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Interregional Connectivity in People with Schizophrenia: A Study Using Visual Evoked Potentials

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Abstract

A parsimonious and complete understanding of schizophrenia continues to be elusive. There are many apparent contributing factors to the development of this disease. These include genetics, environment and developmental factors. Of particular interest to the current thesis are the reported changes in cerebral white matter laterality in people with schizophrenia. There is evidence that within the normal population transfer of information between the two cerebral hemispheres is faster from the right hemisphere to the left hemisphere than the transfer of information from the left to the right hemisphere. It has been proposed that this is a function of a greater ratio of fast conducting axons in the right hemisphere than in the left hemisphere. It has been observed that people with schizophrenia do not display this asymmetry of interhemispheric transfer time (IHTT). Instead, people with schizophrenia display no difference in information transfer time from the right to the left hemisphere and the left to the right hemisphere. It has been postulated that this is due to a reduction in fast conducting axons in the right hemisphere in people with schizophrenia. This thesis aimed to further investigate alterations in cerebral laterality of axonal type in males with schizophrenia.

This experiment used a 128-channel electroencephalogram to record the averaged visual evoked potentials (AEPs), specifically the P100 and N160, generated using the Poffenburger paradigm in people with schizophrenia and control participants. Low Resolution Electromagnetic Tomography (LORETA) was used to estimate the sources of the bilateral AEP components and then to reconstruct the current density dynamics underlying these components. Both the raw AEPs and the source estimated latency data were analysed to compare IHTT and *intra*hemispheric, as well as absolute latencies within and between the groups. It was confirmed that

IHTT in the normal population is faster from the right to the left hemisphere than the inverse and that people with schizophrenia have an altered IHTT. Furthermore, an interesting pattern of *intra*hemispheric and P100 and N160 absolute latencies was observed within both groups, and between groups. The findings from this thesis do indicate that people with schizophrenia have altered timing in visual information processing when compared with the normal population. This is hypothesised to be due to alterations in the distribution of myelinated white matter in the schizophrenia population, which is likely to affect cerebral communication and/or integration of information.

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Introduction

1. Introduction to Schizophrenia

Schizophrenia is a mental disorder that is part of the psychotic group of disorders (American Psychiatric Association (APA), 2000). The syndrome of schizophrenia was first described in 1896 by Emil Kraeplin who termed groupings of behaviour he observed in 'mental asylums' as *dementia praecox*. He divided the symptom clusters into 'catatonic' and 'dementia paranoides' (Boyle, 2001) and believed the disorder was early onset dementia due to brain degeneration (Marenco & Weinberger, 2000). In his 1911 book, *Dementia Praecox or Group of Schizophrenias*, Eugen Bleuler continued Kraeplin's work and developed the label '*schizophrenia'* for the disorder described by Kraeplin. Their work was continued by other researchers, with Kurt Schneider helping to develop the Diagnostic and Statistical Manual of Mental Disorders' early diagnostic criteria for the disorder in the 1950's (Boyle, 2001).

The *Diagnostic and Statistical Manual of Mental Disorders: 4th edition-text revision* (DSM-IV-TR) defines schizophrenia as a disorder of thinking, volition, and affect (American Psychiatric Association, (APA), 2000). For diagnosis, psychotic symptoms must have been significantly present for at least a month, with some indication of the disorder having been present for a six month period. These symptoms are also associated with a decrease in social and/or occupational functioning (APA, 2000). The symptoms of schizophrenia vary between people, but are categorised broadly into positive and negative symptoms. A diagnosis of schizophrenia should not be made if the presenting symptoms are not better accounted for by a schizoaffective disorder, a mood disorder with psychotic features, or by the physiological effects of a substance or medical disorder (APA, 2000).

Schizophrenia affects between 0.5 and 1.5% of the world's population (APA, 2000; Jablensky, 2000). Regier et al. (1993) found the one month prevalence rate of schizophrenia in a sample of areas in the United States of America to be 0.6%. In further analysis they combined people with schizophrenia and schizhophreniform disorder, and found that the prevalence of these disorders was higher in people with a low socioeconomic status (1.2%), compared with a high socioeconomic status (0.3%). Other studies have reported what they termed nonaffective psychosis, which combined schizophrenia, schizhophreniform disorder, schizoaffective disorder, delusional disorder, and atypical psychosis to have a 12 month prevalence rate of 0.5% and a lifetime prevalence rate of 0.7%, respectively.

