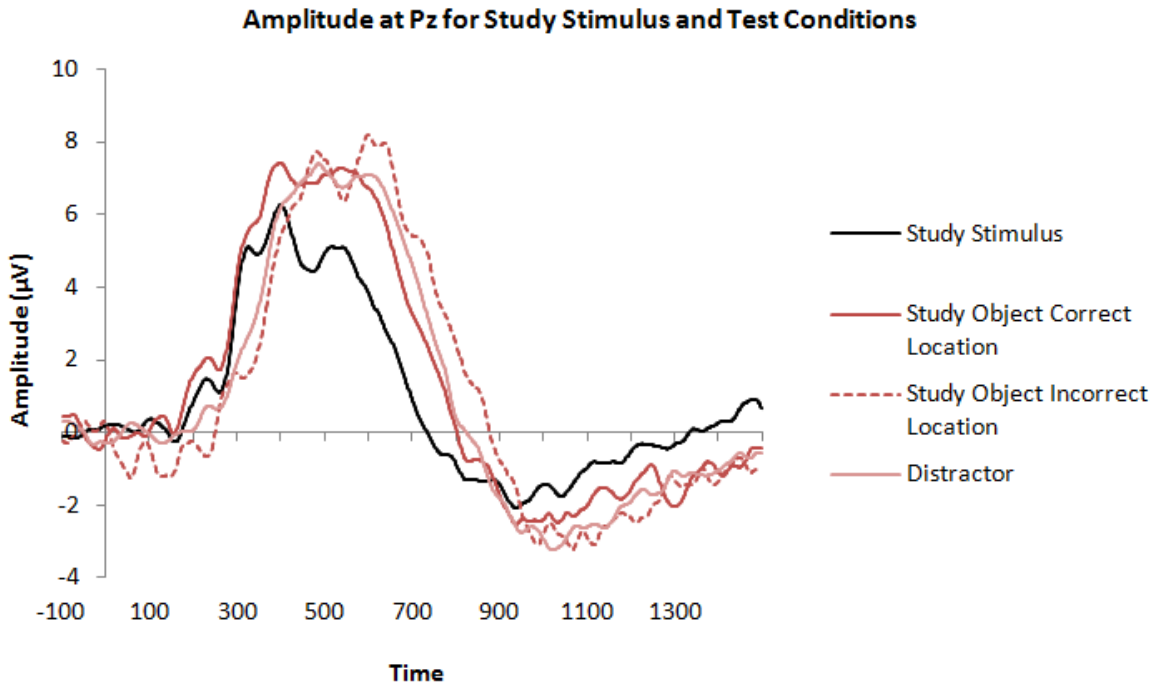


Figure 5.6: *ERP waveform for the overall group for the Study Stimulus and Test conditions at Pz.*

5.3.3.1.2 Mean amplitude analyses.

For the overall group a significant difference in mean amplitude (μV) was observed between the study and test conditions for the overall P300 timeframe of 250ms to 800ms [$F(3, 102) = 8.23$, $p < 0.0005$, partial eta squared = 0.195]. Mean amplitude was lower for the Study Stimulus condition [$M = 3.29$, $SEM = 0.34$] than the Study Object Correct Location [$M = 5.17$, $SEM = 0.48$; $t(36) = -4.88$, $p < 0.0005$], Study Object Incorrect Location [$M = 5.18$, $p = 0.55$; $t(36) = -3.5$, $p = 0.001$] and Distractor Objects [$M = 4.88$, $SEM = 0.46$, $t(34) = -5.58$, $p < 0.0005$] test conditions – see Figure 5.6.

Mean amplitude was examined for the early P300 component timeframe (250ms to 460ms) at Pz. Due to the latency difference observed between conditions waveforms elicited to the Study Object Incorrect Location and Distractor Objects conditions were shifted 80ms in time for the mean amplitude analysis (330ms to 540ms). A significant difference in mean amplitude was observed across conditions [$F(3, 102) = 5.04$, $p = 0.004$, partial eta squared = 0.129]. Mean amplitude was lower for the Study Stimulus condition [$M = 4.44$, $SEM = 0.38$] than the Study Object Correct Location [$M = 5.54$, $SEM = 0.45$; $t(36) = -2.8$, $p = 0.008$], the Study Object Incorrect Location [$M = 5.68$, $SEM = 0.49$; $t(36) = -2.57$, $p = 0.015$] and Distractor Object test conditions [$M = 6.09$, $SEM = 0.54$; $t(34) = -4.22$, $p < 0.0005$], i.e. all test waveforms had larger mean amplitudes – see Figure 5.7.

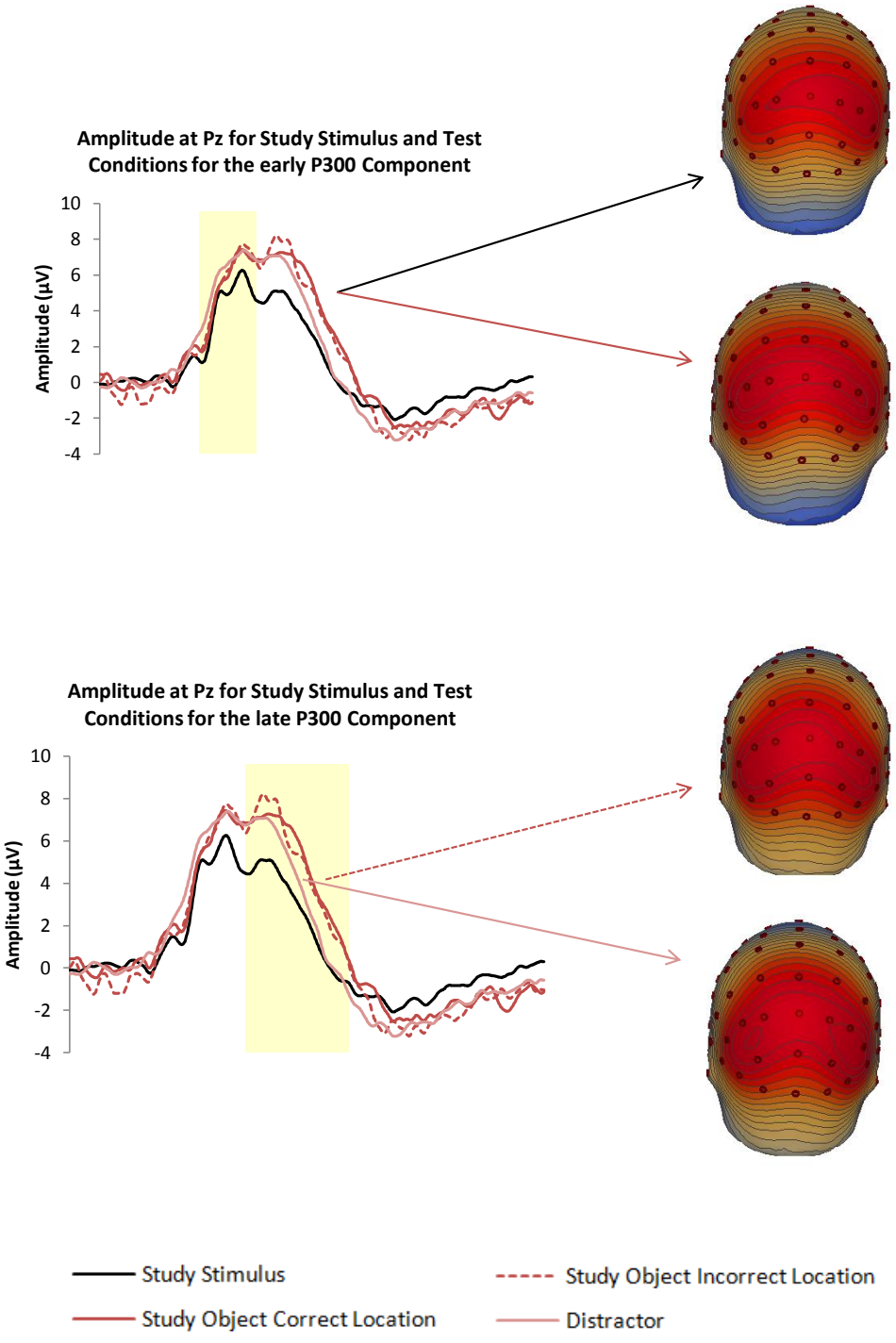


Figure 5.7: *ERP waveform for the overall group for the Study Stimulus and test conditions at Pz for the early and late P300 timeframes. Scalp topographic maps show scalp distributions for conditions at latency of maximal amplitude.*

Mean amplitude was also examined for the late P300 component timeframe (460ms to 800ms) at Pz. Due to the latency difference observed between conditions waveforms elicited to the Study Object Incorrect Location and Distractor Objects conditions were shifted 80ms in time for mean amplitude analysis (540ms to 880ms). A significant effect of Condition was observed for mean amplitude [$F(3, 102) = 6.35$, $p = 0.006$, partial eta squared = 0.16]. Mean amplitude was significantly lower for the Study Stimulus condition [$M = 2.59$, $SEM = 0.37$] than the Study Object Correct Location [$M = 4.95$, $SEM = 0.56$; $t(36) = -5.4$, $p < 0.0005$], Study Object Incorrect Location [$M = 4.85$, $SEM = 0.83$; $t(36) = -2.8$, $p = 0.008$] and the Distractor Objects conditions [$M = 3.69$, $SEM = 0.49$; $t(34) = -3.87$, $p < 0.0005$]. Mean amplitude was also significantly higher for the Study Object Correct Location condition than the Distractor Objects condition [$t(34) = 3.45$, $p = 0.002$] – see Figure 5.7.

5.3.3.2 Group analyses.

5.3.3.2.1 Peak latency analyses.

No between-groups difference was observed in peak latency at Pz when the test conditions (Study Object Correct Location, Study Object Incorrect Location and Distractor Objects) were compared [$F(1, 33) = 0.02$, $p = 0.902$, partial eta squared=0.001]. No Condition*Group interaction was observed [$F(2, 66) = 2.02$, $p = 0.142$, partial eta squared = 0.058] – see Figure 5.8 and Table 5.3.

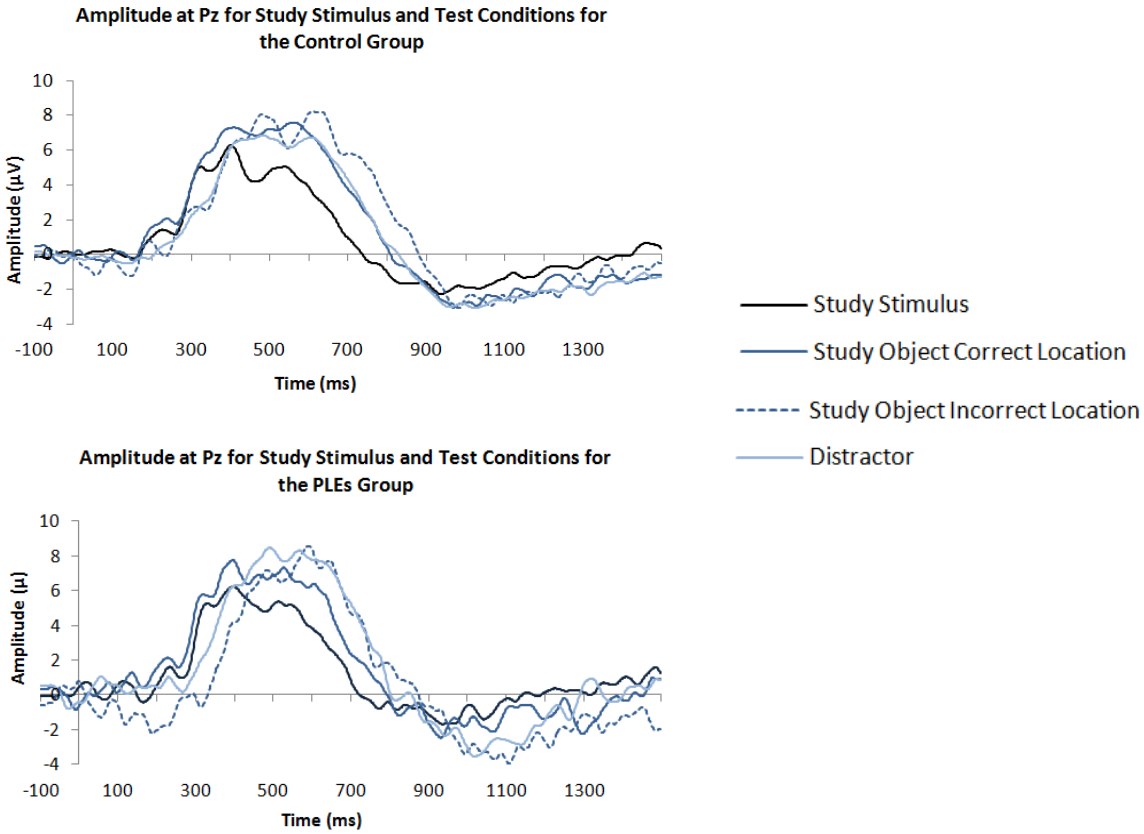


Figure 5.8: *ERP waveform for the control and PLEs groups for the Study Stimulus and test conditions at Pz.*

Table 5.3: *Mean amplitude (top line) and latency (bottom line) scores at Pz for the P300 component for the control and PLEs groups for the Implicit Spatial Memory Task.*

Condition	**Overall (*N*=37)**	**Control (*N*=24)**	**PLEs (*N*=13)**
Study Stimulus	3.29 (0.34)	3.26 (0.4)	3.36 (0.63)
	417.78 (14.47)	416.75 (18.44)	419.69 (24.16)
Correct Location	5.17 (0.48)	5.31 (0.67)	4.91 (0.66)
	460.27 (16.17)	473.5 (21.06)	435.85 (24.18)
Incorrect Location	5.18 (0.55)	5.58 (0.67)	4.44 (0.98)
	535.89 (16.62)	539.25 (22.66)	529.69 (23.13)
Distractor	4.88 (0.46)	4.65 (0.54)	5.33 (0.87)
	498.11 (14.6)	484.7 (18.33)	523.83 (23.26)

5.3.3.2.2 Mean amplitude analyses.

No between-group difference was observed at Pz when the Study Stimulus and test conditions were compared for the overall P300 timeframe of 250ms to 800ms [$F(1, 33) = 0.02$, $p = 0.894$, partial eta squared = 0.001]. No Condition*Group interaction was observed [$F(3, 99) = 1.13$, $p = 0.332$, partial eta squared = 0.033]. Furthermore no between-group differences were observed when the early (250ms to 460ms) and late (460ms to 800ms) timeframes of the P300 component were considered separately with adjusted timeframes for the Study Object Incorrect Location and Distractor Objects conditions from 330ms to 540ms and 540ms to 880ms, respectively [early P300: $F(1, 33) = 0.003$, $p = 0.959$, partial eta squared = 0.001; late P300: $F(1, 33) = 0.004$, $p = 0.948$, partial eta squared = 0.001). No Condition*Group interaction was observed for

either the early P300 [$F(3, 99) = 1.64$, $p = 0.19$, partial eta squared = 0.047] or the late P300 [$F(3, 99) = 0.47$, $p = 0.577$, partial eta = 0.014] components – see Figure 5.9.

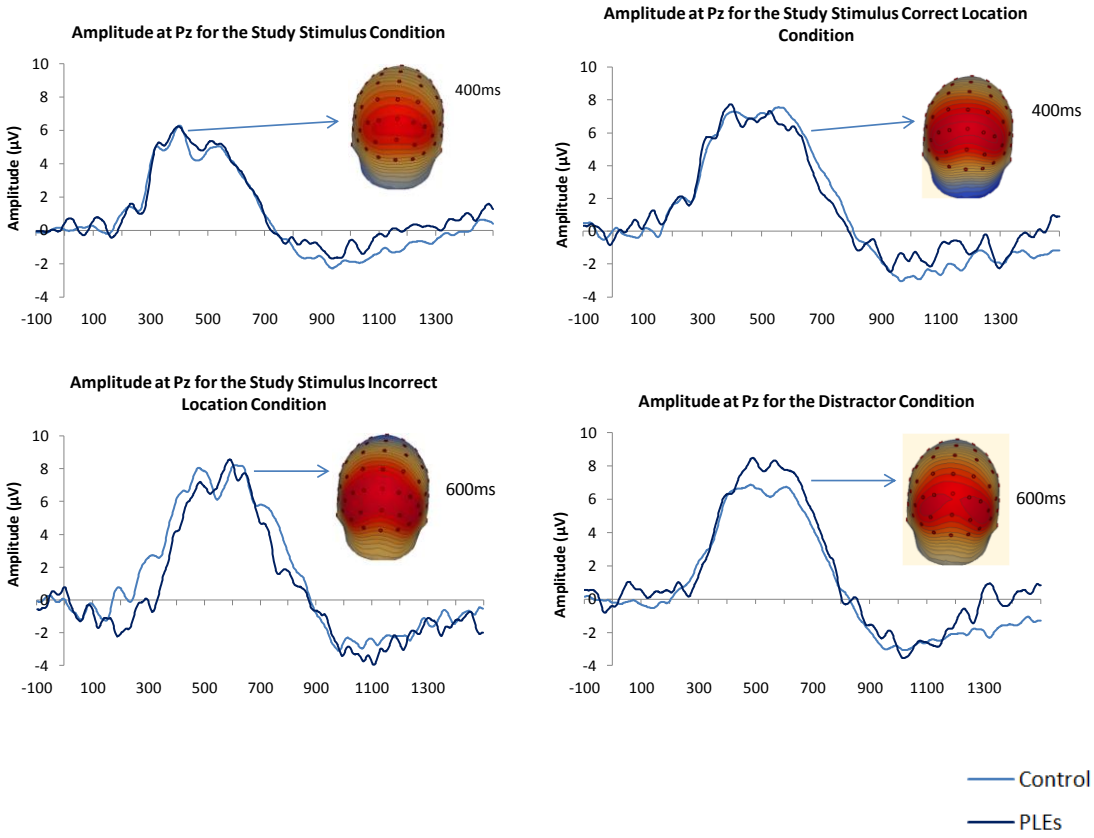


Figure 5.9: *ERP waveforms and scalp topographies showing group comparisons (Control and PLEs) across each condition at Pz.*

5.3.3.2.3 Hemispheric mean amplitude analyses.

For the overall P300 timeframe no main effect of Hemisphere was observed [$F(1, 33) = 1.65$, $p = 0.208$, partial eta squared = 0.048]. No between-groups effect was observed

[$F(1, 33) = 0.03$, $p = 0.87$, partial eta squared = 0.001] and no interaction effects were observed for Hemisphere*Group [$F(1, 33) = 0.11$, $p = 0.747$, partial eta squared = 0.003], Hemisphere*Condition [$F(3, 99) = 2.25$, $p = 0.104$, partial eta squared = 0.06] or Hemisphere*Condition*Group [$F(3, 99) = 0.86$, $p = 0.444$, partial eta squared = 0.025].

No main effect of Hemisphere observed for the early P300 component (250ms to 460ms) with adjusted timeframes for the Study Object Incorrect Location and Distractor Object conditions from 330ms to 540ms [$F(1, 33) = 0.003$, $p = 0.958$, partial eta squared = 0.001]. No between-groups effect was observed [$F(1, 33) = 0.01$, $p = 0.939$, partial eta squared = 0.001] and no interaction effects were observed for Hemisphere*Group [$F(1, 33) = 0.35$, $p = 0.561$, partial eta squared = 0.01], Hemisphere*Condition [$F(3, 99) = 0.4$, $p = 0.726$, partial eta squared = 0.012] or Hemisphere*Condition*Group [$F(3, 99) = 0.95$, $p = 0.41$, partial eta squared = 0.028].

A main effect of Hemisphere was observed for the late P300 component [$F(1, 33) = 4.37$, $p = 0.044$, partial eta squared = 0.117]. No between-groups effect was observed [$F(1, 33) = 0.03$, $p = 0.854$, partial eta squared = 0.001] and no interaction effects were observed for Hemisphere*Group [$F(1, 33) = 0.03$, $p = 0.862$, partial eta squared = 0.001], Hemisphere*Condition [$F(3, 99) = 2.02$, $p = 0.139$, partial eta squared = 0.058] or Hemisphere*Condition*Group [$F(3, 99) = 0.54$, $p = 0.592$, partial eta squared = 0.016]. Subsequent paired-samples t-tests revealed that mean amplitude was reduced in the left hemisphere [$M = 2.31$, $SEM = 0.34$] compared to the right hemisphere [$M = 3.72$, $SEM = 0.35$] for the Study Stimulus condition [$t(36) = -5.2$, $p < 0.0005$]. This result remained significant once a Bonferroni corrected p value of 0.01 was applied.

5.3.4 Summary of Results

No between-group differences were observed for the demographic variables age, gender, handedness or parental SES. In terms of general psychopathology, group scores on the SDQ differed with the PLEs group scoring higher on this measure. In terms of general functioning, group C-GAS scores differed with the PLEs group receiving lower C-GAS scores than the control group. For the overall group reaction times were faster for the Study Object Correct Location condition than the Study Object Incorrect Location condition and slower for the Study Objects condition than for the Distractor Objects condition. No between-group differences in accuracy, reaction times or ERP amplitude or latency were observed.

Earlier peak latency was observed in the Study Object Correct Location condition compared to the Study Object Incorrect Location condition in the overall group. A significant difference in peak latency was also observed between the Study Object Incorrect Location and Distractor Objects conditions, with later peak latency in the Study Object Correct Location condition compared to the Distractor Objects condition. For the overall P300 timeframe mean amplitude was lower for the Study Stimulus condition than the mean amplitude observed for each of the test conditions. Mean amplitude for the early P300 component timeframe (250ms to 460ms) at Pz was lower for the Study Stimulus condition compared to each of the test conditions.

For the late posterior P300 component (460ms to 800ms) mean amplitude was again lower for the Study Stimulus condition than for each of the test conditions. Mean amplitude was also significantly larger for the Study Object Correct Location condition than the Distractor Objects condition. Mean amplitude of the late P300 component was

also found to be reduced in the left hemisphere compared to the right hemisphere for the Study Stimulus condition.

5.4 Discussion

This chapter investigated spatial processing and implicit spatial memory in a group of adolescents who reported PLEs compared to a control group using a computerised Implicit Spatial Memory Task (Murphy et al., 2009). No between-group differences were observed in the behavioural or ERP data for the Implicit Spatial Memory Task indicating that the PLEs group was not impaired in terms of encoding or retrieval on this task which investigated memory for old and new objects as well as implicit memory for object location. The groups were compared on a number of demographic variables and did not differ in terms of age, gender, handedness or parental SES of participants within each group. The groups also did not differ in terms of WRAT scores, which were used as a measure of scholastic ability. Between-groups analysis revealed that the control group had lower total difficulties scores on the SDQ and obtained higher current C-GAS scores than the PLEs group, suggesting more emotional difficulties and lower global functioning in the PLEs group.

Results from the overall group followed a similar pattern to those observed in the original study carried out by Murphy et al. (2009). It was hypothesised that response times would be faster for study objects in their correct locations compared to study objects in an incorrect location, and differences in accuracy scores were also explored. No differences were observed in accuracy scores across each of the test condition but

mean response times were faster for study objects in their correct location compared to study objects presented in an incorrect location. Peak latency of the P300 component was also earlier for the Study Object Correct Location compared to the Study Object Incorrect Location condition. Faster response times and earlier P300 peak amplitudes in the Study Object Correct Location compared to the Study Object Incorrect Location condition provides further evidence of the usefulness of the Implicit Spatial Grid Task (Murphy et al., 2009) as a test of implicit memory for object location.

Differences were observed in the ERP waveforms elicited for study and test stimuli. A P300 ERP component was observed for the Study Stimulus condition and across all test conditions. As observed by Murphy et al. (2009), the P300 elicited by test conditions was distinguished from the P300 observed in the Study Stimulus condition by the extended duration of the later P300 component. Mean amplitude was analysed for both the early and late P300 timeframes separately and it was observed that mean amplitude was reduced for the Study Stimulus condition at both timeframes. For the late P300 component mean amplitude was also significantly larger for the Study Object Correct Location condition than the Distractor Objects condition.

During the Implicit Spatial Memory Task (Murphy et al., 2009) all stimuli are presented to the participant from an egocentric viewpoint (i.e. body-centred). Research using virtual reality experiments suggests that while allocentric memory is impaired in schizophrenia spectrum disorders, egocentric memory may remain largely intact (Weniger & Irle, 2008; Girard, Christensen & Rizvi, 2010). During virtual reality investigations of allocentric processing, participants with schizophrenia were not helped by distal cues suggesting that allocentric spatial learning and navigation strategies may be impaired in this group (Hanlon et al., 2006). Folley, Astur, Jagannathan, Calhoun and Pearlson (2010) reported similar behavioural findings of impaired spatial learning in

schizophrenia, as did Hanlon et al. (2006) using a Morris water task. In addition, Folley et al. (2010) provide fMRI data also to suggest that impaired allocentric spatial learning and memory may be due to an inability to preferentially recruit the appropriate task-dependent neural circuits. Grey matter concentrations and BOLD signal in hippocampal sub regions were associated with task performance in healthy controls but this relationship was absent in schizophrenia.

In addition to the implicit version of the Spatial Grid Task, Murphy and colleagues have also developed a non-implicit Spatial Grid Task to test allocentric memory for object location in which test stimuli are presented from three rotated viewpoints (90° left, 90° right and 180°) in addition to the egocentric viewpoint used in the present version of the task. While the Implicit Spatial Memory Task (Murphy et al., 2009) failed to find group differences between the control and PLEs groups who participated in the present study, other versions of the Spatial Grid Task which present the environmental grid from rotated viewpoints (i.e. allocentric or world-centred viewpoints) may uncover differences in spatial processing between participants who report PLEs and controls.

Spieker et al. (2012) reported spatial memory deficits in schizophrenia using a virtual reality radial arm maze. The maze in their experiment contained eight arms and participants navigated the maze from a first-person explorer (egocentric) viewpoint. Their virtual reality radial arm maze task was based on the radial arm maze used to test spatial learning and memory in rodents (Walker & Olton, 1979). The task requires participants to navigate a maze to locate rewards which are located at the end of four out of the eight arms as quickly as possible. Spieker et al. (2012) note that while the schizophrenia group in their study did learn the task they did not learn it to the same level as their healthy control group. This was indicated by reduced reference memory

errors as well as reduced trial times and distance travelled as the task progressed. They also note that working memory errors persisted in the schizophrenia group while they decreased steadily across trials in the healthy control group, suggesting that there may be a persistent working memory deficit in schizophrenia that does not improve with practice on such tasks.

The extended learning period (64 trials) used in the present study may also have contributed to the result of no between-group differences as differences in the behavioural and ERP results may only be uncovered between groups who report PLEs and controls when visuospatial tasks are more difficult, i.e. in visuospatial working memory tasks with shorter encoding phases. While the results of the present chapter indicate that the PLEs group do not differ from the control group in their ability to encode or retrieve spatial information (including implicit object location information), differences in visuospatial working memory have been observed in individuals with schizophrenia (Kim et al., 2004; Lee & Park, 2005), individuals at high genetic risk for schizophrenia (Glahn et al., 2003; Bachman et al., 2009) and groups considered to be at clinical high risk for schizophrenia (Smith et al., 2006). Visuospatial working memory deficits have also been reported in adolescent-onset schizophrenia (Vance et al., 2006; 2007). A Spatial Working Memory Task was chosen for inclusion in Chapter 6 of the present thesis in favour of further investigations using the Spatial Grid Task. Visuospatial working memory has been repeatedly shown to be impaired in schizophrenia and throughout earlier stages of the illness and in high risk groups, and strong evidence has been uncovered within the neuropsychological, EEG and imaging literature to propose working memory as a neurocognitive trait marker for schizophrenia (Wood et al., 2003).

5.4.1 Chapter Summary

The present chapter aimed to investigate the behavioural and electrophysiological correlates of spatial processing and implicit object location memory in a group of adolescents who reported PLEs compared to a control group. This was achieved using an Implicit Spatial Memory Task. This chapter is to our knowledge the first study to test spatial processing and spatial memory in this sample using ERP measures. Although the pattern of behavioural and ERP responses recorded during the task was similar to those reported in the original study by Murphy et al. (2009), no between-group differences were observed in either the behavioural or electrophysiological data. Chapter 6 which follows will explore retrieval during spatial working memory in a similar group of adolescents reporting PLEs using a Spatial Working Memory Task developed for use with an adolescent population and based on the Sternberg paradigm (Sternberg, 1966).

Chapter 6

Electrophysiological Correlates of Spatial Working Memory in Adolescents Reporting Psychotic-Like Experiences and Controls

Abstract

The following chapter explores spatial working memory in an adolescent sample with reported psychotic-like experiences (PLEs). Deficits in working memory are widely reported in schizophrenia, first-episode psychosis (FEP) and those at high genetic risk for psychosis, as well as those at clinical high risk for a psychotic disorder. Event-related potential (ERP) and imaging data suggest that these differences in working memory performance may be due to aberrant functioning in the prefrontal and parietal cortices. Forty-two participants were divided into those who reported PLEs (N = 17) and those who reported no PLEs, i.e. the control group (N = 25). Behavioural differences in accuracy and reaction time were explored between the groups using a Spatial Working Memory Task developed for use with an adolescent population, which was a variant of the Sternberg paradigm. In addition to the behavioural data, electrophysiological correlates of working memory were also explored between groups. Specifically, differences in the P300 component were explored across load level (low load and high load), location (positive probe and negative probe) and between groups. No between-group differences in either mean accuracy or reaction time were observed however, greater reaction time variability was observed in the PLEs group. Reduced amplitude of the P300 component was observed in the PLEs group relative to the control group at posterior electrode sites. This reduced amplitude was observed for both low and high load and for both positive and negative probes. The findings are discussed in relation to the current literature on schizophrenia, risk for psychotic disorders and working memory.

6.1 Introduction

Working memory refers to the cognitive process (and associated brain systems) that provides temporary storage of small amounts of information over brief periods of time (Baddeley & Hitch, 1974). This brief storage system is essential for cognitive tasks (such as learning, reasoning, comprehension and language) that require the simultaneous storage and processing of information, as it allows for the manipulation of information over a short period of time (Baddeley, 1992). Baddeley (2010) proposed that through influential work carried out with patients such as H.M. (Scoville & Milner, 1957), human memory has come to be conceptualised as comprising a succession of storage systems through which sensory information flows from the environment through a series of temporary sensory buffers, on to a limited capacity short-term memory store and then to long-term memory.

Working memory involves three stages; encoding, maintenance and retrieval/response selection. The term working memory was used by Atkinson and Shiffrin in their influential paper in 1968 and later adopted as the title for a multicomponent model in 1974 by Baddeley and Hitch (see Figure 6.1). The multicomponent model of working memory proposed by Baddeley and colleagues comprises an attentional control system known as the central executive, as well as two short-term storage systems, one for visual information (known as the visuo-spatial sketchpad) and one for acoustic information (known as the phonological or articulatory loop). The model also includes the episodic buffer which is accessible to conscious awareness, in which the various components of working memory can interact and interface with information from perception and long-term memory (Baddeley, 2007).

Memory impairments are widely reported in schizophrenia. A meta-analysis carried out by Aleman, Hijman, de Haan and Kahn (1999) reported an association

between schizophrenia and memory dysfunction. They reported that memory impairments do not seem to be modality specific and that clinical variables such as medication, duration of illness, patient status, severity of psychopathology and positive symptoms did not appear to influence the magnitude of memory impairment. The authors state that their meta-analysis provides no evidence of progressive decline in memory with duration of illness, suggesting that memory impairment may be a trait rather than a state characteristic.

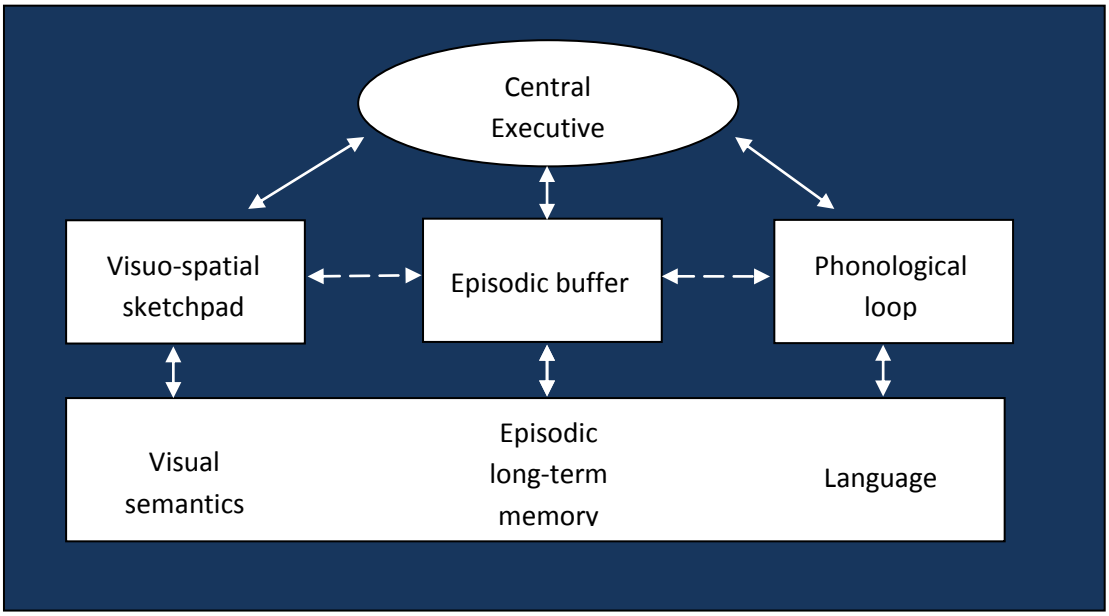


Figure 6.1: *The multicomponent model of working memory – adapted from Baddeley (2010).*

Specifically, working memory deficits have been hypothesised as a core deficit in schizophrenia (Goldman-Rakic, 1994). In a review of the literature, Wood et al. (2003) state that working memory may represent a neurocognitive trait marker for schizophrenia, as it is considerably impaired throughout the illness, involves neural

circuits deemed dysfunctional in the disorder and has been associated with negative symptoms. Both verbal and visuospatial working memory impairments have been observed in schizophrenia and FEP patients (Kim et al., 2004; Gooding & Tallent, 2004; Lee & Park, 2005; Zanello et al., 2009), groups defined as genetically at-risk of developing schizophrenia, such as relatives of schizophrenia patients (Glahn et al., 2003; Brahmbhatt et al., 2006; Horan et al., 2008; Bachman et al., 2009), groups considered clinically at-risk for psychosis or prodrome groups, such as ultra high-risk (UHR) and at-risk mental state (ARMS) groups (Smith et al., 2006; Pflueger et al., 2007; Frommann et al., 2011), as well as groups who report PLEs (Laurens et al., 2008b). Visuospatial working memory deficits have also been reported in adolescent-onset schizophrenia (Vance et al., 2006; 2007).

Numerous studies have investigated the neurophysiological underpinnings of working memory in normal samples. ERP studies have examined the different stages of working memory (encoding, maintenance and retrieval) in the different modalities (i.e. verbal, visuospatial). In a meta-analysis of the literature, Bramon et al. (2004) state that the P300 waveform has been conceptualised as the physiological correlate of a working memory update of changes in the environment (Donchin & Coles, 1988), or as an index of allocation of attentional resources (Posner, 1975).

According to Marchand et al. (2006), many ERP studies of working memory have employed a modified version of the Sternberg task in which participants are presented with a set of digits/letters to memorise, followed by a "probe" digit. The participant must indicate if the probe was part of the original memory set (positive probe) or not (negative probe). Behaviourally, studies have shown that performance on working memory tasks decreases as the memory load (number of items to be remembered) increases. Sternberg (1966) states that when subjects judge whether a test

symbol is contained in a short memorised sequence of symbols, their mean reaction time increases linearly with the length of the sequence.

In a summary of previous research, Marchand et al. (2006) state that the most consistent finding in the literature is the elicitation of a sustained parietal positivity to the probe (irrespective of whether the probe type is positive or negative) with an increase in latency as memory set size increases. Bledowski et al. (2006) propose that the P3b component can be separated into two subcomponents; they propose that the early P3b subcomponent is related to stimulus evaluation processes, whereas the later P3b subcomponent reflects memory search processes in the ventrolateral prefrontal cortex, which access a posterior parietal storage buffer. Polich (2007) proposes that the P3b originates from temporal-parietal activity associated with attention and appears to be related to subsequent memory processes.

Imaging studies of working memory have largely focused on the functioning of the prefrontal and the parietal cortices (Postle, Stern, Rosen & Corkin, 2000; Meda et al., 2008; Grimault et al., 2009). Studies have suggested a role for both the dorsolateral and ventrolateral prefrontal cortex in visuospatial working memory (Curtis & D'Esposito, 2007; Grimault et al., 2009). Zimmer (2008) suggests that dorsolateral prefrontal cortex activation is often found in tasks that require high monitoring and active restructuring. Glahn et al. (2002) reported increases in activity in the dorsolateral prefrontal cortex, the parietal cortex and the superior frontal sulcus as memory load increased. They suggest that the dorsolateral prefrontal cortex may be involved in the short-term maintenance of spatial information.

Working memory deficits in schizophrenia patients and those genetically at-risk have been linked to abnormal brain activity in the prefrontal cortex (Brahmbhatt et al., 2006). Studies have reported both hypoactivation (Cannon et al., 2005; Schlösser et al.,

2008) and hyperactivation (Manoach et al., 1999; Manoach et al., 2000; Perlstein et al., 2001; Callicott et al., 2003) of areas of the prefrontal cortex in patients with schizophrenia. Keshavan et al. (2002) reported decreased activity in the dorsolateral prefrontal and inferior parietal cortex in offspring of individuals with schizophrenia during a spatial working memory task, while Broome et al. (2010) reported decreased activity in the medial prefrontal cortex in a group of ARMS participants.

Functional neuroimaging studies in the verbal domain have indicated reduced activity in the prefrontal, parietal and cingulate cortex in at-risk groups. Specifically, Broome et al. (2009) observed an intermediate level of activity in the prefrontal and anterior cingulate cortex during a verbal fluency task, and in the prefrontal and parietal cortex during an *n*-back task in a group defined as ARMS, relative to a FEP group and a control group. Subsequently, Broome et al. (2010) investigated spatial working memory in an ARMS group, FEP patients and controls. In all groups, increased load was associated with activation in the medial frontal and medial posterior parietal cortices. Reduced activity in the medial frontal cortex and right precuneus was observed in ARMS participants compared to controls on both intermediate and difficult versions of the task. Activity in the FEP group in this study was further reduced compared to the ARMS and control groups.

A reduction of the P300 component in schizophrenia patients is one of the most consistent findings in the literature (Bramon et al., 2004). Galletly et al. (2007) used a Two-In-A-Row (TIAR) auditory oddball task which they argue necessitates the repeated updating of target identity, thus requiring stimuli to be maintained in working memory. They reported reduced P300 amplitude in schizophrenia participants relative to controls for both non-target and target tones in their task. A reduction of the amplitude of the P3b component during encoding and retrieval on a visual working memory task has been reported in patients with early-onset (adolescent) schizophrenia (Haenschel et al.,

2007). Haenschel et al. (2007) propose that the early posterior P3b peak observed in their study may reflect stimulus evaluation while the later P3b peak may reflect consolidation during encoding and template matching during retrieval (Kok, 2001; Bledowski et al., 2006; Galletly et al., 2007).

6.1.1 Aims and Objectives

To date, no electroencephalography (EEG) studies of spatial working memory have been carried out with community-based samples of adolescents who report PLEs in an attempt to uncover possible markers of the developmental trajectory to psychosis and schizophrenia. The present chapter investigates the electrophysiological correlates of working memory in a group of young adolescents considered symptomatically at-risk of developing psychosis compared to a matched group of healthy controls. This is achieved using a Spatial Working Memory Task developed for use with an adolescent population based on the classic Sternberg working memory paradigm (Sternberg, 1966). In this task, following the presentation of a study array showing a number of target stimuli in placeholders, participants make a button press response to indicate whether a probe stimulus was in a correct or incorrect location. The present study employs both behavioural and EEG measures while participants complete the task. It is anticipated that as memory load increases accuracy will decrease and reaction times will increases for the overall group. Sustained amplitude of the P300 component is predicted for the overall group as memory load increases. An increase in the latency of the P300 component is predicted for the overall group as memory load increases.

The hypotheses are as follows:

- It is anticipated that accuracy will be lower and reaction times higher in the PLEs group compared to the control group.
- Differences in ERP mean amplitude and latency of the P300 component are expected between those participants who reported experiencing PLEs and the control group. It is anticipated that the mean amplitude of the P300 component will be reduced in the PLEs group compared to the control group.
- It is also hypothesised that latency of the P300 component will be increased in the PLEs group compared to the control group.

6.2 Methods

6.2.1 Participants

Forty-two participants (21 male; age range 11-13 years; mean age = 12.14 years) completed the Spatial Working Memory Task after completing a clinical interview (see Chapter 2, section 2.1.3 for details of the clinical interview process). Seventeen participants reported PLEs (7 male; age range11-13 years; mean age = 12 years). The control group consisted of twenty-five participants (14 male; age range 11-13 years; mean age = 12.24 years). Participants gave written informed assent, and parental consent was obtained before participation in the study (see Chapter 2, section 2.3.1 for further details). All participants had normal or corrected-to-normal vision and no previous neurological disorders or brain injuries.