The Christchurch Psychiatric Epidemiology Study found the lifetime prevalence rate of schizophrenia in New Zealand to be 0.3% (Oakley-Browne, Joyce, Wells, Bushnell, & Hornblow, 1989; Wells, Bushnell, Hornblow, & Oakley-Browne, 1989), with Māori being diagnosed at twice the rate of non-Māori (Te Puni Kōkiri, 1993). The over representation of people with schizophrenia from minority cultures has been documented internationally in the increased rates of schizophrenia in Afro-Caribbean and African immigrants in the United Kingdom (Jarvis, 1998; Van Os, Castle, Takei, Der, & Murray, 1996), and in immigrants to Holland from Surinam and the Dutch Antilles (Selten & Sijben, 1994). Further research has found that people from non-white ethnic groups in London, England have higher rates of schizophrenia when they live in a areas where they are a minority of the population (Boydell et al., 2001).

1.1. Positive Symptoms

Hallucinations and delusions are classified in the positive grouping of schizophrenia symptoms. These symptoms are an increase in normal behaviours and/ or distortions in these behaviours (APA, 2000). Hallucinations can occur in the visual, olfactory, gustatory, and tactile modalities. However, they are most commonly experienced in the auditory modality. These hallucinations tend to manifest as hearing external voices, which can include hearing voices talking with one another or commenting on the individual's thoughts or behaviour (APA, 2000; Tarrier, 2008).

Delusions refer to altered thought. This often includes misinterpretations of one's perceptions or experiences. Common themes include personal grandiosity, persecution, or loss of sense of personal control ("agency") over one's body or thoughts. Delusions may also be referential and/or religious, and can include believing that song lyrics, other people's gestures, or news items contain content directly intended for, or about the individual (APA, 2000).

Behavioural disturbances often manifest in disorganised speech and distortions in behaviour. The individual's speech may be tangential, opaque, have loose associations, be disorganised, and/or be incoherent. As such, their ability to communicate is impaired (APA, 2000). Behavioural disturbances may also manifest in the form of lack of hygiene, unusual or inappropriate dress, agitation, and problems with goal directed behaviour (APA, 2000). Other behavioural symptoms may include catatonia in the form of reduction of body movements and the maintenance of single posture, lack of response to the environment, or movements without apparent goals or direction (APA, 2000).

1.2. Negative Symptoms

Negative symptoms refer to a decrease in the occurrence of normal behaviours. This may include flat or empty affect, an inability to experience pleasure, and poverty of speech, reflected in a decrease in the quantity and frequency of speech. Additionally, speech content may be empty or have reduced complexity (APA, 2000). Individuals with schizophrenia may also display poor eye contact, an inability to initiate or follow though goal directed behaviours, and/or be physically inactive. As these symptoms commonly occur in other disorders, such as depression, and may also be observed in people without psychological illness, it can be harder to identify when they can be considered to cross from within the normal range of behaviour to clinically significant symptoms of schizophrenia (APA, 2000).

1.3. Onset

The average age of onset of schizophrenia is in the early to mid twenties for males, and in the mid twenties to early thirties for females (APA, 2000; Faraone, Chen, Goldstein, & Tsuang, 1994). Diagnosis before the teenage years is very exceptional (APA, 2000). The lifetime rates of schizophrenia diagnosis for males and females are equal. Although men generally have an earlier onset than women, women have a second spike in onset approximately between the ages of 45 and 54. Due to this, it has been suggested that oestrogen may play a protective role in woman until menopause (Häfner et al., 1993). Onset can be *acute*: symptoms appear within a week; *sub-acute*: symptoms appear and are established in one month, *gradual*: slow development over greater than a one month period, or *insidious*: establishing the time of onset is difficult (Jablensky et al., 1992).

1.4. Course

The course of the disorder can vary. It is considered to have a prodromal phase, defined as a period during which specific symptoms are present before a diagnosis has been made This can appear months to several years before full onset and/or diagnosis (Häfner & an der Heiden, 2003; Yung & McGorry, 1996). During this phase the individual experiences functional decline, and exhibits specific behaviour and cognitions that are considered precursors to an episode of psychosis (Häfner & an der Heiden, 2003; Miller et al., 2003). Prodromal features include reduced concentration and attention, depressed mood, brief psychotic symptoms, and sleep disturbance (Yung & McGorry, 1996). Approximately 40-50% of people who have prodromal symptoms will go on to develop psychosis (Miller, et al., 2003; Yung et al., 2003). Once diagnosed with schizophrenia the disorder can be chronic or acute with exacerbations and remissions (APA, 2000). The long-term prognosis of the disorder is varied. People with schizophrenia can have a remission that is followed by relapse, remission with no further relapse, or have no remission at all. Women have a better long-term prognosis than men, and are more likely to have a permanent remission (Haro, Novic, Suarez, & Roca, 2008).

The lifetime risk of suicide for people with schizophrenia is cited as being between 4% and 10%. The risk is greatest in the early stages of the disorder (Palmer, Pankratz, & Bostwick, 2005; Tsuang, 1978).

1.5. Debate over Construct Validity

There is some debate surrounding the validity of schizophrenia as a diagnostic construct. The symptoms of schizophrenia are varied, and two affected individuals can present without similar symptoms (Jablensky, 2006). That is, a person

manifesting positive symptoms may not share any of the same symptoms as a person with negative symptoms; however, both are diagnosed with schizophrenia. It has been suggested that positive and negative subtypes represent different processes in the brain and, therefore, may represent two different disorders (Crow, 1980). Some attempts have been made to create subtypes of schizophrenia that may more accurately reflect a proposed heterogenetic aetiology (Jablensky, 2006).

Other critiques of the construct of schizophrenia state that the disease is often the result of childhood trauma, such as childhood sexual abuse and neglect (Read, 1997). This challenges theories that propose that schizophrenia is due to an inherited genetic vulnerability and is "independent of the environment" (Crow, Done, & Sacker, 1996, p. 181). Instead, Read (1997) argues that the environment is the major contributor to the aetiology of schizophrenia. This stance, however, does not deny the role of the biological system (Read, van Os, Morrison, & Ross, 2005), but instead proposes that childhood trauma can result in changes in the brain (Read, Perry, Moskowitz, & Connoly, 2001). This has been supported by findings of smaller hippocampal volumes in a study of women with a history of childhood sexual abuse (Stein, Koeverola, Hanna, Torchia, & McClarty, 1997), and findings that child abuse can lead to altered regulation of the hypothalamic-pituitary-adrenal axis (De Bellis et al., 1994; Read, et al., 2001).

Despite these critiques, schizophrenia continues to be included in the DSM-IV-TR (APA, 2000) and the World Health Organisation's 'International Classification of Mental and Behavioural Disorders' (World Health Organisation, 1993), indicating the construct has diagnostic validity.

1.6. Treatment

Schizophrenia is most commonly treated with antipsychotic medication (Tarrier, 2008) and psychosocial therapy (Buckley, 2008). The mechanisms by which antipsychotic medications work are only partly understood and are still the focus of research (Kinon & Lieberman, 1996). Most medications bind to dopamine receptors, and some interact with serotonin receptors (Buckley, 2008). Early antipsychotic medications are normally referred to as 'typical' antipsychotics and are based on dopamine antagonism. These include drugs such as chlorpromazine and haloperidol (Edwards & Smith, 2009; Leuch, Pitschel-Watz, Abraham, & Kissling, 1999). Later developed drugs, termed 'atypical', are both dopamine and serotonin antagonists. These include drugs such as risperidone and quetiapine (Leuch, et al., 1999). Typical antipsychotics often produce side-effects such as tardive dyskinesia and extrapyramidal motor side-effects (Kinon & Lieberman, 1996; Patterson & Leeuwenkamp, 2008). Atypical drugs have been suggested to produce fewer side-effects, but are not completely free from them. They can have side-effect profiles that include weight gain, agranulocytosis, and cardiac problems (Copolov et al., 1998; Kilian, Kerr, Lawrence, & Celermajer, 1999; Newcomer et al., 2002; Sussman, 2001). Atypical medications, particularly clozapine, have been demonstrated to be more effective in treating medication resistant schizophrenia (Breier, 1999) and are more effective at treating negative symptoms, as well as mood and cognitive symptoms (Kapur & Remington, 2001). Despite the increased efficacy of atypical antipsychotics, there remain individuals with schizophrenia who are so called 'treatment resistant' or experience 'incomplete recovery' (Pantelis & Lambert, 2003)