6.2.2 Stimuli

Participants completed a computerised Spatial Working Memory Task which was created for use with a young adolescent population based on the Sternberg working memory paradigm (Sternberg, 1966). The task was written and presented in E-Prime©. Participants were presented with a study array showing a number of target stimuli in fixed placeholders. The task consisted of 128 trials in total. Each block contained 32 test trials in which participants made a button press response, via a mouse with their index or middle finger, to indicate whether a stimulus was in a correct (positive probe) or incorrect (negative probe) location, respectively.

Stimuli were either fish in fishbowls or birds in bird cages generated in Microsoft Word using ClipArt. For each block, participants were instructed to try to remember which placeholders (i.e. fishbowls or bird cages) contained target stimuli (i.e. fish or birds) and that later a target stimulus would appear in one of the placeholders and they would have to remember whether they had seen a target stimulus in that placeholder or not (see Appendix XVI for a full list of instructions given to participants). For the first half of each block participants viewed one study array, following which 16 probe stimuli using the fish/fishbowl stimuli were presented as test stimuli. The second half of each block contained one study array using the bird/birdcage stimuli, followed by a further 16 probe stimuli (see Figure 6.2 for an example of a trial).

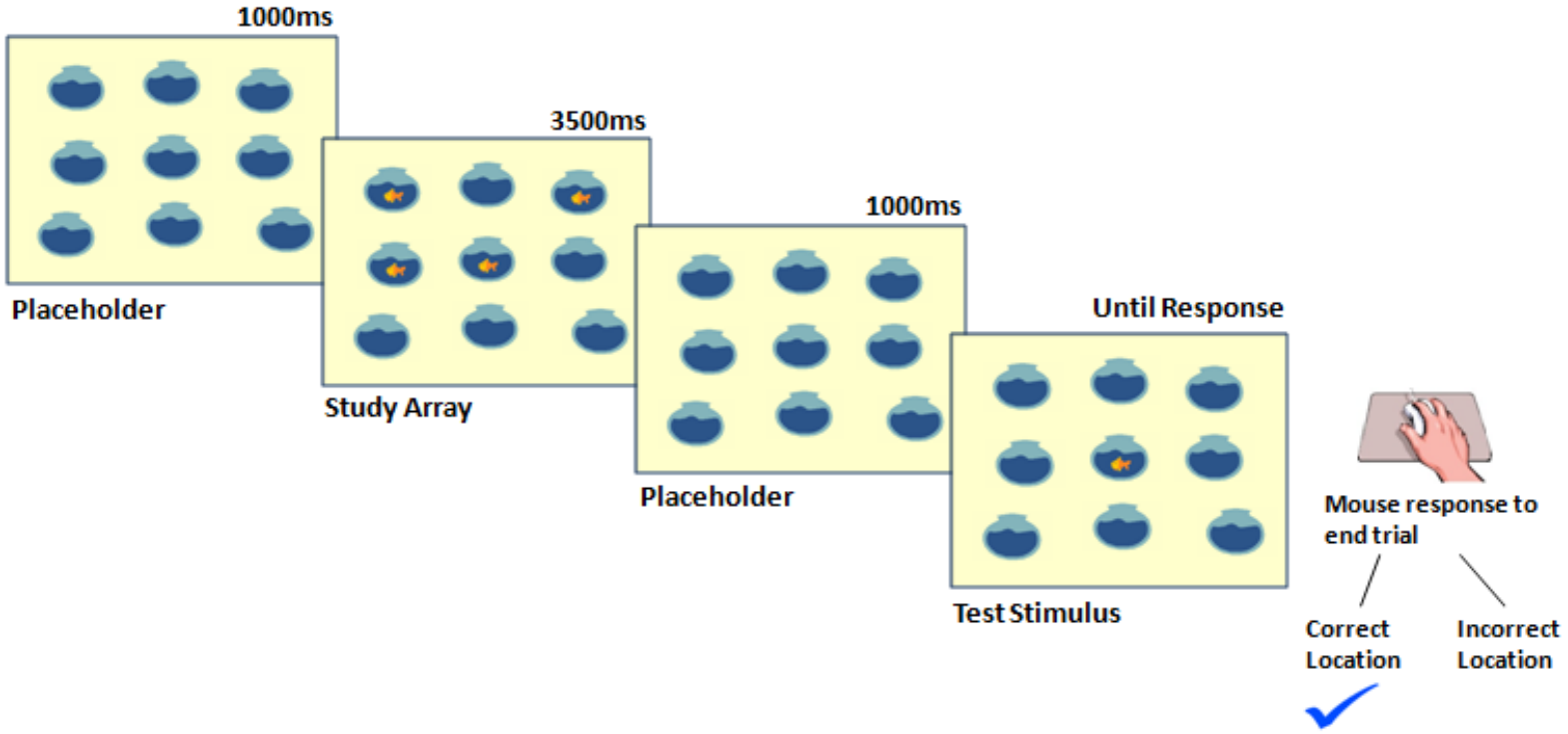


Figure 6.2: *Example from Block 1 (Low Load) of the Spatial Working Memory Task displaying a fish bowl placeholder array, followed by the study array, followed by another placeholder array and a test stimulus in a correct location.*

Specifically, participants were initially presented with the blank placeholder array for 1000ms (which displayed the empty placeholders for that block). Participants were then presented with a study array which displayed a number of target stimuli in a subset of the placeholders. This study array was presented for 3500ms. The presentation of the study array was then followed by another presentation of the blank placeholder array for a further 1000ms. Finally, participants were presented with the test stimulus (one target stimulus presented in the placeholder array), which required the participant to make a button press response using a mouse to indicate whether the test stimulus was in a correct (left button) or incorrect (right button) placeholder.

The task included 4 blocks (2 x low memory load and 2 x high memory load). Blocks 1 and 2 were classed as low memory load, while Blocks 3 and 4 were classed as high memory load. In Block 1, 4 out of 9 placeholders in the study array contained a target stimulus (as in Figure 6.2). In Block 2, 5 out of 12 placeholders in the study array contained a target stimulus. In Block 3, 6 out of 15 placeholders in the study array contained a target stimulus, while in Block 4, 7 out of 18 placeholders in the study array contained a target stimulus.

6.2.3 Procedure and Data Analysis

6.2.3.1 Procedure.

Details of the electrophysiological setup and recording are reported in Chapter 2 (section 2.3.3). E-Prime© logged response times for each participant and sent Transistor-Transistor Logic (TTL) triggers to the EEG acquisition PC to allow stimulus presentations (stimulus type) and responses to be logged in real time on the EEG recording. Response times were measured as the time between presentation of the

stimulus and the response, and were recorded for all trials. Response latencies and accuracy were calculated automatically by E-Prime© and average response times were collated in E-Prime© for each block.

EEG data were recorded in μV from 62 scalp sites. The nasion was used as a reference. Vertical eye movements (VEOG) were recorded from electrodes located above and below the left eye and horizontal eye movements (HEOG) were recorded from the electrodes positioned at the outer canthus of each eye. Blinks were averaged off-line and a blink reduction algorithm was applied to the data. This algorithm involved automatic artifact correction (Berg & Scherg, 1991; Ille et al., 2002). Stimulus-locked average ERPs were obtained by averaging the EEG using the test stimulus presentation as the trigger. ERP component time windows were chosen based on previous literature and visual inspection of grand averaged waveforms.

6.2.3.2 Data analysis.

Stimulus-locked epochs were defined as -100ms pre-stimulus presentation until 1000ms after stimulus presentation. Data were averaged for each participant and grand averages for each block were compiled. Only epochs in which participants made correct responses were included for group comparisons of ERP mean amplitude and latency analysis. Statistical analyses were carried out using SPSS Statistics version 20 for Windows. Data was tested for normality using Kolmogorov-Smirnov tests. Demographic variables were compared using independent-samples t-tests and chi-square analyses. Separate 2x2 repeated measures ANOVA were used to examine differences in mean accuracy scores and mean reaction times (defined in milliseconds - ms) between high and low loads for the overall group. Independent-samples t-tests were

used to statistically test between-group differences in mean accuracy and mean reaction times.

Separate 2x2x2 mixed factorial ANOVAs were utilised to examine mean amplitude differences, with Load Level (low, high) and Location (positive probe, negative probe) as within-subjects variables and Group (control, PLEs) as the between-subjects variable to test for differences at each of the electrode sites chosen for further analysis (Fz, Pz, POz). The P300 timeframe was defined as 250ms to 750ms post-stimulus, with further analyses exploring the early and late timeframes of the P300 component separately. 2x2x2x2 mixed factorial ANOVAs were used to further examine mean amplitude difference at Pz and POz with Load Level (low, high), Location (positive probe, negative probe) and Time (250ms to 430ms, 430ms to 750ms) as within-subjects variables and Group (control, PLEs) as the between-subjects variable. Latency was defined as the most positive data point within the timeframe 250-430ms and a 2x2 mixed factorial ANOVA was used to examine the effect of Load (low, high) across Groups (control, PLEs). Independent-samples t-tests were then used to further examine observed between-group differences. For each ANOVA, an alpha value of 0.05 was used for main and interaction effects. Levene's tests were employed to test for homogeneity of variances and Greenhouse-Geisser correction was employed where the assumption of sphericity was violated.

6.3 Results

6.3.1 Demographic and General Functioning Comparisons

Groups were compared on the following demographic variables; age, gender, handedness and parental socioeconomic status (SES) – see Table 6.1. Groups were also compared for general functioning and scholastic ability on scores on the Strengths and Difficulties Questionnaire (SDQ; Goodman 1997; Goodman et al., 1998), overall current Children's Global Assessment Scale from the K-SADS-PL interview schedule (C-GAS; Shaffer et al., 1983) and the Wide Range Achievement Test 4 (WRAT-4; Wilkinson and Robertson, 2005)

No between-group differences in mean age [$t(40) = 0.97$, $p = 0.336$], gender [$\chi^2(1) = 0.14$, $p = 0.708$], parental SES [$\chi^2(1) = 0.001$, $p = 1.000$] handedness [$\chi^2(1) = 0.04$, $p = 0.844$] or WRAT scores [$t(34) = -0.35$, $p = 0.728$] were observed. A between-group difference in scores on the SDQ [$t(40) = -3.52$, $p = 0.001$] was observed with the control group [$M = 9.04$, $SEM = 0.78$] scoring lower on this measure than the PLEs group [$M = 13.29$, $SEM = 0.92$]. A between-groups difference was also observed in current C-GAS scores [$t(38) = 2.4$, $p = 0.026$] with the control group [$M = 84.88$, $SEM = 2.33$] achieving a higher mean score on this measure than the PLEs group [$M = 71.31$, $SEM = 5.16$].

Table 6.1: *Demographic and general functioning details for the control and PLEs groups for the Spatial Working Memory Task.*

Variable	**Overall (*N*=42)**	**Control (*N*=25)**	**PLEs (*N*=17)**	**Result**
Mean Age (SEM)	12.14 (0.12)	12.24 (0.17)	12 (0.17)	$t(40) = 0.97$, $p = 0.336$
Gender	21 males (50%)	14 males (56%)	7 males (41.18%)	$\chi^2(1) = 0.14$, $p = 0.708$
Handedness	1 left (2.38%)	0 left (0%)	1 left (5.88%)	$\chi^2(1) = 0.04$, $p = 0.844$
SES	17 (40.47%)	10 (40%)	7 (41.18%)	$\chi^2(1) = 0.001$, $p = 1.000$
SDQ scores* **(SEM)**	10.76 (0.67)	9.04 (0.78)	13.29 (0.92)	***t*(40) = -3.52, *p* = 0.001**
C-GAS scores (SEM)	79.45 (2.67)	84.88 (2.33)	71.31 (5.16)	***t*(38) = 2.4, *p* = 0.026**
WRAT scores (SEM)	47.28 (1.56)	46.8 (2.4)	47.88 (1.9)	$t(34) = -0.35$, $p = 0.728$

**Higher scores reveal greater impairment.
Significant differences are highlighted in bold.
SES 1 – professional and managerial, SES2 – other.

6.3.2 Behavioural Data

6.3.2.1 Overall group.

Accuracy scores and reaction times for the overall group for each block are presented in Table 6.2. Overall mean accuracy for the task was 96.62 (*SEM* = 1.8). Mean accuracy at low load [*M* = 52.8, *SEM* = 1.14] was significantly higher than at high load [*M* = 44.85, *SEM* = 0.83; $t(40) = 6.02$, $p < 0.0005$]. Overall mean reaction time for correct responses for the task was 1485.42ms (*SEM* = 96.28). Mean reaction time for correct responses was significantly lower at low load [*M* = 1320.2, *SEM* = 76.7] compared to high load [*M* = 1668.04, *SEM* = 132.22; $t(40) = -3.86$, $p < 0.0005$].

Table 6.2: *Mean accuracy scores and reaction times for correct responses for the overall group for the Spatial Working Memory Task.*

Block		Mean Accuracy (SEM)	Mean Reaction Time (ms) (SEM)
1	**Low Load**	27.52 (1.02)	1171.62 (59.28)
2		25.31 (0.4)	1451.58 (99)
3	**High Load**	24.56 (0.5)	1567.57 (121.56)
4		20.29 (0.48)	1771.8 (151.36)

6.3.2.2 Group analyses.

Overall mean accuracy for the control group was 95.6 (*SEM* = 2.56) and 98.12 (*SEM* = 2.41) for the PLEs group. No significant differences in overall mean accuracy scores were observed between the control and PLEs groups [$F(1, 39) = 0.07$, $p = 0.801$, partial eta squared = 0.002]. No interaction effect was observed between Load and Group [$F(1, 39) = 0.73$, $p = 0.399$, partial eta squared = 0.018]. A main effect of Load was observed [$F(1, 39) = 36.73$, $p < 0.0005$, partial eta squared = 0.485; see Figure 6.3] with accuracy higher for low load than at high load.

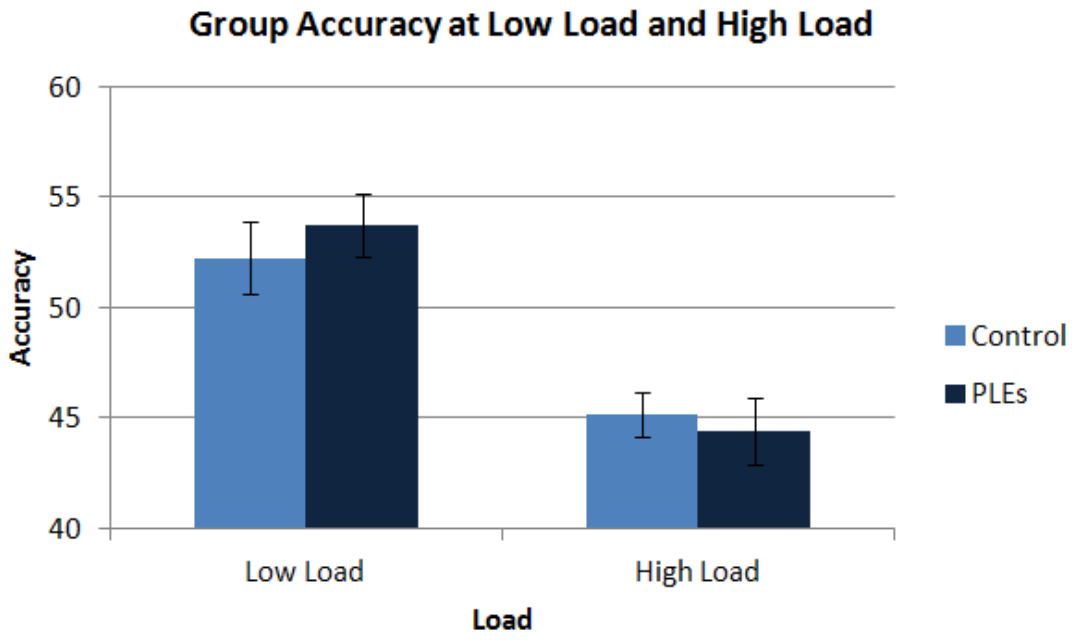


Figure 6.3: *Mean accuracy at low and high load for the control and PLEs groups (Note: Error bars indicate SEM).*

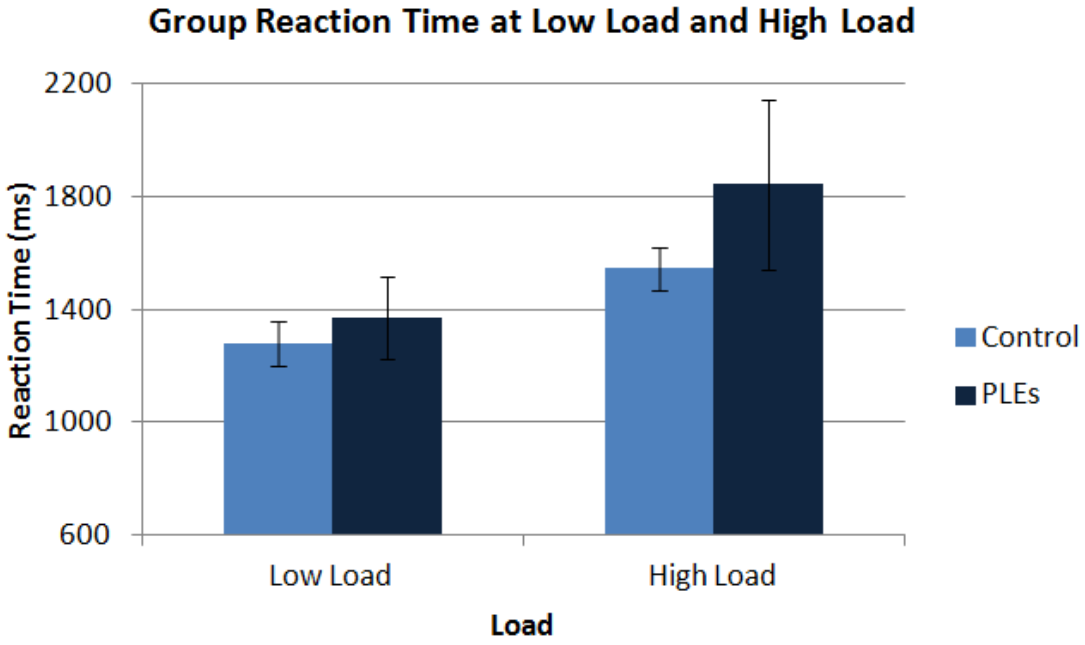


Figure 6.4: *Mean reaction times for correct responses at low and high load for the control and PLEs groups (Note: Error bars indicate SEM).*

Overall mean reaction time for correct responses for the control group was 1402.45ms (*SEM* = 70.58) and 1607.44ms (*SEM* = 214.79) PLEs group. No significant differences in overall mean reaction time scores for correct responses were observed between the control and PLEs groups [$F(1, 39) = 0.94$, $p = 0.338$, partial eta squared = 0.024]. No interaction effect was observed between Load and Group [$F(1, 39) = 1.36$, $p = 0.251$, partial eta squared = 0.034]. The main effect of Load reached statistical significance [$F(1, 39) = 16.17$, $p < 0.0005$, partial eta squared = 0.293; see Figure 6.4], with slower responses for high load.

Due to the presence of large SEMs in the high load PLEs group, the coefficient of variation (standard deviation/mean) was calculated for reaction time data for both

groups for both low and high load. This was expressed as a percentage and was found to be 28% and 24% for the control group at low and high load, respectively. For the PLEs group the coefficient of variation was 44% at low load and 67% at high load, indicating greater response time variability in the PLEs group.

6.3.3 Electrophysiological Data

6.3.3.1 Overall group.

For the overall group no differences in mean amplitude (μV) were observed between low and high load at either Pz [Low Load: *M* = 4.63, *SEM* = 0.29; High Load: *M* = 4.4, *SEM* = 0.37; *t*(39) = 0.7, *p* = 0.49] or POz [Low Load: *M* = 3.79, *SEM* = 0.36; High Load: *M* = 3.79, *SEM* = 0.45; *t*(39) = -0.17, *p* = 0.863] for the timeframe 250ms to 750ms post-stimulus. For the timeframe 250 to 430ms post-stimulus no differences in mean latency (ms) was found between low load and high load at POz [Low Load: *M* = 347.49, *SEM* = 4.36; High Load: *M* = 350.85, *SEM* = 4.21; *t*(39) = -0.75, *p* = 0.459] or Pz [Low Load: *M* = 371.86, *SEM* = 4.48; High Load: *M* = 372.99, *SEM* = 3.59; *t*(39) = -0.26, *p* = 0.796] for the overall group.

6.3.3.2 Group analyses.

6.3.3.2.1 Mean amplitude analyses.

No between-groups effect on mean amplitude was observed at electrode site Fz for the timeframe 330ms to 850ms post-stimulus [*F*(1, 38) = 1.29, *p* = 0.263, partial eta squared = 0.033]. No main effects of Load [*F*(1, 38) = 0.44, *p* = 0.509, partial eta squared = 0.012] or Location [*F*(1, 38) = 1.35, *p* = 0.252, partial eta squared = 0.034] were

observed, and no interaction effect for Load*Group [$F(1, 38) = 2.04$, $p = 0.162$, partial eta squared = 0.051], Location*Group [$F(1, 38) = 0.07$, $p = 0.789$, partial eta squared = 0.002], or Load*Location*Group [$F(1, 38) = 0.57$, $p = 0.455$, partial eta squared = 0.015] were observed at electrode site Fz for this timeframe.

A between-groups effect was observed for mean amplitude at electrode sites Pz [$F(1, 38) = 4.44$, $p = 0.042$, partial eta squared = 0.105] for the timeframe 250ms to 750ms post-stimulus, with mean amplitude reduced in the PLEs group [Low Load: $M = 4.15$, $SEM = 0.46$; High Load: $M = 3.57$, $SEM = 0.6$] relative to the control group [Low Load: $M = 4.94$, $SEM = 0.37$; High Load: $M = 4.96$, $SEM = 0.44$]. A between-groups effect was also observed for mean amplitude at electrode site POz [$F(1, 38) = 7.53$, $p = 0.009$, partial eta squared = 0.165], again with mean amplitude reduced in the PLEs [Low Load: $M = 2.86$, $SEM = 0.55$; High Load: $M = 2.57$, $SEM = 0.68$] group relative to the control group [Low Load: $M = 4.42$, $SEM = 0.44$; High Load: $M = 4.61$, $SEM = 0.53$] – see Figure 6.5.

For the same timeframe, no main or interaction effects of Load or Location were observed at posterior electrode sites Pz [Load: $F(1, 38) = 0.69$, $p = 0.413$, partial eta squared = 0.018; Location: $F(1, 38) = 1.05$, $p = 0.313$, partial eta squared = 0.027; Load*Location*Group interaction: $F(1, 38) = 0.8$, $p = 0.377$, partial eta squared = 0.021] or POz [Load: $F(1, 38) = 0.01$, $p = 0.937$, partial eta squared = 0.001; Location: $F(1, 38) = 0.53$, $p = 0.471$, partial eta squared = 0.014; Load*Location*Group interaction: $F(1, 38) = 0.08$, $p = 0.784$, partial eta squared = 0.002].

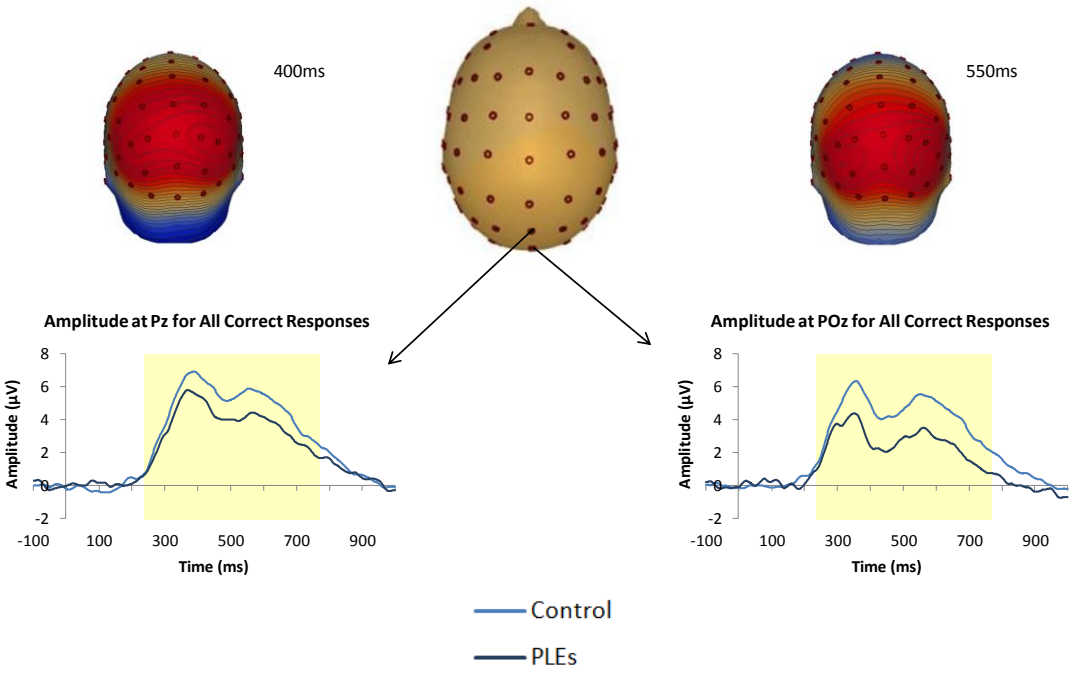


Figure 6.5: *ERP waveforms and corresponding scalp topographic maps (control group) showing differences in mean amplitude for correct responses at Pz and POz.*

Independent-samples t-tests revealed that when all correct responses were examined together, regardless of probe type, ERP amplitude at electrode site POz was reduced for both low load [$t(40) = 2.21$, $p = 0.033$] and high load [$t(38) = 2.37$, $p = 0.023$] for the timeframe 250 to 750ms post-stimulus for the PLEs group compared to the control group. Significantly reduced mean amplitude was observed in the PLEs group relative to the control group at low load for positive probes [$t(40) = 2.25$, $p = 0.03$] and at high load for negative probes [$t(38) = 2.67$, $p = 0.011$] at electrode site POz – see Figure 6.6.

Due to the presence of two subcomponents of the P300, mean amplitude was assessed at Pz and POz for the timeframes 250ms to 430ms and 430ms to 750ms, respectively – see Figure 6.6. A between-groups difference was observed at both electrodes [Pz: $F(1, 38) = 4.11$, $p = 0.05$, partial eta squared = 0.098; POz: $F(1, 38) = 7.76$, $p = 0.008$, partial eta squared = 0.17]. A Load*Time interaction [$F(1, 38) = 7.18$, $p = 0.011$, partial eta squared = 0.159] and a Load*Time*Group interaction were observed at POz [$F(1, 38) = 5.68$, $p = 0.022$, partial eta squared = 0.13]. Mean amplitude at POz was significantly reduced in the PLEs group at both early [250ms to 430ms; $t(38) = 2.52$, $p = 0.016$] and late time windows [430ms to 750ms; $t(38) = 2.53$, $p = 0.016$]. Further independent-samples t-tests revealed that mean amplitude for the PLEs group was reduced at low load for early [$t(40) = 2.57$, $p = 0.014$] and at high load for late [$t(38) = 2.5$, $p = 0.017$] time windows. A trend towards reduced mean amplitude was observed in the PLEs group at Pz for high load at the late timeframe [$t(38) = 2.00$, $p = 0.052$]. In addition, mean reaction time was found to correlate negatively with mean amplitude at Pz at high load for the overall group [$r = -0.398$, $p = 0.011$; control: $r = -0.326$, $p = 0.12$; PLEs group: $r = -0.483$, $p = 0.058$].

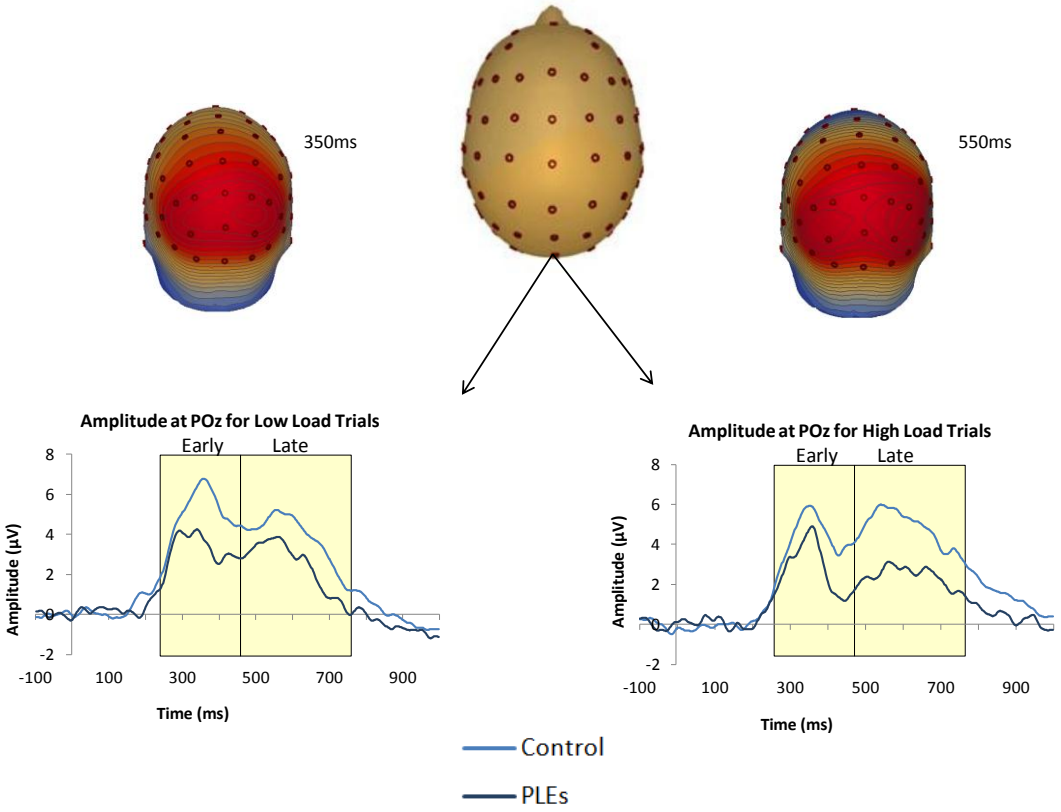


Figure 6.6: *ERP waveforms and corresponding scalp topographic maps (control group, Low Load 350ms and High Load 550ms) showing differences in mean amplitude for correct responses at Low Load and High Load at POz.*

6.3.3.2.2 Peak latency analyses.

No main effect of Load was observed for the latency of early P300 component at Pz [$F(1, 38) = 0.01$, $p = 0.929$, partial eta squared = 0.001] or POz[$F(1, 38) = 0.61$, $p = 0.441$, partial eta squared = 0.016] for the timeframe 250 to 430ms post-stimulus. In addition, no between-group differences in the latency of the P300 component were

observed at Pz [$F(1, 38) = 0.1$, $p = 0.756$, partial eta squared = 0.003] and POz [$F(1, 38) = 0.97$, $p = 0.332$, partial eta squared = 0.025] and no interaction effects were observed between Load and Group at either electrode site [Pz: $F(1, 38) = 0.68$, $p = 0.414$, partial eta squared = 0.018 ; POz: $F(1, 38) = 0.07$, $p = 0.788$, partial eta squared = 0.002].

6.3.4 Summary of Results

In summary, no between-group differences were observed for the demographic variables age, gender, handedness or parental SES. In terms of general psychopathology and general functioning, group scores on the SDQ differed with the PLEs group scoring higher on this measure and group C-GAS scores differed with the PLEs group receiving lower C-GAS scores than the control group. No differences in WRAT scores were observed between the groups. As memory load increased, accuracy decreased and reaction times increased for the overall group. No between-group differences in accuracy scores or reaction times were observed.

No difference in mean amplitude was observed at electrode site Fz between the control and PLEs groups for the timeframe 330ms to 850ms post-stimulus. Reduced amplitude of the P300 was observed at parietal electrode sites Pz and POz for the timeframe 250ms to 750ms post-stimulus. When all correct responses were examined together, regardless of probe type, activity at POz was reduced for both low load and high load for the PLEs group compared to the control group. Mean amplitude of the P300 ERP component was further examined at Pz and POz for the timeframes 250ms to 430ms and 430ms to 750ms. Mean amplitude at POz was significantly reduced in the PLEs group relative to the control group during both timeframes and a trend towards reduced amplitude at Pz for the late timeframe was observed in the PLEs group. No between-group differences in the latency of the P300 component were observed.

6.4 Discussion

The present chapter reports a reduction of the P300 component during spatial working memory retrieval on a in a group of adolescents reporting PLEs compared to a control group. This chapter investigated spatial working memory in a group of adolescents who reported PLEs compared to a control group using a computerised task based on the Sternberg working memory paradigm (Sternberg, 1966). The groups were compared on a number of demographic variables and did not differ in terms of age, gender, handedness or parental SES of participants within each group. The groups also did not differ in terms of WRAT scores, which were used as a measure of scholastic ability. As observed in previous chapters between-groups analysis revealed that the control group scored lower total difficulties scores on the SDQ and obtained higher current C-GAS scores than the PLEs group, suggesting more emotional difficulties and lower global functioning in the PLEs group.

The present chapter reports reduced parietal positivity related to spatial working memory retrieval in a group of adolescents who reported PLEs. A sustained posterior positivity was observed in all conditions of the task with reduced P300 amplitude at posterior electrode sites in the PLEs group relative to the control group. Although the groups were matched behaviourally, subtle differences in the EEG data were observed. Mean reaction times were found to correlate negatively with mean amplitude at Pz at high load for the overall group, indicating those participants who took longer to respond at high load also had reduced amplitude at posterior electrode sites for the more difficult levels of the task. Although this correlation did not remain significant when each group was examined separately, the result for the overall group was mainly affected by a trend within the PLEs group (p = 0.06). When the P300 component observed at Pz and POz was divided and the early (250ms to 430ms) and late (430ms to 750ms) aspects of the

component were examined separately reduced amplitude was observed in the PLEs group relative to the controls for both timeframes. Reduced amplitude was observed for low load at the early time window and high load at the late time window at POz and a similar trend was also observed at Pz for high load at the late time window.

As anticipated, for the overall group statistically significant decreases in accuracy scores and increases in mean reaction time were observed from low load to high load, i.e. as difficulty increased from Block 1 to Block 4 of the task. Accuracy and reaction time scores did not differ between the control and PLEs groups overall or at either low load or high load. Despite no statistically significant differences in the behavioural data, the pattern of responses indicates that at high load the PLEs group were slower to respond with greater deviation from the mean response time.

Reduced amplitude for the later part of the P300 component at high load indicates that, unlike the control group, the PLEs group did not show the same level of sustained parietal positivity to the probe at the more difficult levels of the task which other evidence supports (Marchand et al., 2006). The P300 ERP has been conceptualised as the physiological correlate of working memory updating of changes in the environment or as an index of allocation of attentional resources and memory search processes (Posner, 1975; Donchin & Coles, 1988). Haenschel et al. (2007 interpreted a decrease in the amplitude of the early P3b component during working memory retrieval in a group with early-onset schizophrenia to reflect a deficit in the evaluation of the probe stimulus against the stimulus representations held in memory. The reduced amplitude of the early P300 observed in the present study may reflect disrupted neural processes underlying stimulus evaluation in the PLEs group which has not yet reached a level which would cause behavioural impairment. Reduced amplitude

of the P300 component, particularly the late P300 at high load, could reflect an underlying reduced attention and memory retrieval capacity in the PLEs group.

Working memory has been proposed as a core deficit in schizophrenia and reduction of the P300 component is one of the most consistent findings in the literature (Goldman-Rakic, 1994; Bramon et al., 2004). In recent years deficits in working memory have been reported in groups considered clinically at-risk for psychosis such as prodromal, UHR and ARMS groups (Smith et al., 2006; Pflueger et al., 2007; Frommann et al., 2011) and groups who report PLEs (Laurens et al., 2008b). The current study adds to this literature by including EEG measures along with behavioural data from a group reporting PLEs.

A previous study by Jacobson et al. (2010) found evidence of disrupted prefrontal-temporal connectivity in a group of adolescents reporting PLEs. Polich (2007) hypothesised that the later P3b component may reflect attention and subsequent memory processes, and may originate from temporal-parietal activity associated with these processes. Evidence for parietal dysfunction at the earliest stages of psychosis has also been proposed by Whalley et al. (2005). Reduced amplitude of the P300 component observed in the present study may reflect an underlying reduced attention and memory retrieval capacity in the PLEs group. Despite performing at a similar level to the control group behaviourally, the reduced P300 component may reflect a disrupted temporal-parietal network in the PLEs group.

This chapter used electrophysiological measures to investigate the neurophysiological underpinnings of spatial working memory in an adolescent sample with self-reported PLEs. Limitations of the present study include the small sample size and the poor spatial resolution of ERPs. Further research is needed in order to uncover the relationship between spatial working memory tasks and risk for psychotic disorder.

The results of this study suggest that the neural networks involved in spatial working memory may be disrupted early in adolescence prior to the onset of a psychotic disorder such as schizophrenia.

6.4.1 Chapter Summary

The present chapter aimed to investigate the behavioural and electrophysiological correlates of spatial working memory in a group of adolescents who reported PLEs compared to a control group. This was achieved using a Spatial Working Memory Task developed for use with an adolescent population and based on the Sternberg paradigm (Sternberg, 1966). This chapter is to our knowledge the first study to test spatial working memory in this sample using ERP measures. Behaviourally, as memory load increased accuracy decreased and reaction times increased for the overall group as expected. No between-group differences in the accuracy and reaction time data were observed however, greater reaction time variability was observed in the PLEs group. Reduced mean amplitude of the P300 component was observed in the PLEs group relative to the control group at parietal electrode sites.

The present chapter expands existing findings of reduced P300 amplitude in adolescent onset schizophrenia (Haenschel et al., 2007) by revealing reduced P300 amplitude in the treatment-naïve extended psychosis phenotype. This reduction in P300 amplitude may reflect disrupted neural processes underlying stimulus evaluation and template matching during retrieval in the PLEs group. Reduced amplitude of the P300 component, particularly the late P300 at high load, observed in the present study could also reflect an underlying reduced attention and memory retrieval capacity in individuals with PLEs. These results identify neural correlates of neurocognitive dysfunction associated with population level psychotic symptoms and provide insights

into ERP abnormalities associated with the extended psychosis phenotype. Follow-up studies may elucidate whether reduced P300 amplitude on spatial working memory tasks confers greater risk for developing a psychotic disorder in adulthood.

Chapter 7

General Discussion

Overview

The present thesis investigated electrophysiological correlates of auditory processing and spatial memory, including implicit spatial memory and spatial working memory, in a community-based sample of adolescents reporting psychotic-like experiences (PLEs) compared to control groups matched for age and gender. The present thesis is the first study to investigate the electrophysiological correlates of auditory and spatial processing in adolescents reporting PLEs. In addition the present thesis investigated neuropsychological functioning in the PLEs group and resting state brain activity in the delta, theta and alpha frequency bands. A community-based sample of adolescents reporting PLEs was chosen due to recent research which has suggested that self-reports of psychotic symptoms during adolescence may be significantly associated with the development of a psychotic disorder in adulthood (Poulton et al., 2000; Turetsky, et al., 2009). A report by Kelleher and Cannon (2011) highlighted the shared risk factors between the psychosis phenotype (schizophrenia and other psychotic disorders) and the non-clinical psychosis phenotype (individuals who do not have psychotic disorders but who report experiencing psychotic symptoms). These risk factors include genetic and early developmental deficits as well as social risk factors, adverse childhood experiences and substance abuse. In addition, shared cognitive and neuroanatomical risk factors have been identified between the non-clinical and clinical psychosis phenotypes. Studying adolescents who report PLEs in the general population provides an opportunity to study symptomatic risk for psychosis during adolescence and within the context of development.

The prevalence and relevance of psychotic symptoms in adolescent groups in relation to risk for psychotic disorders and other psychopathology has been studied by a number of research groups. The present thesis was carried out as part of the Adolescent

Brain Development Study (ABD Study) which was the first Irish study to carry out an in-depth investigation of psychotic symptoms in a community-based sample of adolescents and their relationship to clinical and neuropsychological variables in an attempt to identify risk markers for disorder in the general adolescent population. Positive psychotic symptoms such as hallucinations and delusions were the focus of the ABD Study rather than negative symptoms due to their reported association with risk for disorder in adulthood in previous studies (Poulton et al., 2000; Welham et al., 2009b). The present thesis adds to the findings of the ABD Study and current literature on risk for psychosis by investigating the electrophysiological correlates of auditory processing and spatial memory in this group, and exploring the usefulness of such tasks as biological markers of PLEs in the non-clinical psychosis phenotype.