Psychotherapy such as family-oriented therapies, group therapy and individual psychotherapy can play a role in helping an individual with schizophrenia to cope

with family and social relationships. It also provides support and teaches methods and skills to cope with everyday problems. It can also add to the efficacy of pharmacotherapy (Kaplan, Sadock, & Grebb, 1994). Indeed, psychosocial therapy combined with medication has been demonstrated to improve the outcomes of people with schizophrenia when compared with medication alone (Patterson & Leeuwenkamp, 2008). Cognitive-behavioural therapy has been demonstrated to reduce psychotic symptoms by 50% or more in people with medication resistant chronic schizophrenia (Tarrier et al., 1998) and also decrease the severity of delusions (Pinninti, Rissmiller, & Steer, 2010). In their review of cognitive-behavioural therapy for schizophrenia, Turkington, Kingdon and Weiden (2006) conclude that it is an effective treatment for some people with medication resistant symptoms.

2. Aetiology

Currently the aetiology of schizophrenia is unknown. There are various theories regarding its cause. These include a genetic hypothesis, cortical disconnection syndrome, neurotransmitter dysfunction, failure to establish cerebral asymmetry, and a neuro-developmental syndrome. It should be noted that these possible causes may be linked, and are not considered mutually exclusive.

The current thesis focuses on Miller's (1996, 2008) hypothesis. This will be discussed below, and followed by a brief discussion of some other current theories and hypotheses regarding the possible aetiology of schizophrenia.

2.1 Miller's Hypothesis

There is a strong theme of altered lateralisation in the literature on schizophrenia. Miller (1996, 2008) has provided a comprehensive theory that proposes that the underlying enduring abnormal psychological traits observed in

people with schizophrenia, as opposed to episodes of active psychosis, can be viewed as the result of an alteration in normal cerebral lateralisation. Miller proposes that the functional specialisation seen within each hemisphere, namely the location of language in the left hemisphere and visuospatial processing in the right hemisphere (in the right-handed, neurologically normal population) is due to a greater ratio of fast-conducting myelinated and large calibre axons to slow conducting unmyelinated and small calibre axons in the right hemisphere when compared to the left hemisphere. This greater ratio of fast conducting axons in the right hemisphere allows for fast parallel processing of visuospatial information. While the greater number of unmyelinated and small calibre axons in the left hemisphere affords the greater temporal resolution needed for speech and language functions located in that hemisphere. Furthermore, Miller proposes that this asymmetry of axonal myelination and calibre type is global within each hemisphere, as opposed to being present only within regions involved in language and visual processing (Miller, 1996). Miller also suggests that callosal projections are made up of axons projecting from one hemisphere to the other. This results in the common finding of faster right-to-left, relative to left-to-right, interhemispheric transfer times (IHTT) in the right-handed normal population (Barnett & Corballis, 2005; Brown, Larson, & Jeeves, 1994; Iwabuchi & Kirk, 2009; Marzi, Bisiacchi, & Nicoletti, 1991; Moes, Brown, & Minnema, 2007; Norwicka, Grabowska, & Fersten, 1996)

Miller (1996, 2008) has proposed that the underlying enduring psychological traits seen in people with schizophrenia are the result of an general loss of rapidly conducting axons, myelinated and large calibre. It is postulated that this impacts on the functioning of the right hemisphere, and possibly also the left hemisphere, as the right hemisphere's functions rely on faster axonal conduction velocity. Miller

suggests that this reduction of fast conducting axons is due to a developmental anomaly in people with schizophrenia. Evidence for Miller's theory is based on inferences from large number of studies, not direct studies, due to ethical constraints. As such, it is difficult to provide a summary of the evidence that supports this theory here in this thesis, see Miller (1996, 2008) for a comprehensive review of the literature supporting his hypothesis. An example of the literature that Miller cites that supports his theory is disturbance in right hemisphere functions in people with schizophrenia, such as failure to use prosody and deficits in the comprehension of metaphors (Addington, et al., 2008; Kucharska-Pietura & Klimkowski, 2002; Murphy & Cutting, 1990) Another finding in the literature that Miller proposes supports his hypothesis is the observation that left to right, and right to left interhemispheric transmission times are not significantly different in people with schizophrenia (Barnett & Kirk, 2005). This is expanded on here, and in later sections, as it is evidence that this thesis tests and expands on. Barnett et al. (2005) also found that people with schizophrenia had reduced evoked potential (EP) amplitudes in the right hemisphere after stimulus presentation to the left-visual-field, relative to EP amplitudes in the right hemisphere after stimulus presentation to the left-visual-field. Reduced right hemisphere amplitudes in schizophrenia have also been reported by Friedman (1991). It has been hypothesised that these findings could be due to fewer fast conducting axons in the right hemisphere, or a decrease in activation of the right hemisphere in people with schizophrenia (Barnett, et al., 2005; Barnett & Kirk, 2005; Miller, 1996).

This thesis will further explore Miller's hypothesis using electroencephalography (EEG) to investigate the differences in IHTT and intrahemispheric visual average evoked potentials (AEPs) latencies in people with

schizophrenia and people in a control group. Source localisation will also be employed to identify and reconstruct activity within the brain that is believed to underlie the AEPs. The latency calculations will be remade on the reconstructed source current density dynamics and compared with those based on the raw AEPs

2.2. Genetic Hypothesis

Literature from twin studies and the analysis of the incidence of schizophrenia in genetically related individuals suggest there is genetic involvement in the development of schizophrenia. First-degree biological relatives of people with schizophrenia are 10 times more likely to develop schizophrenia than the general population (Evans, Muir, Blackwood, & Porteous, 2001). One review of studies of fraternal and monozygotic twins, found the concordance rates of schizophrenia in identical twins and fraternal twins to be 0.46 and 0.14, respectively (Plomin, DeFries, & McClearn, 1990). Similarly, another review calculated the concordance rate for schizophrenia in identical twins as between approximately 48% and approximately 17% for fraternal twins (Cardno & Gottesman, 2000). Moreover, sibling pairs concordant for schizophrenia often have similar symptom profiles (Kendler et al., 1997; Ross et al., 2000). Ross, et al. (2000) concluded that there was a familial contribution to the type of schizophrenia the siblings developed, but were unable to state whether it was genetic or environmental.

2.2.1. Specific genes

Meta-analysis of genetic linkage studies has found strong evidence of susceptibility for schizophrenia on loci 13q, 22q11-12 (which were also susceptibility loci for bi-polar disorder) and 8p21-22. There is also evidence for susceptibility on

many other loci (Badner & Gershon, 2002; DeLisi, Crow, et al., 2002; Levinson, Lewis, & Wise, 2002; Lewis et al., 2003; Tandon, Keshavan, & Nasrallah, 2008). Some rare specific genetic aberrations have been implicated in the development of schizophrenia in some individuals. These include microdeletions of part of chromosome 22q11.2, which leads to a 20-fold increase in risk for schizophrenia (Bassett et al., 2005), and deletions in 1q21.1, 15q11.2, and 15q13.3 (Stefansson et al., 2008). These microdeletions may account for up to 2% of schizophrenia (Bassett, et al., 2005). Other genes implicated in rare causes of schizophrenia include Val66Met (Gratacòs et al., 2007), GAD1 (Straub et al., 2007), and DISC1 (disrupted in schizophrenia 1) (Hennah, Thompson, Peltonen, & Porteous, 2006). Furthermore, Neuroregulin 1 (NRG1), COMPT (catechol-*O*-methyl-transferase), DTNBP1 (dysbindin), ALC6A3, DRD3 and SLC184 are also implicated in schizophrenia (Duan et al., 2007; Nicodemus et al., 2007; Riley et al., 2009; Tan et al., 2007). Moreover, McClellan, Susser and King (2007) suggest that having only a few highly penetrant heterozygous genetic polymorphisms can also cause schizophrenia in family groups and individuals, and that these specific genetic aberrations may be different in different families and people with schizophrenia.