The active auditory oddball and spatial memory experiments were chosen for use with EEG as both have shown reduced amplitude of ERP components in schizophrenia, first-episode psychosis (FEP) and clinical at-risk groups including ultra high-risk (UHR) and at-risk mental state (ARMS) groups. Both the P300 elicited to target tones during active auditory oddball tasks and working memory have been proposed as trait markers for psychotic disorders (Wood et al., 2003; Özgürdal et al., 2008). A reduction of the P300 to target tones on active auditory oddball tasks has been reported throughout all stages of psychotic illness, most recently in prodromal groups (van der Stelt et al., 2005; Özgürdal et al., 2008). Spatial working memory deficits have also been reported throughout the course of psychotic illness as well as in adolescent-onset schizophrenia (Vance et al., 2006; 2007) and most recently in groups meeting criteria for prodromal risk syndromes (Kelleher et al., 2012d). The aim of the present thesis was to examine whether similar deficits are present in adolescents reporting PLEs in the general population.

The experiments contained within the present thesis were adapted for use with an adolescent population and designed to investigate amplitude and latency differences in the event-related potential (ERP) components associated with auditory processing and spatial memory between the PLEs group and a control group matched for age and gender. The main findings from the present thesis are presented in section 7.1 and these findings are interpreted within the context of the literature on risk factors for psychotic disorders such as schizophrenia in section 7.2. The practical and theoretical implications of these findings are discussed in section 7.3 and suggestions for future research in this area are discussed in section 7.4.

7.1 Findings from the Experiments Contained Within the Present Thesis

7.1.1 Neuropsychological Test and Resting State EEG Findings

In Chapter 3, between-group differences were explored on a number of neuropsychological tests taken from the MATRICS Consensus Cognitive Battery (MCCB) and in resting state EEG data across three frequency bands (delta, theta and alpha). Between-group differences were observed on two speed of processing measures, the Trail Making Test B (TMTB) and the BACS Symbol Coding Task (BACS SC). The psychotic-like experiences (PLEs) group obtained higher mean scores on the TMTB indicating greater impairment on the task. In addition, the PLEs group attained lower mean scores in the BACS SC task with lower scores revealing slower processing speed. No between-group differences were observed in the resting state data for the delta, theta

or alpha EEG frequency bands during eyes open or eyes closed recordings over anterior, posterior or fronto-temporal electrode sites.

7.1.2 Active Auditory Oddball Task Findings

In Chapter 4 a modified two-tone Active Auditory Oddball Task was used to test for group differences in P300 amplitude, based on the task previously used by Bramon et al. (2005) and Frangou et al. (1997). For the Active Auditory Oddball Task no between-group differences were observed on accuracy scores to target and non-target tones or reaction times to target tones. For the overall group mean amplitude of the P300 component was greater for target than non-target tones across central and midline electrode sites FCz, Cz, CPz, Pz, C1 and C2 as expected. No between-group differences in the amplitude of the P300 were observed at either central or midline electrode sites. However when a within-groups analysis was carried out mean amplitude to target tones was found to be significantly greater than mean amplitude to non-target tones in the control group at electrode site FCz. This result was not observed within the PLEs group.

In addition mean amplitude of the N100 auditory evoked potential (AEP) component was explored. Between-group differences in the mean amplitude of the N100 AEP component was observed at frontal (Fz, F1, F2) and fronto-central (FCz, FC1, FC2) electrode sites. Mean amplitude of the N100 AEP component was increased in the PLEs group relative to the control group for non-target tones.

7.1.3 Implicit Spatial Memory Task Findings

In Chapter 5 an Implicit Spatial Memory Task (Murphy et al., 2009) was used to explore spatial processing and implicit spatial memory for object location. No between-

group differences were observed on the behavioural or EEG data for this task. For the overall group reaction times were faster for the Study Object Correct Location condition than the Study Object Incorrect Location condition and slower for the Study Objects condition than for the Distractor Objects condition. This indicates that participants were quicker to process objects if they appeared in the same location as shown in the study block, i.e. participants were faster to classify objects when using implicit spatial memory.

Earlier peak latency was observed in the Study Object Correct Location condition compared to the Study Object Incorrect Location condition in the overall group, providing electrophysiological evidence to support the behavioural finding that participants were faster at classifying objects when using implicit memory for spatial location. A significant difference in peak latency was also observed between the Study Object Incorrect Location and Distractor Objects conditions, with later peak latency in the Study Object Correct Location condition compared to the Distractor Objects condition. Mean amplitude was reduced in the left hemisphere compared to the right hemisphere for the Study Stimulus condition, and lower for the Study Stimulus condition than each of the test conditions for the overall P300, P3a and P3b timeframes.

7.1.4 Spatial Working Memory Task Findings

A Spatial Working Memory Task developed for use with an adolescent population and based on the classic Sternberg paradigm was employed to explore group differences in spatial w orking memory. As memory load increased, accuracy decreased and reaction times increased for the overall group as expected. No between-group differences in accuracy scores or reaction times were observed.

Table 7.1: *ERP findings from the present thesis and other published papers from the ABD Study.*

Task	Component(s)	Result	Possible Areas Involved
Present Thesis:			
Active Auditory Oddball	N100, P300	Increased amplitude of the N100 AEP to non-target tones in PLEs group Within-groups difference in P300 amplitude noted at fronto-central electrode sites with PLEs failing to elicit greater amplitude to target relative to non-target tones	N100 -Primary auditory cortex, frontal and parietal cortices P300 – Temporal cortex
Implicit Spatial Memory	P300	No between group differences	Frontal, temporal and parietal lobe areas
Spatial Working Memory	P300	Reduced P300 amplitude in the PLEs group for spatial working memory retrieval at posterior electrode sites accompanied by greater variability in the reaction times scores for the PLEs group	Prefrontal and parietal cortices
Other ABD Study Papers:			
Passive Auditory Oddball *Murphy et al. (2013)*	MMN, P3a	Reduced duration deviant MMN in the PLEs group at frontal and temporal electrode sites No between-group differences on P3a amplitude or latency	Auditory cortices and the prefrontal cortex as part of a distributed fronto-temporal network
Receptive Language *Murphy et al. (2012)*	P300	Reduced P300 amplitude at fronto-central electrode sites at difficult task levels together with decreased accuracy on difficult levels of the task in the PLEs group	Frontal and temporal lobe areas

Reduced amplitude of the P300 was observed at parietal electrode sites Pz and POz for the timeframe 250ms to 750ms post-stimulus. When all correct responses were examined together, regardless of probe type, activity at Pz and POz was reduced for both low load and high load for the PLEs group compared to the control group. Mean amplitude of the P300 ERP component was further examined at POz for the timeframes 250ms to 430ms and 430ms to 750ms. Mean amplitude at POz was significantly reduced in the PLEs group relative to the control group during both timeframes. No between-group differences in the latency of the P300 component were observed (See Table 7.1 for a summary of the ERP findings from the present thesis and other published papers from the ABD Study).

7.2 Findings from the Present Thesis within the Context of the Literature on Risk for Psychosis

7.2.1 Overview

The findings from the present thesis provide further support for the continuum model of psychosis (Dutta et al., 2007; van Os et al., 2009; Polanczyk et al., 2010) by revealing that a large percentage of adolescents from a community-based, general population sample report PLEs. Deficits observed on measures of speed of processing in Chapter 3 provide further evidence that speed of processing may be one of the key neuropsychological deficits observed in psychotic disorder and may be impaired before a clinical disorder manifests (Dickinson et al., 2007; 2008; Kelleher et al., 2012c; 2012d). Reduced amplitude of the P300 observed in Chapter 6 provides further evidence that the neural processes underlying spatial working memory may be disrupted

in the non-clinical psychosis phenotype, providing further evidence for spatial working memory as a possible trait marker for disorder. Taken together these results support the neurodevelopmental model, which suggests that individuals who develop schizophrenia often show signs of neurodevelopmental deficits as children. The neurodevelopmental model suggests that schizophrenia is the behavioural outcome of an aberration in neurodevelopmental processes that begins long before the clinical symptoms appear and is caused by a combination of factors, including environmental and genetic factors (Cardno et al., 1999; Singh et al., 2004; Rapoport et al., 2005).

7.2.2 Psychotic-Like Experiences and Neuropsychological Deficits

Of the 95 participants who took part in the EEG Study, 33 reported PLEs (34.7%) and the remaining 62 participants (65.3%) were included as a control group. This figure provides support for the continuum model of psychosis which proposes that these sub diagnostic symptoms of psychosis may exist on a continuum on which a psychotic disorder (such as schizophrenia) is positioned at the extreme end (Dutta et al., 2007; van Os et al., 2009; Polanczyk et al., 2010). The high percentage of participants who reported PLEs is in line with reports from other studies with similar age groups (Yoshizumi et al., 2004; Horwood et al., 2008; Kelleher et al., 2012a) and data from the overall ABD Study (Kelleher et al., 2012f). Given the high rates of PLEs reported by participants and recent reports of the shared risk factors between PLEs (or the non-clinical psychosis phenotype) and the clinical psychosis phenotype, it is crucial to understand the link between PLEs and underlying risk for psychotic disorders.

The present thesis observed group differences on two neuropsychological tests which measure speed of processing (TMT B and BACS SC) reflecting previous findings by Blanchard et al. (2010) and Kelleher et al. (2012c; 2012d). The PLEs group

were found to have reduced processing speed on both measures and these speed of processing deficits were observed despite resting state EEG recordings in both groups being similar in the delta, theta and alpha frequency bands for eyes open and eyes closed recordings. Speed of processing may be one of the key neuropsychological deficits associated with self-reports of PLEs from community-based samples of adolescents (Kelleher et al., 2012c; 2012d). Some researchers have proposed that speed of processing deficits, as measured by symbol coding tasks in particular, may in fact be one of the core deficits in schizophrenia (Dickinson et al., 2007; 2008). In contrast to other neuropsychological task which might be attributed to specific anatomical regions or neural networks, it has been argued that speed of processing tasks reflect integration and coordination between distributed brain networks and measure a systems-based process (Dickinson et al., 2008; Kelleher et al., 2012c).

Reported speed of processing deficits may also reflect or contribute to difficulties in other higher-order cognitive functions such as working memory. The ability to reason and solve problems requires information to be held in working memory. This information is subject to loss due to decay or interference; as a result faster processing is more likely to permit reasoning and problem solving to be completed before the necessary information is lost (Miller & Vernon, 1996; Fry & Hale, 2000). It is possible that processing speed is related to working memory capacity as faster rehearsal allows for more information to be held in working memory (Baddeley, 1981; 1986).

It is possible that underlying differences may not have been uncovered by quantitative EEG methods in the present study due to the age of the participant sample. All participants in the present study were aged between 11 and 13 years when the data were collected. While it has been reported that by age 12 years a strong increase in

alpha power and decrease in theta power can be observed (Somsen et al., 1997), it has also been noted that EEG power, particularly within the alpha frequency range is positively related to brain maturity and increases from childhood to adulthood (Kilmesch, 1999). It is possible that abnormalities in brain development may not be uncovered using quantitative EEG techniques until later a later stage in development and other imaging techniques may be more useful in the attempt to uncover changes in resting state brain activity. Previous research by Jacobson et al. (2010) investigated the structural brain correlates of psychotic symptoms in a similar group of 11 to 13 year olds and using diffusion tensor imaging (DTI) found decreased fractional anisotropy (FA) values in fibre tracts including the inferior fronto-occipital fasiculus and the inferior longitudinal fasiculus. These results indicate altered fronto-temporal connectivity in the psychotic symptoms group.

Results from the Jacobson et al. (2010) study are in line with the dysconnection hypothesis of schizophrenia (Friston & Frith, 1995), showing structural and functional changes in particular in white matter tracts connecting the prefrontal and temporal cortices. Reduced white matter integrity along the inferior fronto-occipital fasiculus, left hippocampus and the inferior longitudinal fasiculus were observed with Jacobson et al. (2010) suggesting that aberrant signalling and axonal integrity in the temporal and occipital lobes in particular may contribute to the experience of positive symptoms.

While the ABD Study focused on positive symptoms such as self-reported hallucinations and delusions in order to classify participants as at-risk or not, previous studies have focused on negative symptoms of psychosis and their association with EEG resting state anomalies in at-risk groups. Zimmermann et al. (2010) found positive correlations between EEG power in the delta, theta and beta frequency bands and negative symptoms of psychosis in an ARMS group who later transitioned to psychosis.

The results of these correlations were similar to those previously reported by Gschwandtner et al. (2009) in a FEP group, and opposite to the ARMS group who did not later transition to psychosis. Due to the heterogeneous nature of schizophrenia spectrum disorders it is likely that alterations in resting state EEG may emerge as a result of negative rather than positive symptoms of the disorder. Further studies are necessary to investigate the link between positive symptoms and resting state EEG changes in clinically at-risk groups and in the non-clinical psychosis phenotype.

Working memory deficits have been proposed as a core deficit in schizophrenia and a trait marker for schizophrenia spectrum disorders (Goldman-Rakic, 1994; Wood et al., 2003). Although the groups in Chapter 3 of the present thesis did not differ on measures of verbal or non-verbal working memory, deficits in spatial working memory have consistently been reported in at-risk groups including UHR and ARMS groups (Smith et al., 2006), adolescent-onset schizophrenia (Vance et al., 2006; 2007), groups reporting PLEs and community-based samples of adolescents who met formal criteria for prodromal syndromes (Kelleher et al., 2012c; 2012d). An Implicit Spatial Memory Task and a Spatial Working Memory Task were employed in Chapters 5 and 6 of the present thesis, respectively, in order to further investigate spatial memory functioning in adolescents reporting PLEs. Kelleher et al. (2012c; 2012d) previously reported impaired non-verbal working memory in a larger sample of 212 adolescents from the ABD Study using the Wechsler memory scale- spatial span in addition to impaired non-verbal speed of processing, indicating that spatial working memory may also be a sensitive marker of neurodevelopmental dysfunction in adolescent groups reporting PLEs. Spatial processing and spatial working memory will be discussed further in section 7.2.3.

7.2.3 Psychotic-Like Experiences and Auditory Oddball Paradigms

The present thesis reports within group differences in the P300 ERP recorded at fronto-central scalp sites in adolescents reporting PLEs. While a larger ERP amplitude was observed for target tones compared to non-target tones in the control group, the increased P300 amplitude to target tones relative to non-target tones was absent in the PLEs group. This indicates that the groups may have processed the tones in different ways; however, in the absence of a between-groups difference being observed on this task, the Active Auditory Oddball Task cannot be proposed as a potential trait marker of psychotic symptoms in the general population. In a bigger sample a between-groups difference in amplitude may have emerged.

Recently, reduced P300 amplitude has been reported in prodromal populations. Van der Stelt et al. (2005) reported P300 amplitude reductions in prodromal cases which were of similar severity to those found in patients with recent onset, as well as chronic schizophrenia. Özgürdal et al. (2008) have also reported reduced amplitude of the P300 waveform in participants with ARMS for schizophrenia. They state that their finding of reduced P300 amplitude in prodromal participants is in line with other studies that investigated the trait aspect of P300 amplitude in healthy siblings or biological relatives of schizophrenia patients, as well as high-risk individuals with schizotypal personality trait where reductions of P300 amplitude were also found (Blackwood et al., 1999; Mannon et al., 2001).

To date no other studies have reported reduced P300 in adolescents reporting PLEs during active auditory oddball tasks. While reduced P300 amplitude has been observed in ARMS and putatively prodromal groups, because prodromal populations are generally help-seeking individuals who may already be reporting symptoms which have reached a level which is causing distress, the participants in these studies may be

further on the developmental trajectory to a psychotic disorder, and this may explain why reduced P300 in this population has been observed. The reduced P300 amplitude reported by studies such as van der Stelt et al. (2005) and Özgürdal et al. (2008), for example, may reflect state influences or progression of a disorder. The usefulness of active auditory oddball tasks such as the one used in the present thesis as a trait marker for psychotic disorders may be limited due to the effects of state influences on the amplitude of the P300 component elicited during these tasks.

It has been proposed that the reduced P300 observed in prodromal groups may reflect abnormalities in temporal regions which are the main generators of P300 amplitude at Pz, and abnormalities in temporal regions have been linked to positive symptoms (Mc Carley et al., 1995, Özgürdal et al., 2008). It is possible that as positive symptoms progress to a level which begins to cause distress, alterations in temporal regions may also progress which in turn may influence the amplitude of the P300 ERP component recorded during active auditory oddball tasks. Further research is necessary in order to determine the exact nature of trait and state influences on the P300 observed during active oddball tasks.

Murphy et al. (2013) employed a duration deviant *passive* auditory oddball task and reported reduced amplitude of the mismatch negativity (MMN) component at frontal and temporo-parietal areas in line with previous reports of reduced MMN amplitude in schizophrenia patients (Umbricht & Krljes, 2005), FEP (Atkinson et al., 2011) and groups defined as clinically at-risk for psychotic disorders (Shin et al., 2009; Atkinson et al., 2011). While the P300 elicited by *active* auditory oddball tasks is likely to reflect context updating, stimulus evaluation or allocation of attention resources to stimuli which are actively attended to (Donchin, 1979; Desmedt, 1981; Posner, 1975), the MMN waveform is thought to be a measure of preattentive information processing

or sensory memory (Näätänen, 1995). Due to evidence that the P300 elicited during active oddball paradigms may reflect state as well as trait influences while the MMN has been suggested as a reliable and robust trait marker for schizophrenia, it is likely that differences in the MMN waveform may be better suited for detecting risk for psychosis in the non-clinical psychosis phenotype.

It is likely that too few trials were included in the Active Auditory Oddball Task used in Chapter 4 of the present thesis, and more trials could have produced a more distinct P300 component over parietal scalp location. The task was designed based on a study reported by Bramon et al. (2005) which included 400 trials (20% target tones); this was shortened due to testing and timing constraints and the age of the participants in the present study. MMN paradigms may also be more useful for younger populations due to their passive nature; the MMN waveform can be observed without the participant attending to stimuli, thus eliminating issues with fatigue during testing by making the task less tedious for the participant.

In addition, the N100 AEP component elicited to non-target tones was greater for the PLEs group than the control group in Chapter 4 of the present thesis. This indicates that the groups differed in processing the more frequent non-target tones in the task. The N100 AEP is thought to arise from generators in the frontal and parietal cortices, as well as sources in the primary auditory cortex, and marks a crucial auditory sensory processing period (Giard et al., 1994; Molholm et al., 2006; Foxe et al., 2010). The N100 is thought to be modulated by selective attention (Hillyard, Hink, Schwent & Picton, 1973; Hillyard, Mangun, Woldorff & Luck, 1995). The increased N100 to non-target stimuli in the PLEs group observed in the present chapter may indicate increased attention to irrelevant stimuli. While this did not impair the behavioural performance of the PLEs group on the present task, the persistence of attention to task irrelevant stimuli

may prove detrimental if this continues throughout development. Selective attention deficits have been linked to positive symptoms and reality monitoring failure in schizophrenia (Brébion, Smith, Gorman & Amador, 1996).

This result adds to previous findings of reduced MMN amplitude by Murphy et al. (2013) on a passive auditory oddball task, by uncovering group differences on an early sensory ERP component observed during an active task. This finding is in contrast to previous reports of a reduced N100 AEP component to non-target tones in schizophrenia, FEP and first-degree relatives of schizophrenia patients relative to controls (O'Donnell et al., 2004; Ahveninen et al., 2006; Foxe et al., 2010). The usefulness of the auditory N100 component has been questioned in a critical review by Rosburg et al. (2008) who stated that more than half of the studies on unmedicated patients reviewed were unable to show N100 amplitude reductions. Foxe et al. (2010) have also acknowledged that the picture is still quite unclear, with a number of studies confounded by the inclusion of first-degree relatives with existing axis I disorders (Force, Venables & Sponheim, 2008; Turetsky et al., 2008). Given these conflicting findings, more research is necessary with schizophrenia and FEP groups, as well as clinical risk groups, in order to determine influence of psychotic disorder on the N100 AEP component before it could be suggested as a trait marker for disorder and deemed useful in general population studies such as the ABD Study. In conclusion, the P300 and N100 AEP components elicited during active tasks may not be as useful as the MMN component which is observed during passive tasks in the search for biomarkers of psychotic disorder in the general population.

7.2.4 Psychotic-Like Experiences and Spatial Processing

Working memory has been shown to be a reliable trait marker for psychotic illness. The P300 ERP component elicited during the spatial working memory task in the present thesis was reduced in the PLEs group across all conditions of the task even though the groups did not differ in terms of their behavioural performance on the task (i.e. the groups did not differ on accuracy and reaction times). This finding, in conjunction with reported deficits in spatial working memory from the overall ABD Study (Kelleher et al., 2012c; 2012d), indicates that spatial working memory may be a useful trait marker for disorder in adolescents reporting PLEs. The present thesis expands existing findings of reduced P300 amplitude in adolescent onset schizophrenia (Haenschel et al., 2007) by revealing reduced P300 amplitude in the treatment-naive extended psychosis phenotype. This reduction in P300 amplitude may reflect disrupted neural processes underlying stimulus evaluation and template matching during retrieval in the PLEs group. Reduced amplitude of the P300 component, particularly the late P300 at high load, observed in the present thesis could also reflect an underlying reduced attention and memory retrieval capacity in individuals with PLEs.