Much of the literature suggests that the probability that schizophrenia is the function of a variation in a single gene is low. Instead, it is more widely held that the genetic contribution to schizophrenia is the result of the interaction of a large number of genes (Lichtermann, Karbe, & Maier, 2000; McGue, Gottesman, & Rao, 1985; The International Schizophrenia Consortium, 2009; Tsuang & Faraone, 1995). It has been suggested that schizophrenia and other psychiatric disorders, such as bipolar disorder, have some overlap in contributing genes (Craddock & Owen, 2005; Hodgkinson et al., 2004; The International Schizophrenia Consortium, 2009), and that it is

environmental or epigenetic impact on the genetic loading that determines the type of psychiatric disorder developed by each individual (Sullivan, Kendler, & Neale, 2003).

It has been proposed that the current classification of schizophrenia is over inclusive (Jablensky, 2006) and the classification schizophrenia into behavioural subtypes would improve research into the genetics of schizophrenia (Ginsburg et al., 1996). Many subtyping systems have been proposed (see Jablensky, 2006 for a review). However, it appears that none has gained dominance or consensus in the literature. Genetic influences in the development of schizophrenia appear to be strongly supported by the literature.

2.3. Neurotransmitter Dysfunction Hypotheses

2.3.1. Dopamine

Dopamine has been widely regarded as a neurotransmitter that is important in the pathology of schizophrenia. Drugs that block dopamine receptors, specifically D2 receptors (Carlsson, Carlsson, & Milsson, 2004), have an ameliorating affect on schizophrenia symptoms (Creese, Burt, & Snyder, 1996), and those that increase the action of dopamine exacerbate symptoms (Snyder, 1972). As such it has been postulated that excess dopamine is partly responsible for schizophrenia (Willner, 1997). However, dopamine antagonist 'typical antipsychotics' are not effective for all people with schizophrenia and are only partially effective for others (Kane, 1989), indicating that other processes or neurotransmitters may be involved in the disease.

2.3.2. Serotonin, glutamate and γ-aminobutyric acid

Cerebral serotonin imbalances have been implicated in schizophrenia. Second generation antipsychotics are, amongst other actions, serotonin antagonists (Meltzer,

Matsubara, & Lee, 1989), and are more effective for treatment resistant schizophrenia than typical antipsychotics (Bondolfi et al., 1998). Serotonin antagonists have also proved effective in the treatment of negative symptoms (Duinkerke et al., 1993). However, the exact mechanism via which serotonin plays a role in schizophrenia is not fully understood (Duncan, Zorn, & Lieberman, 1999).

Another neurotransmitter that has been implicated in schizophrenia is glutamate. This hypothesis was drawn from the ability of glutamate agonists, such as Ketamine, to produce quasi psychotic symptoms in the normal population and in people with schizophrenia (Malhotra et al., 1996, 1997). A review of glutamate in schizophrenia found evidence for impaired glutamate receptor composition and function in people with schizophrenia (Goff & Coyle, 2001). It has been hypothesised that the role of glutamate in schizophrenia may be related to its role in increasing dopamine release in subcortical structures (Grace, 1999). Glutamate receptors are also considered to play a role in cortico-cortico interactions and communication. The disruption caused by glutamate receptor antagonists may mimic a disconnection in cortical communication in schizophrenia (Allen & Young, 1978; Friston, 1998).

The inhibitory neurotransmitter γ-aminobutyric acid (GABA) has also been proposed to play a role in schizophrenia. Post-mortem studies of the brains of people with schizophrenia have found abnormalities in the GABA neurotransmitter system in the frontal lobes (Benes, Vincent, Marie, & Khan, 1996; Sherman, Davidson, Baruah, Hegwood, & Waziri, 1991). GABA plays an important function in working memory, and it has been proposed that these GABA reductions may be linked to deficits in working memory found in schizophrenia (Lewis, Hashimoto, & Volk, 2005; Lewis, Volk, & Hashimoto, 2004; Volk & Lewis, 2002).