Typically, working memory retrieval is thought to engage a network of areas including the prefrontal and parietal cortices (Wagner & Smith, 2003). D'Esposito (2007) suggests that working memory is not localised to a single brain region, but may involve functional interactions being the prefrontal cortex and the rest of the brain. The reduced P300 component indicates that an altered network may be engaged in this group during spatial working memory retrieval. Jacobson et al. (2010) found evidence of disrupted prefrontal-temporal connectivity in a group of adolescents reporting PLEs, and evidence for parietal dysfunction at the earliest stages of psychosis has also been proposed by Whalley et al. (2005).

While spatial working memory may specifically be impaired in adolescents reporting PLEs, spatial processing on other tasks such as object-locations tasks may remain unimpaired. This may be due to different networks underlying performance on different measures. While the Implicit Spatial Grid Task has been reported to engage a network of frontal, parietal and temporal areas, subdivisions of the parahippocampal gyrus have also been implicated, particularly during retrieval on this task (Murphy et al., 2009). It is possible that performance on the Implicit Spatial Grid Task may be more dependent on the structure of the hippocampus given its link with object-location memory (Save et al., 1992; Lee et al., 2005). Velakoulis et al. (2006) found that patients with chronic schizophrenia had bilaterally smaller hippocampi and that left-sided hippocampal volume reduction is seen in first-episode patients with schizophrenia. They examined two UHR groups and found that neither the UHR group who converted to psychosis, nor the UHR group who did *not* covert to psychosis, exhibited hippocampal volume changes. Aspects of spatial memory such as object location memory or implicit spatial memory may not be impaired until a psychotic disorder has already emerged and been diagnosed. In contrast, spatial working memory deficits may be as a result of dysfunction in the frontal and parietal cortices and may emerge at an earlier stage in the disorder.

7.2.5 Psychotic-Like Experiences, General Functioning and Risk for Psychopathology

Lower C-GAS scores were consistently observed in the PLEs group indicating lower general functioning in this group compared to the control group. Despite this group difference, all participants were still attending mainstream schools with normal occupational functioning. Recently, Kelleher and colleagues have highlighted the

importance of self-reported psychotic symptoms during adolescence in terms of risk for a number of disorders, not exclusively psychotic disorders. The prevalence of reported psychotic symptoms during adolescence has also been examined by a number of studies investigating the link between sub-clinical psychotic symptoms and risk for psychosis and other disorders.

Although an association between reported PLEs (or psychotic symptoms) during childhood and the later development of a psychotic disorder has been reported (e.g. Poulton et al., 2000; Welham et al., 2009b), a large proportion of PLEs reported in childhood are transient in nature. Kelleher et al. (2012a) reported data from 2 studies of early adolescents and found that while 21 to 23 percent of 11 to 13 years old reported PLEs, this figure dropped to 7 percent in participants from their mid-adolescence group aged 13 to 16 years. Similarly reports of the prevalence of PLEs during adolescence have been published by Yoshizumi et al. (2004) who reported that 21 percent of 11 to 12 year olds reported experiencing hallucinations on a questionnaire. In a nationally representative Australian sample, Scott et al. (2009) reported that 8.4 percent of adolescents aged 13 to 17 years experienced auditory and/or visual hallucinations. Horwood et al. (2008) found that nearly 40 percent of 12 year olds in their sample self-reported at least one or more psychotic symptoms in response to questions about 12 psychotic items; when the same children were assessed using a semi-structured clinical cross-examination, this figure fell to 13.7 percent. A recent meta-analysis of prevalence studies of psychotic symptoms in young people carried out by Kelleher et al. (2012b) demonstrated a median prevalence rate of 17 percent in children aged 9 to 12 years and 7.5 percent in adolescents aged 13 to 18 years.

Kelleher et al. (2012a) report that adolescents from the general population who experience psychotic symptoms (reported through questionnaires and clinical

interviews) may be at increased risk of having multiple co-occurring diagnoses thus highlighting the relevance of these symptoms in terms of risk for anxiety and affective disorders as well as psychotic disorders. PLEs may be indicative of higher risk for a number of disorders including anxiety, affective and behavioural disorders and the persistence of PLEs through mid-adolescence may be a risk marker for psychopathology. In addition, it was shown that psychotic symptoms were associated with increased risk of multiple pathology (having more than one DSM diagnosis), and with increasing age psychotic symptoms were increasingly predictive of psychopathology. Indeed, this indicates that although self-reports of psychotic symptoms in childhood and early adolescence may be transitory in nature and may occur in normal development, the persistence of these symptoms in later adolescence may become increasingly associated with a higher risk of developing a psychotic disorder. Similarly, a number of studies have reported a link between psychotic symptoms and depression (Nishida et al., 2008; Varghese et al., 2011) and parent-reported behavioural and emotional symptoms (Bartels-Velthuis et al., 2011).

Reports of psychotic symptoms during adolescence have also been associated with self-harm and risk for suicidal behaviour in recent studies (Kelleher et al., 2012e; in press). Kelleher et al. (2012e) report that while psychotic symptoms were associated with a 10-fold increase in odds of suicidal behaviour (suicidal ideation, plans, or acts) in early (11 to 13 years) and middle (13 to 15 years) adolescence, the risk of suicidal behaviour was further increased when psychotic symptoms were experienced by those participants with a depressive disorder. Adolescents with depressive disorders who reported psychotic symptoms were at 14-fold increased odds of suicidal behaviour (plans and acts) than those with depressive disorders who did not report psychotic symptoms. Among those who reported suicidal ideation, those who also reported psychotic symptoms were at nearly 20-fold increased odds of suicide plans or acts.

7.3 Implications of the Findings

7.3.1 Practical and Theoretical Implications

Traditionally risk for schizophrenia has been explored in groups considered to be at genetic risk for developing the disorder, i.e. first degree relatives of patients with a schizophrenia spectrum disorder. While the genetic high-risk approach is useful, more recently research has begun to look at populations considered to be at 'symptomatic' rather than genetic risk for disorder. Adolescents reporting PLEs in the general population represent the non-clinical psychosis phenotype and provide an opportunity to study symptomatic risk for psychosis during adolescence and within the context of development.

A great deal of research has been carried out in recent years with prodromal groups with the suggestion of including a risk for psychosis category in the DSM-5, due for publication in 2013. A DSM-5 Psychosis Work Group was appointed to examine the evidence for and against inclusion of the "Attenuated Psychosis Syndrome" (the proposed criteria for this syndrome are outlined in Table 7.2). It has recently emerged that a psychosis risk syndrome will not be included in this upcoming edition of the DSM. Prodromal groups are typically help-seeking individuals who present with prodromal symptoms of psychosis but do not meet the criteria for a diagnosis of a psychotic disorder (see Appendix I for a full list of prodromal symptoms).

The fact that prodromal groups are generally help-seeking individuals who are distressed by their symptoms sets them apart from those who report psychotic symptoms in the general population but are often not distressed by these symptoms and do not seek help for them. The decision not to include the "Attenuated Psychosis Syndrome" in DSM-5 was met with favour by many researchers with some suggesting

that this group are too heterogeneous in presentation and that a diagnosis of this syndrome without future conversion to a psychotic disorder may lead to stigmatisation and unnecessary treatment with anti-psychotic medication in some cases (Fusar-Poli & Yung, 2012). Dutta et al. (2007) suggest that while the DSM-IV criteria for schizophrenia include the prodromal phase as a construct, it best describes a retrospective concept because it cannot be defined until there is a first-episode or established psychotic episode. Others agree that participants in many studies should be considered as "at-risk" rather than within the prodrome phase (Ballon et al., 2008). Murray and Jones (2012) state that the presence of psychotic symptoms in themselves should not necessarily be seen as a prodrome to psychotic illness as the most common psychiatric outcomes for people young people who experience psychotic symptoms are more common mental disorders rather than severe psychotic illnesses.

A number of recent publications have highlighted the fact that the non-clinical and clinical psychosis phenotypes share a number of risk factors (Kelleher & Cannon, 2011) emphasising the usefulness of this group as a "symptomatic" at-risk group. Recent research has identified a number of differences in ERPs between adolescents reporting PLEs and age-matched controls on tasks which examine the electrophysiological correlates of processing in areas proposed as trait markers for schizophrenia. A reduction of the P300 ERP component has been reported on a receptive language test (Murphy et al., 2012). Reduced MMN amplitude has been reported on a duration deviant passive auditory oddball task (Murphy et al., 2013). Disrupted error monitoring has also been reported by Laurens et al. (2010) who provided evidence for reduced error-related negativity (ERN) in adolescents presenting a triad of putative antecedents of schizophrenia, using a Go/No Go task. The triad antecedents of schizophrenia included PLEs, as well as speech and/or motor development lags/problems and internalizing, externalizing, and/or peer-relationship

problems in the clinical range. Relative to typically developing children, children who presented with a triad of putative antecedents of schizophrenia were characterized by reduced ERN amplitude but unaffected correct response negativity (CRN), later error-positivity (Pe), and correct response positivity (Pc) amplitudes. No group differences were observed in the latency of any of the components.

Table 7.2: *Proposed Criteria for Attenuated Psychosis Syndrome – adapted from Carpenter and van Os (2011).*

Criteria: All six of the following:	
A	Characteristic symptoms: at least one of the following in attenuated form with intact reality testing, but of sufficient severity and/or frequency that it is not discounted or ignored: (1) delusions (2) hallucinations (3) disorganised speech
B	Frequency/currency: symptoms in criterion A must be present in the past month and occur at an average frequency of at least once per week in the past month
C	Progression: symptoms in criterion A must have begun in or significantly worsened in the past year
D	Distress/disability/treatment seeking: symptoms in criterion A are sufficiently distressing and disabling to the patient and/or parent/guardian to lead them to seek help
E	Symptoms in criterion A are not better explained by any DSM-5 diagnosis, including substance-related disorder
F	Clinical criteria for any DSM-5 psychotic disorder have never been met

The present thesis provides further evidence of the usefulness of employing community-based samples of adolescents (i.e. the non-clinical psychosis phenotype) to study the developmental trajectory to schizophrenia and adds to the growing body of research in this area. The present thesis adds to reports of spatial working memory impairments in adolescents reporting PLEs (Kelleher et al., 2012c) by providing electrophysiological evidence that the neural circuits underlying retrieval on a spatial working memory task may be disrupted in adolescents with PLEs even before behavioural impairment may arise. The present thesis also shows that this impairment may be specific to spatial working memory, as spatial processing and implicit spatial memory (as assessed by the Implicit Spatial Memory Task) were unimpaired.

The findings of the present thesis also indicate that despite the fact that adolescents reporting PLEs may perform more poorly than controls on neuropsychological tests assessing functions such as speed of processing, no differences are present in resting state EEG recordings of absolute power in the delta, theta or alpha frequency bands. The P300 elicited to target tones during the Active Auditory Oddball Task did not differ between groups in the present thesis; however, the control group showed a within-groups difference in the amplitude of the P300 at fronto-central sites indicating that the groups may have processed the tones differently. The amplitude of the N100 AEP elicited to non-target tones during the Active Auditory Oddball Task was greater for the PLEs group than the controls group; this indicates that the PLEs group processed the more frequent non-target tones differently than the control group.

7.3.2 EEG data and ERPs as Biomarkers

When exploring biological markers associated with risk for disorders it is important that tasks are chosen in which group differences have previously been reported at all stages

of the disorder. In relation to psychotic disorders, in order for a particular cognitive impairment, imaging or ERP finding to be considered as a trait marker for the disorder it would need to be observed in severe psychotic illness, FEP and groups considered to be at clinical high risk for developing a psychotic disorder. Additional support can also be gained from studies of populations at genetic risk for disorder. Tasks which have been shown to be reliable trait markers for disorder in these clinical and at-risk groups need to be employed when considering risk factors in general population studies. Furthermore, exploring potential biomarkers of psychotic illness in clinical at-risk groups who later convert to a disorder versus those for which psychotic symptoms are transitory is vital.

While the present thesis reports reduced amplitude of the P300 ERP component on a Spatial Working Memory Task in the PLEs group, the groups did not differ on amplitude of the P300 elicited to target tones in the Active Auditory Oddball Task as anticipated. The P300 waveform has been associated with a number of different cognitive processes including context updating (Donchin, 1979), termination of stimulus evaluation (Desmedt et al., 1980), the allocation of attentional resources (Posner, 1975) or the formation of a decision (O'Connell, Dockree & Kelly, 2012). While the P300 elicited during the Spatial Working Memory Task can be attributed to working memory retrieval, the P300 elicited during Active Auditory Oddball Tasks is not as well understood. While reduced amplitude of the P300 is one of the most widely reported findings in the literature on schizophrenia, the majority of tasks report this reduced P300 amplitude on active oddball tasks. Tasks which investigate the effects of working memory capacity on this component may be better suited in the search for biomarkers of risk for disorder in adolescent populations reporting PLEs.

7.4 Strengths and Limitations of the Thesis and Future Directions

The present thesis is the first study to investigate the electrophysiological correlates of auditory processing using an active oddball task and spatial memory in a community-based sample of adolescents reporting PLEs. Follow-up studies are necessary in order to determine the link between reports of PLEs in adolescent populations and risk for disorder. As the majority of PLEs are transitory in nature, it is likely that a number of co-occurring risk factors may result in a later diagnosis of a psychotic disorder. Research carried out by Laurens et al. (2010) for example, categorises adolescents as "at-risk" based on a triad of putative antecedents of schizophrenia which include speech and/or motor development lags/problems and internalizing, externalizing, and/or peer-relationship problems in the clinical range in addition to reports of PLEs. Follow-up studies using neuropsychological tests, EEG and imaging data may further determine which combination of risk factors best distinguish those who later develop a psychotic disorder from those who do not.

In line with the risk model for psychosis put forward by Dutta et al. (2007 – see Figure 1.2, section 1.3.2), it is possible that a number of pro- and anti-psychotic factors contribute to an individual's likelihood of developing a psychotic disorder. While pro-psychotic factors such as biological vulnerability and cannabis use may increase an individual's risk of developing a psychotic disorder, it is also possible that anti-psychotic factors may decrease this risk. While stress may be considered as a pro-psychotic factor, individual resilience or the ability to cope with stress may act as a protective factor in terms of risk for psychosis. Factors such as self-esteem and social support may also act as protective factors in addition to coping skills. Low self-esteem has been has been associated with vulnerability for psychotic disorders and distress

associated with the onset of psychotic symptoms in FEP (Vracotas, Schmitz, Joober & Malla, 2007; Romm et al., 2011). Social support has been linked to lower levels of positive symptoms in a three-year follow-up of FEP patients (Norman et al., 2005). It has been suggested that coping styles may also play a role in transition along the psychosis continuum (Krabbendam, Myin-Germeys, Bak & van Os, 2005). Emotion-oriented coping is associated with the persistence of subclinical psychotic experiences in adolescents from the general population (Lin et al., 2011). Longitudinal studies are particularly helpful in determining the link between coping styles and the persistence or reduction of subclinical symptoms. Longitudinal research may also result in the development of interventions which target coping styles (e.g. task-oriented coping) to prevent the persistence of subclinical symptoms. It is important that anti-psychotic factors are taken into account in future studies.

One of the strengths of the present thesis is that reports of PLEs were determined by clinical interviews rather than based solely on self-report measures, given that higher reports of PLEs are often observed on self-report measure than interviews (Horwood et al., 2008). The clinical interviews carried out employed the K-SADS-PL which allowed information relating to all Axis-I psychiatric disorders to be collected. Positive psychotic symptoms such as delusions and hallucinations were the focus of the ABD Study due to their reported association with risk for disorder in adulthood (Poulton et al., 2000; Welham et al., 2009b). A limitation of the present study is that negative psychotic symptoms were not specifically assessed using suitable questionnaires and as a result negative symptoms cannot be taken into account in analysis.

While the ABD Study recruited participants from a number of local schools in Co. Kildare and north Co. Dublin, the schools contacted were all large, mixed-gender,

state primary schools. No fee-paying or private schools were included in the study and none of the schools were from areas which were particularly disadvantaged. Given that increased incidences of social deprivation, income inequality and population density have all been associated with increased incidences of nonaffective psychosis, the study sample may not have been representative of adolescents from less well off areas.

A large number of tasks were included for EEG testing in the ABD Study. While this allowed for data to be collected using a wide range of tasks, the sample sizes for each of the tasks outlined in the present thesis were small as a result, reducing the statistical power of each study. While group differences were observed on a number of EEG tasks used in the ABD Study, replication of the findings from the present thesis in larger samples is necessary. More EEG testing is needed using working memory and oddball paradigms to further investigate the electrophysiological correlates of these processes in adolescents reporting PLEs. Tasks which probe speed of processing deficits could also be designed for use with fMRI and EEG.

No group differences were observed in terms of accuracy or reaction times on the Active Auditory Oddball Task, the Implicit Spatial Memory Task or the Spatial Working Memory Task. Despite the absence of between-groups differences in the behavioural data, an increased N100 AEP component was observed in the Active Auditory Oddball Task to non-target tones and a decreased P300 ERP component was observed in the Spatial Working Memory Task. Increased variability was observed in the reaction time scores for the PLEs group on the Spatial Working Memory Task. No time limit for responses was enforced in the Spatial Working Memory Task employed in the present thesis, test stimuli remained onscreen until participants made their response. Manipulation of the task conditions, such as a time limit applied for response selection in this task, may reveal the conditions under which processing is compromised

and impairments in the PLEs group are revealed. If the groups were under time pressure to complete the test trials in this task, a trade-off between speed and accuracy may have been observed in the PLEs group. Similarly, manipulation of the inter-stimulus interval and other testing conditions used in each task may provide further insight into processing in the PLEs group. Stimulus intensity, inter-stimulus interval, arousal and attention have all been shown to affect the N100 AEP and P300 components (Polich, Ellerson & Cohen, 1996; Rosberg et al., 2008).

7.5 Concluding Remarks

Schizophrenia is a heterogeneous disorder with a varied range of positive, negative and cognitive symptoms leading to diagnosis. Undoubtedly a variety of risk factors contribute to susceptibility to schizophrenia and other psychotic disorders including genetic, obstetric, early developmental and neuroanatomical risk factors, as well as social risk factor, substance abuse and exposure to trauma during early childhood. Those who report psychotic symptoms in general populations studies (i.e. the non-clinical psychosis phenotype) have been shown to share many of the same risk factors as the clinical psychosis phenotype (schizophrenia). The non-clinical psychosis phenotype approach allows us to explore the possible risk factors and biomarkers for psychotic disorders prior to the onset of disorder, therefore increasing our understanding of the processes and changes in neuropsychological functioning and brain anatomy underlying these disorders.

The present thesis adds to our knowledge of PLEs in early adolescence by reporting reduced P300 during spatial working memory retrieval in this group while

spatial processing and memory as assessed by an Implicit Spatial Memory Task remain unimpaired. The finding of reduced P300 in the PLEs group on the Spatial Working Memory Task adds to previous findings of impaired spatial working memory in this group reported by Kelleher et al. (2012c), and expands existing findings of reduced P300 amplitude in adolescent onset schizophrenia (Haenschel et al., 2007) by revealing reduced P300 amplitude in the treatment-naïve extended psychosis phenotype. Results from the Active Auditory Oddball Task are less clear however, with no group difference observed for the P300 timeframe as anticipated, indicating that electrophysiological correlates of spatial working memory rather than active auditory oddball tasks may be more useful tasks to employ in future research in this area.

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Appendices

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Appendix I: DSM-III-R criteria necessary for a diagnosis of Schizophrenia, Schizophreniform Disorder and Brief Reactive Psychosis and Prodromal and Residual Symptoms

Schizophrenia	A.	Characteristic psychotic symptoms of the active phase. Either (1), (2) or (3) for **at least one week** (or less of symptoms are successfully treated): 1. Two of the following (a) Delusions, (b) Prominent hallucinations (throughout the day for several days or several times a week for several weeks and each hallucinatory experience is not limited to a few brief moments), (c) Incoherence or marked loosening of associations, (d) Catatonic behaviour, (e) Flat or grossly inappropriate affect 2. Bizarre delusions (i.e. involving a phenomenon that the individuals subculture would regard as totally implausible e.g. thought broadcasting, being controlled by a dead person) 3. Prominent hallucinations (as defined in 1 [b] above) of a voice with content having no apparent relation to depression or elation, or a voice keeping up a running commentary on the individual's behaviour or thoughts, or two or more voices conversing with each other
	B.	During the course of the disturbance, functioning in such areas as work, social relations, and self-care is markedly below the highest level achieved prior to the disturbance (or with onset in childhood or adolescence, failure to achieve expected level of social development)
	C.	Major depressive or manic syndrome, if present during the active phase of the disturbance (symptoms in A), was brief relative to the duration of the disturbance. Schizoaffective disorder and mood disorder with psychotic features ruled out.
	D.	Continuous signs of disturbance for **at least six months**. The six-month period must include an active phase (of at least one week, unless symptoms have been successfully treated) during which there are psychotic symptoms characteristic of schizophrenia (symptoms in A), and either a prodromal or residual phase if the active phase was of less than six-months duration.
	E.	It cannot be established that an organic factor initiated and maintained the disturbance
	If there is a history of Autistic Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present	
Prodromal and Residual Symptoms	1.	Marked social isolation or withdrawal
	2.	Marked impairment in role (functioning as wage-earner, student or homemaker)
	3.	Marked peculiar behaviour (e.g. collecting garbage, talking to self in public, hoarding food)
	4.	Marked impairment in personal hygiene and grooming, blunted, flat or inappropriate affect
	5.	Digressive, vague, over elaborate, or circumstantial speech, or poverty of speech, or poverty of content of speech
	6.	Odd beliefs or magical thinking influencing behaviour and inconsistent with subcultural norms e.g. superstitiousness, belief in

		clairvoyance, telepathy, sixth sense, "others can feel my feelings", overvalued ideas, ideas of reference
	7.	Unusual perceptual experience e.g. recurrent illusions, sensing the presence of a force or person not actually present
	8.	Marked lack of initiative, interests or energy
Schizophreniform Disorder	A.	Meets criteria A and C of Schizophrenia
	B.	An episode of the disturbance (including prodromal, active and residual phase) lasts less than six months
	C.	Does not meet the criteria for Brief Reactive Psychosis and not due to an Organic Mental Disorder
Brief Reactive Psychosis	A.	Presence of incoherence or marked loosening of associations, delusions, hallucinations, or catatonic or disorganised behaviour
	B.	Emotional turmoil (e.g. rapid shifts from one intense affect to another)
	C.	Appearance of the symptoms in A and B shortly after, and apparently in response to, one or more events that singly or together, would be markedly stressful to almost anyone in a similar situation
	D.	Absence of prodromal symptoms of Schizophrenia
	E.	Duration of episode not more than one month, with eventual return to premorbid level of functioning
	F.	Not due to a Psychotic Mood Disorder

Appendix II: DSM-IV criteria necessary for a diagnosis of Schizophrenia, Schizophreniform Disorder and Brief Reactive Psychosis

Schizophrenia	A. Characteristic psychotic symptoms: At least two of the following, each present for a significant portion of time during a one month period (or less if symptoms successfully treated): 1. Delusions, 2. Hallucinations, 3. Disorganised speech (e.g. frequent derailment, incoherence, or marked loosening of associations) 4. Grossly disorganised or catatonic behaviour, 5. Negative symptoms (e.g. affective blunting, alogia or avolition) Note: Only one symptom is required if delusions are bizarre or hallucinations consist of a voice keeping a running commentary on the person's behaviour or thoughts, or two or more voices conversing B. During the course of the disturbance, functioning in such areas as work, social relations, and self-care is markedly below the highest level achieved prior to the disturbance (or with onset in childhood or adolescence, failure to achieve expected level of social development C. Continuous signs of disturbance for at least six months. The six-month period must include an active phase (of at least one week, unless symptoms have been successfully treated) during which there are psychotic symptoms characteristic of schizophrenia (symptoms in A), and either prodromal or residual phase if the active phase was of less than six-month duration D. Major depressive or manic syndrome, if present during the active phase of the disturbance (symptoms in A), was brief relative to the duration of the disturbance. Schizoaffective disorder and mood disorder with psychotic features ruled out. E. Organic and pharmacological etiology ruled out
Schizophreniform Disorder	A. Meets criteria A, D, and E of Schizophrenia B. An episode of the disturbance (including prodromal, active and residual phase) lasts at least one month but less than six months
Brief Reactive Psychosis	A. The presence of disorganised speech, delusions, hallucinations, or catatonic or disorganised behaviour B. Duration of episode at least one day and no more than one month, with eventual return to premorbid level of functioning C. Not due to a psychotic Mood Disorder, Schizophrenia, organic cause, or psychopharmacological etiology Specify if: With Marked Stressor(s); Without Marked Stressor(s); or Post-partum onset

Appendix III: Information leaflets distributed in schools

Website: www.beaumont.ie

Ospidéal Beaumont

BEAUMONT HOSPITAL
P. O. Box 1297 Beaumont Road Dublin 9
Telephone: 809 3000 / 837 7755 Facsimile: 837 6982

Adolescent Brain Development Study
Education and Research Centre
Royal College of Surgeons in Ireland
Beaumont Hospital
Dublin 9
Tel: 01-809 3855

Parent/Guardian Information Sheet

Dear Parent,

Your child is being invited to take part in a research study investigating brain function and development in early adolescence. We can learn a lot just by asking some questions and carrying out some simple and fun tasks. As part of this, your child will get to experience some of the exciting work being carried out in science and medicine.

You should clearly understand what participation in this study involves before you agree to allow your child to take part – this process is known as Informed Consent. Please take the time to read this information sheet and feel free to contact us if you have any further questions. You may change your mind at any time (before the study starts or at any time during the study) for whatever reason without having to justify your decision.

Who is organising and funding this study?

This study is funded by the Health Research Board and is being run by Professor Mary Cannon, a Consultant at Beaumont Hospital and Associate Professor with the Royal College of Surgeons in Ireland.

What will my child have to do in the study?

If you and your child both say 'yes', your child can take part in the study. To understand how the adolescent brain develops, we would like to find out about your child's

thoughts and their experiences of the world around them. We would also ask them to do simple pen-and-paper tasks that will test attention and problem-solving abilities. This will all be done by distributing a questionnaire, which your child can fill in by themselves. This will take about 20 minutes and will be carried out in your child's classroom together with the rest of the children who have agreed to participate. Children will work independently and will not see each other's answers.

What will you do with the information?

All information will be used purely for research purposes and will not be passed on to other bodies. Your child's details will remain entirely confidential and they will never be identified with this information.

What else will my child need to do?

That's it! We will, however, be carrying out a further study which would involve you and your child coming to see us for a morning or afternoon during the summer holidays. If you and your child would like to hear more about our other study please leave your contact details on the consent form and we will send on full details.

What should I do now?

Once you have decided whether you consent or do not consent to your child taking part, please sign the Consent Form and return it to us. We ask you to return this form whether **or not** you choose to consent.

Thank you for your help in our work

If you have any questions, please feel free to contact the doctor in charge:

Professor Mary Cannon,

Education and Research Centre

Royal College of Surgeons in Ireland and Beaumont Hospital

Telephone: 01-809-3855

Appendix IV: Consent forms distributed in schools

ABD Study

Department of Psychiatry

RCSI Education and Research Centre

Beaumont Hospital

Tel: 01-8093855

Parent/Guardian Consent Form

I confirm that:

- I have read and understood the information sheet about the study
- I can contact the doctor in charge with any questions
- I understand that all the information about my child will be kept strictly confidential
- I understand that my child's participation in this study is entirely voluntary and that I may withdraw my child from this study at any time
- I agree for my child to take part in this study Yes ☐ No ☐

Your full name: .....

Your signature: .....

Today's date: .....

Your child's name: .....

Please tick this box and include contact details of you would like to hear more about the second part of the study ☐

Contact Details (Address/Phone number):

.....

.....

.....

Appendix V: ABD Study Questionnaire including items from the SDQ and the 7-item APSS

Adolescent Brain Development Study Questionnaire

Please tick one box for each question

	No, Never	Maybe	Yes, Definitely
I try to be nice to other people. I care about their feelings	☐	☐	☐
I am restless, I cannot stay still for long	☐	☐	☐
I get a lot of headaches, stomach-aches or sickness	☐	☐	☐
I usually share with others, for example CDs, games, food	☐	☐	☐
I get very angry and often lose my temper	☐	☐	☐
I would rather be alone than with people of my age	☐	☐	☐
I usually do as I am told	☐	☐	☐
I worry a lot	☐	☐	☐
I am helpful if someone is hurt, upset or feeling ill	☐	☐	☐
I am constantly fidgeting or squirming	☐	☐	☐
I have one good friend or more	☐	☐	☐
I fight a lot, I can make other people do what I want	☐	☐	☐
I am often unhappy, depressed or tearful	☐	☐	☐
Other people my age generally like me	☐	☐	☐
I am easily distracted, I find it difficult to concentrate	☐	☐	☐
I am nervous in new situations. I easily lose confidence	☐	☐	☐
I am kind to younger children	☐	☐	☐
I am often accused of lying or cheating	☐	☐	☐
Other children or young people pick on me or bully me	☐	☐	☐
I often offer to help others (parents, teachers, children)	☐	☐	☐
I think before I do things	☐	☐	☐
I take things that are not mine from home, school or elsewhere	☐	☐	☐
I get along better with adults than with people my own age	☐	☐	☐
I have many fears, I am easily scared	☐	☐	☐
I finish the work I'm doing. My attention is good	☐	☐	☐
Some people believe that their thoughts can be read by another person. Have other people ever read your mind?	☐	☐	☐
Have you ever had message sent <u>just</u> to you through TV or radio?	☐	☐	☐
Have you ever felt that you were under the control of some special power?	☐	☐	☐
Have you ever heard voices or sounds that no one else can hear?	☐	☐	☐
Have you ever seen things that other people could not see?	☐	☐	☐
Have you ever felt that you have <u>extra-special</u> powers?	☐	☐	☐
Have you ever thought that people are following you or spying on you?	☐	☐	☐

Thank you very much for your help!

Appendix VI: Interview and neuropsychological testing information leaflets

Parent/Guardian Information Leaflet

Protocol Title:

Adolescent Brain Development Study

Principal Investigator: **Prof. Mary Cannon**

Beaumont Hospital

Telephone No: **01 8093855**

Dear Parent

Your child is being asked to take part in a research study. Before you decide whether or not you wish to give your consent for your child's participation, you should read the information provided below carefully and if you wish discuss it with your family, friends or GP. Take time to ask questions – do not feel rushed or under any obligation to make a hasty judgement. You should clearly understand the requirements of participating in this study so that you can make a decision that is right for you and your child– this process is known as Informed Consent.

You may change your mind at any time (before the start of the study or even after your child has commenced the study) for whatever reason without having to justify your

decision. If you decide that you would like to consent to your child taking part in the study we will arrange to meet you and your child and go through the information sheet with you in detail before signing the consent form. Please phone us at any time with your questions – 01 809 3855.

WHY IS THIS STUDY BEING DONE?

This project aims to identify brain changes related to certain thoughts and experiences that can occur in adolescence.

WHO IS ORGANISING AND FUNDING THIS STUDY?

This study is funded by the Health Research Board. The primary investigator is Prof. Mary Cannon, Consultant Psychiatrist at Beaumont Hospital and Associate Professor with The Royal College of Surgeons in Ireland.

HOW WILL IT BE CARRIED OUT?

This study commenced in March 2007 for a period of up to 5 years. 120 adolescents aged 17 years or under will take part.

WHAT WILL HAPPEN TO MY CHILD IF I GIVE MY CONSENT FOR HIS/HER PARTICIPATION?

Once you have expressed an interest in participating in the study, one of our study team will arrange to meet with you at the National University of Ireland (NUI) Maynooth and answer any questions. Once you have had a chance to answer all your questions and are satisfied with the information given we will ask you to sign a consent form witnessed and co-signed by our researcher.

This is some information on the tests to be carried out during the day of testing. The tests will not necessarily be done in any particular order:

1) Interview: an interview enquiring about the child's thoughts and feelings will be carried out lasting about 1 hour. Following this, the parent will also be interviewed about their child and asked questions about the child's development.

2) Neurocognitive Testing: this is an assessment of 'brain functions', such as memory and smell identification using a computer and pencil and paper tasks. This will take approximately 1 hour.

3) Speech and Language assessment: a speech and language therapist will ask some questions relating to the child's speech and language skills. This will take approximately 40 minutes.

4) DNA Test

Each participant will be asked to give a cheek swab or a saliva sample (whichever is preferable to you and your child). The sample will be stored in Beaumont Hospital and will be used to look at the relationship between genes and brain function. The sample will be stored and disposed of according to the guidelines of the Irish Council for Bioethics. This will take just a minute.

Please Note: The data collected during this study will be kept in the strictest confidence. Participants will be assigned a code number following their first contact with the researcher. This number will be used throughout the experiment and will be the only identifier on behavioural and physiological data; the identity of participants will not be revealed at scientific meetings, in publications or other vehicles of public communication.

POSSIBLE BENEFITS OF THE STUDY

Although your child will not receive a direct medical benefit from participation in this study, information that we collect will help us to better understand the function of the developing human brain.

WHAT ARE THE RISKS ASSOCIATED WITH THE STUDY?

There are no risks associated with this study. No part of the study is in any way painful. You or your child may choose to discontinue participation at any time.

WHAT IF SOMETHING GOES WRONG AS A RESULT OF MY CHILD'S PARTICIPATION IN THIS STUDY?

Participation in this study is covered by an approved policy of insurance. Professional indemnity for all research activity is with Royal Sun Alliance.

WILL THERE BE ANY ADDITIONAL COSTS INVOLVED?

Any expense incurred as a result of participation in this study will be reimbursed, including taxis or parking.

OUR RESPONSIBILITIES AS INVESTIGATORS

If the investigators become aware of any information during the course of the study that may affect your willingness to allow you child to continue to participate you will be told immediately.

CONFIDENTIALITY ISSUES

Your child's GP will be informed of his/her participation in this study but will not be informed of the results without your express permission. We will not disclose any identifying information about your child. When the results of the research are published or discussed in conferences, no information will be included that could identify participants. Any information obtained in connection with this project and that can identify your child will remain confidential. In any publication arising from this research, only results from the group as a whole will be published, and individual results will not be identifiable.

IF YOU REQUIRE FURTHER INFORMATION

If you have any further questions about the study, or if you wish to withdraw your child from the study you may do so without justifying your decision. We would be delighted to answer any questions you may have before, during or after the study.

Appendix VII: Children's Global Assessment Scale (C-GAS)

CHILDREN'S GLOBAL ASSESSMENT SCALE

Use intermediary levels (eg., 35, 58, 62). Rate actual functioning regardless of treatment or prognosis. The examples of behaviour provided are only illustrative and are not required for a particular rating.

100 - 91 Superior functioning in all areas (at home, at school, and with peers); involved in a wide range of activities and has many interests (eg., hobbies or participates in extracurricular activities or belongs to an organized group such as Scouts, etc); likeable, confident; "everyday" worries never get out of hand; doing well in school; no symptoms.

90 - 81 Good functioning in all areas; secure in family, school, and with peers; there may be transient difficulties and "everyday" worries that occasionally get out of hand (eg., mild anxiety associated with an important exam, occasional "blowups" with siblings, parents, or peers).

80 - 71 No more than slight impairment in functioning at home, at school, or with peers; some disturbance of behavior or emotional distress may be present in response to life stresses (eg., parental separations, deaths, birth of a sib), but these are brief and interference with functioning is transient; such children are only minimally disturbing to others and are not considered deviant by those who know them.

70 - 61 Some difficulty in a single area, but generally functioning pretty well (eg., sporadic or isolated antisocial acts, such as occasionally playing hooky or petty theft; consistent minor difficulties with school work; mood changes of brief duration; fears and anxieties which do not lead to gross avoidance behavior; self-doubts); has some meaningful interpersonal relationships; most people who do not know the child well would not consider him/her deviant but those who do know him/her well might express concern.

60 - 51 Variable functioning with sporadic difficulties or symptoms in several but not all social areas; disturbance would be apparent to those who encounter the child in a dysfunctional setting or time but not to those who see the child in other settings.

50 - 41 Moderate degree of interference in functioning in most social areas or severe impairment or functioning in one area, such as might result from, for example, suicidal preoccupations and ruminations, school refusal and other forms of anxiety, obsessive rituals, major conversion symptoms, frequent anxiety attacks, poor or inappropriate social skills, frequent episodes of aggressive or other antisocial behavior with some preservation of meaningful social relations.

40 - 31 Major impairment in functioning in several areas and unable to function in one of these areas, is, disturbed at home, at school, with peers, or in society at large, eg., persistent aggression without clear instigation; markedly withdrawn and isolated

behavior due to either mood or thought disturbance, suicidal attempts with clear lethal intent; such children are likely to require special schooling and/or hospitalization or withdrawal from school (but this is not a sufficient criterion for inclusion in this category)

30 - 21 Unable to function in almost all areas, eg., stays at home, in ward, or in bed all day without taking part in social activities or severe impairment in reality testing or serious impairment in communication (eg., sometimes incoherent or inappropriate)

20 - 11 Needs considerable supervision to prevent hurting others and self (eg., frequently violent, repeated suicide attempts) or to maintain personal hygiene or gross impairment in all forms of communication, eg., severe abnormalities in verbal and gestural communication, marked social aloofness, stupor, etc.

10 - 1 Needs constant supervision (24-hr care) due to severely aggressive or self-destructive behavior or gross impairment in reality testing, communication, cognition, affect or personal hygiene.

CHILDREN'S GLOBAL ASSESSMENT SCALE (Use Rating Scale Above)

CURRENT

___Rate the subject's level of general functioning for the past two weeks by selecting the level which describes his/her functioning on a hypothetical continuum of health-illness.

MOST SEVERE PAST

___Rate the subject's level of general functioning during his/her most severe past episode of psychiatric illness. Record time period rated___.

HIGHEST PAST

___During the past year, rate the child's highest level of functioning.

Appendix VIII: Psychosis section of the K-SADS-PL

PSYCHOSIS

I. Hallucinations

P C S

0 0 0 No information

1 1 1 Not present

2 2 2 Subthreshold: Suspected or likely

3 3 3 Threshold: Definitely present

PAST: _ _ _

P C S

Sometimes children, when they are alone, hear voices or see things, or smell things and they don't quite know where they come from.

Has this ever happened to you? Tell me about it.

Has there ever been a time you heard voices when you were alone? What did you hear? Have you ever heard someone call your name when there was no one around? What kind of things did you hear? Did you ever hear music which other people could not?

Has there ever been a time when you saw things that were not there? What about shadows or other objects moving? Did you ever see ghosts?

When? Did this only happen at night while you were trying to sleep, or did it happen in the daytime too?

What did you see?

Has there ever been a time when you had an unusual smell about yourself?

Note: If hallucinations possibly present prior to scoring this item, assess the subject's conviction of the reality of the hallucinations with the probes below.

What did you think it was?

Did you think it is your imagination or real?

Did you think it was real when you (heard, saw, etc.) it?

What did you do when you (heard, saw, etc.) it?

These voices you heard (or other hallucinations), did they occur when you were awake or asleep? Could it have been a dream? Did they happen when you are falling asleep? Waking up? Only when it's dark? Did they happen at any other time also?

Were you sick with fever when they occurred?

Have you ever been drinking beer, wine, liquor?, or taking any drugs when it happened?

Was it like a thought or more like a voice (noise) or a vision?

II. Delusions

Do you know what imagination is? Tell me.

Has there ever been a time your imagination played tricks on you?

What kind of tricks?

Tell me more about them.

Did you ever have any ideas about things that you didn't tell anyone because you were afraid they might not understand?

What were they?

Did you believe in things that other people didn't believe in?

Like what?

Ask about each of the delusions surveyed below:

Has there ever been a time you felt that someone was out to hurt you? Who? Why?

Did you ever think that you were an important or great person?

When you were with people you did not know, did you think that they were talking about you?

Was there ever a time when you felt something was happening to your body? Like did you believe it was rotting from the inside or that something was very wrong with it?

Did you ever feel convinced that the world was coming to an end?

How often did you think about _____?

P C S

0 0 0 No information

1 1 1 Not present

2 2 2 Subthreshold: Suspected or likely delusional

3 3 3 Threshold: Definite delusions

PAST: _ _ _

P C S

__ IF RECEIVED A SCORE OF 3 ON THE CURRENT RATINGS ON EITHER OF THE PREVIOUS ITEMS, COMPLETE THE CURRENT SECTION OF SUPPLEMENT #2, PSYCHOTIC DISORDERS, AFTER FINISHING THE SCREEN INTERVIEW.

__ IF RECEIVED A SCORE OF 3 ON THE PAST RATINGS ON EITHER OF THE PREVIOUS ITEMS, COMPLETE THE PAST SECTION OF SUPPLEMENT #2, PSYCHOTIC DISORDERS, AFTER FINISHING THE SCREEN INTERVIEW.

__ NO EVIDENCE OF PSYCHOSIS.

NOTES: (Record dates of possible current and past hallucinations and delusions).

Appendix IX: Study guidelines for rating PLEs

Essentially a strong PLE refers to experiencing hallucinations and/or delusions. Not all such phenomena are of equal clinical significance, however. The following characteristics help to separate hallucinations and delusions of potential clinical significance from hallucinations and delusions that are of limited or no clinical significance.