2.4. Neurodevelopmental Hypothesis

Some gestational and perinatal factors have been found to significantly increase the risk of developing schizophrenia in later life. These include prenatal famine; high levels of maternal distress in the first trimester; low birth weight; and shorter gestation (Jones, Rantakallio, Hartikainen, Isohanni, & Sipila, 1998; Khashan et al., 2008; St Clair et al., 2005; Susser et al., 1996). Obstetric complications have also been linked to the later development of schizophrenia. These include preeclampsia (which is linked to foetal malnutrition); caesarean section due to foetal distress, manual extraction of the baby; haemorrhage during delivery; and premature delivery (Byrne, Agerbo, Bennedsen, Eaton, & Mortensen, 2007; Dalman, Allebeck, Cullberg, Grunewald, & Köster, 1999). It has been proposed that these events confer some form of brain damage, such as hypoxia to the foetus, which is linked to the later development of the disorder (Geddes et al., 1999; Marenco & Weinberger, 2000). Winter and spring birth and older paternal age at conception are also linked to the development of schizophrenia (Davies, Welham, Chant, Torrey, & McGrath, 2003; Wohl & Gorwood, 2007; Wu, Liu, Zhao, Ma, & Li, 2011).

Foetal exposure to a virus during the first two trimesters has also been linked to the development of schizophrenia. For example, a seven-fold increase for the risk of developing schizophrenia has been found in people exposed to a maternal influenza during their first trimester (Brown et al., 2004). It is proposed that this exposure may initiate a cascade of abnormalities during development that leads to the later development schizophrenia (Meyer, Yee, & Feldon, 2007). Another hypothesis is that the increased levels of maternal cytokines during the infection affect neural development (Brown, et al., 2004).

Anatomical abnormalities present in schizophrenia, such as increased ventricular size and decreased brain volume, lend further support to the neurodevelopmental hypothesis (McCarley et al., 1999). Other evidence includes less asymmetry between the cerebral hemispheres of people with schizophrenia (Gur & Chin, 1999), and less right hand dominance in people with schizophrenia relative to the normal population (Dragovic & Hammond, 2005). These are discussed in greater detail below (see section 4).

2.5. Cortical Dysconnection Syndrome Hypothesis

The dysconnection hypothesis states that schizophrenia is caused by disturbance (decrease or increase) in the connections between brain regions due to reduced synaptic plasticity and structural aberrations in the brain (Stephen, Baldeweg, & Friston, 2006). This results in a lack of functional integration between brain regions and a reduction in the ability of synapses to modulate plasticity in memory systems, emotions, and learning, which results in a lack of reinforcement of adaptive behaviour (Friston, 1998, 1999).

In people with schizophrenia there appears to be a disruption in the anterior cingulate cortex's (ACC) modulation of the temporal and the prefrontal areas (Fletcher, McKenna, Friston, Frith, & Dolan, 1999). Fletcher et al. (1999) propose that the lack of integration between these two areas by the ACC may result in the deficits in attention (Bench, Grasby, & Friston, 1993), performance monitoring (Carter et al., 1998), and willed action (Frith, Friston, Liddle, & Frackowiak, 1991) found in people with schizophrenia. Moreover, reduced electrical oscillation coherence between the frontal and temporal regions, which may also reflect a dysconnection between these two regions, has been linked to auditory hallucinations (Ford, Mathalon, Whitford, Faustman, & Roth, 2002). Using fMRI Honey et al.

(2005) showed people with schizophrenia had altered functional networks between the ACC, and the cerebellum and the pre- and post-central gyrus. The same study found that people with schizophrenia with predominantly negative symptoms also had aberrant connectivity between the ACC and the supplementary motor area (Honey, et al., 2005). Another fMRI study also found aberrant connectivity between the frontal, parietal, and temporal lobes, which was significantly correlated with illness duration (Liu et al., 2008). It has been proposed that these aberrant networks create spatial and temporal disturbances in cortical coordination, which may result in the cognitive and behavioural symptoms of schizophrenia (Liu, et al., 2008; Rubinov et al., 2009). Studies using fMRI have also found people with schizophrenia to have different spatial activation patterns in frontal, posterior cingulate, lateral parietal, medial, prefrontal, cerebellar regions, and parahippocampal gyri during resting state (Bluhm et al., 2007; Garrity et al., 2007). Moreover, activation levels in the medial frontal gyrus, the precuneus, the left middle temporal gyrus, and posterior cingulate have been significantly correlated to psychotic symptoms (Bluhm, et al., 2007; Garrity, et al., 2007).