Hallucinations:

Auditory hallucinations may involve voices or other sounds. A formed hallucination involves hearing one or more voices saying at least one word and is classed as a strong PLE in general (see notes below for notable exceptions). Common formed auditory hallucinations, classed as strong PLEs, include

- Voice commenting on behaviour
- Voice giving commands
- Voices conversing

Unformed auditory hallucinations may involve whispering voices, voices at normal volume or shouting voices where the words cannot clearly be distinguished by the individual. These are classed as strong PLEs in general

Auditory hallucinations may also include non-vocal sounds, such as music playing or animal noises but these are generally classed as weak PLEs. E.g., hearing music playing for a short period of time when none is playing would be classed a weak PLE unless it is distressing or disorganizing, when it would be classed a strong PLE. Experiences that are very common such as occasionally hearing footsteps or knocking, are not classed as PLEs unless these experiences are associated with delusional ideation.

Visual hallucinations are classically thought to be associated with organic pathology but are not uncommon types of PLEs in the general population. They often occur in individuals who also experience auditory hallucinations. Common visual hallucinations, which are rated as strong PLEs, include seeing

- People
- Faces

- Ghosts
- Aliens

Tactile hallucinations are common but most could be considered trivial and would not be classed as PLEs. For example, most people report experiencing their mobile telephone vibrating when it had not really done so or occasionally feeling something brush lightly against their skin when nothing was there. These experiences would not be classed as PLEs unless they involved delusional attributions (e.g., believing it was a ghost that was brushing against them). Isolated tactile hallucinations that would be classed as PLEs are unusual but may occur ocassionally (e.g., recurring feeling of forceful physical touch when nobody was there), but would generally be rated as weak PLEs in the absence of delusional attributions.

Olfactory and gustatory hallucinations are not uncommon but are rarely significant enough to warrant classification as a strong PLE. Occasional experiences of smells or tastes which are not distressing are not classed as PLEs. Some individuals may report recurrent experiences of clearly smelling a particular food (often one the individual desires) which they have found odd; this type of experience would be rated as a weak PLE.

Note on rating formed hallucinations

Exceptions, which are not considered PLEs, include experiences that are very common if not universal, including the experience of hearing one's own name when no one has called it, unless such experiences are associated with delusional beliefs (e.g., a ghost is calling my name).

Brief experiences of gedankenlautwerden (the experience of hearing one's own thoughts aloud even though the individual did not speak them) are common in childhood and early adolescence and are classed as weak PLEs as long as they are brief in duration (a few words or one sentence), are not associated with delusional ideation and are not experienced as significantly distressing or disorganising. Frequency of gedankenlautwerden varies, but does not in-and-of-itself impact on rating.

Note on illusions

Common illusions such as occasionally hearing the doorbell or the telephone while the TV or radio are playing, or seeing a coat from the corner of one's eye and briefly believing it to be a person, are not classed as PLEs. However, more elaborate illusions,

for example thinking that a face in a picture or poster had been moving, would be classed as a weak PLE.

Note on hypnagogic and hypnopompic hallucinations

Hypnagogic and hypnopompic hallucinations are generally not classed as PLEs. However, it is important to distinguish between hypnopompic/hypnagogic and simply being in bed – if the individual is not actually in the process of waking up or falling asleep then the hallucination should not be dismissed as hypnopompic/hypnagogic; it is often at night time that individuals are alone and hallucinatory experiences may be more likely to occur and these experiences are classed the same as any other PLE.

Hallucinations that occur only when the individual is tired (but not falling asleep or awakening) and are brief in duration would be classed as weak PLEs (e.g., a vague but identifiable image of a person moving past the doorway). Prolonged hallucinations would be classed as strong PLEs even if the individual is tired.

Note on hallucinations versus pseudohallucinations

Insight into the hallucination (a 'pseudohallucination') does not preclude it from being classed as a strong (or weak) PLE.

Note on hallucinations and daydreaming

Very brief hallucinations that occur only when daydreaming would generally be classed as weak PLEs.

Note on illness and intoxication

Hallucinations that occur as the result of an organic illness (e.g., a fever) are not classed as PLEs. Whether or not to include PLEs that are associated with drug use is unclear; we would generally include PLEs that occur other than during acute intoxication.

Delusions:

Significant delusions most commonly occur in individuals who also experience hallucinations and often relate to the content of the hallucination, though they may also occur in individuals with no hallucinations. The following are experiences that are commonly encountered.

- A vague feeling of unease associated with the occasional feeling that someone may be watching the individual would be classed as a weak PLE. More frequent or more concrete ideas about being watched, such as being able to suggest a certain person or organisation as being responsible or the belief that cameras have been set up to watch the individual, would be classed as a strong PLE.

- Recurrent, unfounded or very exaggerated ideas that others (generally more than one person or group) are saying negative things about the individual would be classed as a strong PLE. Care must be taken, however, to distinguish paranoia from self-consciousness (e.g., about clothes or physical appearance), which is not classed as a PLE.

- Bizarre attributions for experiences (e.g., the belief that ghosts/deceased relatives/aliens are the cause of the experience) are not uncommon. A belief that ghosts/spirits can influence events is in-keeping with many cultures/subcultures and would not be considered a PLE. However, the belief that ghosts are directly communicating with the individual in question (for example, the ghost of a dead relative) would be considered a strong PLE.

- Subcultural beliefs about that the world may be coming to an end are not uncommon among young people and are often in-keeping with ideas from books or film. These would generally be classed as weak PLEs unless they are of a psychotic level of intensity (unshakable conviction), when they would be classed as strong PLEs.

- A belief that one can read minds or that one's mind has been read is usually somewhat in-keeping with subcultural beliefs about psychics and is generally classed as a weak PLE at most. In some circumstances, however, it would be classed as a strong PLE, for example, if it was associated with paranoia, such as the individual believed that others had singled out him/her and were aiming to read their mind for a particular (usually nefarious) reason.

- A vague unsubstantiated but persistent feeling that something strange is going on or that the individual feels he or she might be 'going crazy' despite no specific or concrete examples of hallucinations or delusions would be classed as a weak PLE.

- Note: magical thinking, such as a belief that one had predicted the future, is very common and is generally classed as a weak PLE at most, unless, for example, it is distressing or disorganising.

<u>Note on severity of hallucinations and delusions</u>

The significance of the severity of the hallucination or delusion is unclear at present. However, there are a range of severities in the experiences that can be considered strong PLEs.

Appendix X: Examples of strong PLEs reported during clinical interviews

Auditory Hallucinations:

“Once in school, sitting down, I heard the man saying 'turn around', my friend was sneaking up behind me”, distress: 10/10.

"I half believe there's someone in the attic", hears noises of creaking, always thinks at night that someone is there. I think I can hear a sound of my old (dead) cat meowing, happens when I'm in bed, happened this morning when she woke up and kept going for 15secs, sounds like a ghost (of a cat), started last year, has happened a few times, terrified by it, sounds come from down in the kitchen, sounds as loud as a cat in pain, a weird meow, no one else hears it, only happens when waking up, but continues to hear it for up to 10 seconds after waking.

Faint mumbling and a person talking, started one year ago, “I can hear words but I can't make sense of it, most of time just a middle aged man but sometimes a woman as well,” twice a week, distress 8/10.

Visual Hallucinations:

Once when swimming he saw a black girl walking around the dressing rooms he looked twice and saw her, she was gliding around, thought it was a ghost – definitely a ghost no other explanation.

“On holidays, last Christmas, I was on the balcony and thought I saw someone in pool drowning, called mum and then there was no one there”, distress: 6/10.

Delusions:

Has there ever been a time when you felt someone was out to hurt you?: “Yes, walking home from school, man and dog-staring at me every day, once he opened his mouth to talk to me”.

Appendix XI: Information sheets posted to participant's parents/guardians prior to EEG testing

Adolescent Brain Development Study

Education and Research Centre

Royal College of Surgeons in Ireland

Beaumont Hospital

Dublin 9

Tel: 01 809 3855

Information Leaflet for under 16s

Adolescent Brain Development Study

Invitation:

We are asking you if you would like to take part in a study about brain development. You do not have to take part if you do not want to. Take your time to read this and to make sure you understand everything. If you have any questions, you can ask your parents or guardians to explain.

Why are we doing this study?

During adolescence certain changes in your brain occur as you develop. We are doctors and scientists who are studying these changes and we want to find out how they are related to thoughts and experiences that occur at this point in life.

An EEG test

We would like to carry out an EEG test (See the picture above). This EEG test allows us to measure electrical activity ("brainwaves") in different parts of the brain. To record EEG what we will do is place a soft cap over your head (like a swimming cap). There are several holes in the cap for the electrodes and a special gel (similar to hair gel) is put in the holes. While we are putting on the cap, you can watch a DVD of your choice. When we have finished preparing the cap, you will sit and carry out some tests at a computer screen. You can have your parent or guardian with you throughout the study session if you like. If you start to get tired or bored, we will take short break or stop the study early. You may stop the study for any reason at any time. When the session is over, we will remove the cap and gently remove the gel. The entire EEG session takes about one and a half hours.

Will it hurt?

There is nothing in this study that should cause you any pain or discomfort. If you do not like any part of the study, you can stop

at any time. We can organise your travel to and from Maynooth. We will carry out the tests during school holidays or at the weekend.

Do I have to take part?

No, if you do not want to be in this study, you do not have to. You will not get into any trouble and there is no problem if you do not want to do this. Talk to your parents or guardians and think about what you want to do. If you decide you would like to take part, there is a form that we will need you to sign. The doctor that you normally go to when you are sick will be told that you are taking part in this study.

Information Taken
Any important information that we learn about you during the study will be passed on to your parents or guardians and your family doctor.

If you have any questions, your parents or guardians can ring:

Prof. Mary Cannon, Consultant Psychiatrist, Beaumont Hospital.

Telephone: 01-809-3855

Adolescent Brain Development Study

Education and Research Centre

Royal College of Surgeons in Ireland

Beaumont Hospital

Dublin 9

Tel: 01-809 3855

Parent/Guardian Information Leaflet

Protocol Title:

Adolescent Brain Development Study

Principal Investigator: **Prof. Mary Cannon**

Beaumont Hospital

Telephone No: **01 8093855**

Dear Parent

Your child is being asked to take part in a research study. Before you decide whether or not you wish to give your consent for your child's participation, you should read the information provided below carefully and if you wish discuss it with your family, friends

or GP. Take time to ask questions – do not feel rushed or under any obligation to make a hasty judgement. You should clearly understand the requirements of participating in this study so that you can make a decision that is right for you and your child– this process is known as Informed Consent.

You may change your mind at any time (before the start of the study or even after your child has commenced the study) for whatever reason without having to justify your decision. If you decide that you would like to consent to your child taking part in the study we will arrange to meet you and your child and go through the information sheet with you in detail before signing the consent form. Please phone us at any time with your questions – 01 809 3855

WHY IS THIS STUDY BEING DONE?

This project aims to identify brain changes related to certain thoughts and experiences that can occur in adolescence.

WHO IS ORGANISING AND FUNDING THIS STUDY?

This study is funded by the Health Research Board. The primary investigator is Prof. Mary Cannon, Consultant Psychiatrist at Beaumont Hospital and Associate Professor with The Royal College of Surgeons in Ireland.

HOW WILL IT BE CARRIED OUT?

This study is due to take place in July and August 2009. Approximately 40 adolescents, aged 11- 13 years will take part.

WHAT WILL HAPPEN TO MY CHILD IF I GIVE MY CONSENT FOR HIS/HER PARTICIPATION?

This project will be carried at the National University of Ireland in Maynooth (NUIM). There may also be follow up sessions after one year. This would require separate consent.

Information and consent: Once you have expressed an interest in participating in the study, we will arrange for you and your child to come to NUIM for a morning or afternoon. During this meeting we will go through the information sheet in detail, taking time to answer any queries you might have. Once you are satisfied with the

information given we will ask you to sign a consent form witnessed and co-signed by our researcher.

EEG: We would like to carry out a test of electrical activity in the brain while your child is watching a computer screen. This would involve putting an electrode cap on your child, which can 'read' the electrical activity coming from the brain through the skull. The electrode cap looks like a swimming cap with wires. During this part of the study your child will look at a screen and carry out some simple tests like games. Afterwards we will remove the electrode cap and clean the gel off your child's hair. This whole test (including putting on and removing the cap) will take approximately 1.5 hours. None of the testing will be in any way painful.

POSSIBLE BENEFITS OF THE STUDY

Although your child will not receive a direct medical benefit from participation in this study, information that we collect will help us to better understand the function of the developing human brain.

WHAT ARE THE RISKS ASSOCIATED WITH THE STUDY?

When operated by appropriately qualified individuals, EEG presents virtually no risk, as there is **NO** exposure to x-rays or radioactivity with these procedures.

WHAT IF SOMETHING GOES WRONG AS A RESULT OF MY CHILD'S PARTICIPATION IN THIS STUDY?

Participation in this study is covered by an approved policy of insurance.

WILL THERE BE ANY ADDITIONAL COSTS INVOLVED?

Any expense incurred as a result of participation in this study will be reimbursed

OUR RESPONSIBILITIES AS INVESTIGATORS

If the investigators become aware of any information during the course of the study that may affect your willingness to allow you child to continue to participate you will be told immediately.

CONFIDENTIALITY ISSUES

Your child's GP will be informed of his/her participation in this study. We will not disclose any identifying information about your child. When the results of the research are published or discussed in conferences, no information will be included that could identify participants. Any information obtained in connection with this project and that can identify your child will remain confidential. In any publication arising from this research, only results from the group as a whole will be published, and individual results will not be identifiable.

***By providing my consent I agree that*:**

I have been informed of the discomforts and risks that my child may reasonably expect to experience as part of this study. I have been informed that when used on appropriately qualified individuals, EEG presents virtually no risk. There will be no exposure to x-rays or radioactivity in this study.

I understand these risks and am consenting to my child's participation in this research. I understand that I can withdraw my child's participation at any time from the study.

IF YOU REQUIRE FURTHER INFORMATION

If you have any further questions about the study, or if you wish to withdraw your child from the study, you may do so without justifying your decision. For additional information now or any future time please contact:

Prof. Mary Cannon
Education and Research Centre
Beaumont Hospital
Phone: 809 3855

Appendix XII: Interview and EEG assent forms

Adolescent Brain Development Study

Education and Research Centre

Royal College of Surgeons in Ireland

Beaumont Hospital

Dublin 9

Tel: 01 809 3855

ASSENT FORM for Minors (under 16)
Adolescent Brain Development Study

I have read and understood the Information Leaflet for Under 16s.

I would like to take part in this study about Adolescent Brain Development.

I understand that I will be asked to give some of my DNA as part of this study.

SIGNED: ……

DATED: ……..

Appendix XIII: Interview and EEG consent forms

CONSENT FORM

Protocol Title:

Adolescent Brain Development

Please tick the appropriate answer.

- I confirm that I have read and understood the Parent/Guardian Information Leaflet dated _____ attached, and that I have had ample opportunity to ask questions all of which have been satisfactorily answered.

□Yes □ No

- I understand that my child's participation in this study is entirely **voluntary** and that I may withdraw his/her participation at any time, without giving a reason. If my child is in receipt of treatment from a doctor, my decision to withdraw from this study will not affect his/her treatment or standard of care.

□Yes □ No

- I understand that my child's identity will remain confidential at all times.

□Yes □ No

- I have been given a copy of the Patient Information Leaflet and this Consent form for my records.

□Yes □ No

- I agree that I will not restrict the use to which the results of this study may be put. I give my approval that anonymous data/specimens concerning my child's person may be stored or electronically processed for the purpose of scientific research and may be used in related or other studies in the future. (This would be subject to approval by an independent body which safeguards the welfare and rights of people in biomedical research studies - the Beaumont Hospital Ethics (Medical Research) Committee.)

□Yes □ No

_____

Signature and dated Name in block capitals

To be completed by the Principal Investigator or his/her nominee.

I the undersigned, have taken the time to fully explained to the above patient the nature and purpose of this study in a manner that he/she could understand. I have explained the risks involved, the experimental nature of the treatment, as well as the possible benefits and have invited him/here to ask questions on any aspect of the study that concerned them.

_____

Signature, qualifications and date Name in block capitals

In accordance with Good Clinical Practice if there is a dependent relationship between the Physician and the Subject then another physician should obtain consent. Likewise the person obtaining consent should be fully conversant with the study and be suitably trained and qualified.

3 copies to be made: 1 for patient, 1 for PI and 1 for hospital records.

Appendix XIV: Verbatim instructions for the Active Auditory Oddball Task

Participants were presented with the following set of instructions:

You will hear beeps coming from the speakers. Some of the beeps will differ in tone from others.

Press the spacebar to continue.

When you hear a tone that differs from the normal tone (more high-pitched), press the left mouse button. Keep your eyes open and try not to move around too much or blink. There will be one break where you can move and readjust yourself. Ask the experimenter now if you have any questions.

Press the spacebar to continue.

Appendix XV: Verbatim instructions for the Implicit Spatial Memory Task

Participants were presented with the following instructions:

The experiment will involve a study phase and a test phase.
The study phase will begin shortly.

Study block instructions:

In this phase you will be shown a series of scenes. These scenes will always contain two fixed objects (or "landmarks") that will always be present.
A number of different objects will also appear in the scenes, one at a time.

All you have to do is try to remember the objects that appear. You will be tested on your recall of them later.
Press the spacebar when you're ready to begin.

Test block instructions:

Next you will be presented with different objects.
If you recognise an object FROM THE STUDY PHASE ("old" objects) click on the LEFT mouse button with your index finger.
If you see a new object that is NOT FROM THE STUDY PHASE ("new" objects) click on the RIGHT mouse button with your middle finger.
Press the spacebar when you are ready to begin.

Appendix XVI: Verbatim instructions for the Spatial Working Memory Task

Participants were presented with the following instructions:

Try to remember which fishbowl contains a fish

Later, a fish will appear in one bowl and you have to remember if you have seen the fish in that bowl

Click the LEFT button for 'YES'

If there was no fish in that bowl,

click the RIGHT button for 'NO'

Please press space to continue

Appendix XVII: Summary of results from the experimental chapters

	Neuropsychological Tests and Resting State Data	**Active Auditory Oddball**	**Implicit Spatial Memory**	**Spatial Working Memory**
No. of Participants	Controls: 18 PLEs: 11 Total: 29	Controls: 17 PLEs: 11 Total: 28	Controls: 24 PLEs: 13 Total: 37	Controls: 25 PLEs: 17 Total: 42
Gender	M: 17 F: 12	M:17 F: 11	M: 21 F: 16	M: 21 F: 21
Frequency Bands/Components Examined	Delta, Theta, Alpha	P300, N100	P300	P300
Electrode Sites	Anterior: AF3, AF4, F1, Fz, F2, FC1, FCz, FC2 Posterior: CP1, CPz, CP2, P1, Pz, P2, PO3, POz, PO4 Fronto-temporal: FT7, T7, FT8, T8	FCz,Cz, CPz, Pz C1,C2 FCz, FC1, FC2 Fz, F1, F2	P3,P1, Pz, P2, P4	Fz Pz, POz
Relation to Neurocognitive Function	Speed of Processing, Working Memory, Verbal Learning, Visual Learning, Reasoning and	Auditory Discrimination	Implicit Spatial Memory Encoding and Retrieval	Visuo-spatial Working Memory Retrieval

	Problem Solving			
Band Settings/Epoch	Delta: 1.5-3.5Hz Theta: 3.5-7.5Hz Alpha: 7.5-12.5Hz	-100ms pre-stimulus to 1000ms post-stimulus	-100ms pre-stimulus to 1500ms post-stimulus	-100ms pre-stimulus to 1000ms post-stimulus
Correlations		P300 correlates with measures of speed of processing and spatial working memory	None	None
Main Group Differences (Controls v PLEs)	The PLEs group performed worse on 2 tests of non-verbal speed of processing (TMTB and BACS SC) No between-group differences were observed in the resting state EEG data	Within-groups difference in mean amplitude of the P300 at FCz, PLEs group failed to elicit a larger P300 to target tones than non-target tones at this site Increased amplitude of N100 AEP to non-target tones in PLEs group	No group differences in the behavioural or ERP data	Reduced P300 in the PLEs group across all memory load conditions in the task
Conclusions	The PLEs group were impaired on non-verbal speed of processing tests as measured by the MCCB	The within-groups differences observed in P300 amplitude at FCz may indicate a very early stage of frontal dysfunction. Increased N100 may indicate early stages of dysfunction in temporal cortex	The PLEs group performed similarly to the control group and are not impaired on the Implicit Spatial Memory Task	Possible altered network engaged during retrieval on the Spatial Working Memory Task