Positron emission tomography has demonstrated aberrant cortical connections between semantic processing areas in the cerebellum, and temporal and occipital lobes (Kim et al., 2005), and between the prefrontal and parietal lobes during a working memory task performed by people with schizophrenia (Kim et al., 2003). Similarly, during a working memory task, disrupted interactions between frontal and temporal regions have been observed in people with schizophrenia using positron emission tomography and EEG imaging (Meyer-Lindenberg et al., 2001; Peled et al., 2001). Deficits in parieto-motor area interactions have also been found in a study of

medicated and non-medicated people with schizophrenia using a trascranial magnetic stimulation (Koch et al., 2008).

After commissurotomy some patients experience 'psychotic' thoughts that are similar to those experienced in schizophrenia (David, 1994), further implying a link between cortical connectivity and schizophrenic symptoms. Moreover, there is evidence that there may be alterations in the connections and communication between the hemispheres in people with schizophrenia (Barnett, Corballis, & Kirk, 2005; Endrass, Mohr, & Rockstroh, 2002). These findings appear to consistently point towards an altered association or connectivity between several brain regions in people with schizophrenia.

2.6. Brain Anatomical Differences in Schizophrenia

Structural differences between the brains of people with schizophrenia and people without schizophrenia show that there is no one reliable deviation in brain structure observed in every person with schizophrenia. However, commonly found structural abnormalities include a decrease in cerebral volume and increase in ventricle size (Fannon et al., 2000; McCarley, et al., 1999; Shenton, Dickey, Frumin, & McCarley, 2001; Steen, Mull, McClure, Hamer, & Lieberman, 2006; Wright et al., 2000). Meta-analysis has found abnormalities in the medial-temporal lobe structures (amygdala, hippocampus, and parahippocampal gyrus), corpus callosum, and frontal lobes, as well as reduced volume in the occipital, and parietal lobes (McCarley, et al., 1999; Shenton, et al., 2001). One meta-analysis also reported that 20% of the studies they reviewed found an increase in the size of the fourth ventricle (Shenton, et al., 2001). Another meta-analysis, however, found no enlargement of the fourth ventricle in people with schizophrenia (McCarley, et al., 1999).

A meta-analysis of 66 studies found people experiencing their first-episode of schizophrenia display reductions in whole brain and hippocampal volume, and increased ventricle size (Steen, et al., 2006), and yet another meta-analysis of 65 studies of neuroleptic naive people with schizophrenia found abnormalities in the medial temporal, thalamic, and prefrontal areas (Torrey, 2002), indicating that these changes are part of the disease process, rather than medication effects.

3. Corpus Callosum

The corpus callosum (CC) is the largest of the commissures in the brain (Keshavan et al., 2002). Its primary role is to facilitate the rapid transfer of information between homologous regions, and beyond, in the left and right hemispheres of the brain (Aboitiz, Scheibel, Fisher, & Zaidel, 1992; Jarbo, Verstynen, & Schinder, 2012)**.** The size of the CC increases into adult years (Pujol, Vendrell, Junqué, Martí-Vilalta, & Capdevila, 1993). Meta-analysis has found that people with schizophrenia have reductions in the size of the corpus callosum (Woodruff, McManus, & David, 1995). Moreover, a meta-analysis of MRI studies found 67% of the studies reviewed reported people with schizophrenia had differences in the CC when compared to the normal population (Shenton, et al., 2001). Specifically, reductions in the width and volume of the splenium, genu, isthmus, and area of the anterior midbody of the CC have been reported in people with schizophrenia (Bersani, Quartini, Iannitelli, Paolemili, & Ratti, 2010; Knöchel et al., 2012; Walterfang et al., 2009; Walterfang et al., 2008). This suggests that there may be alterations in information transfer between the cortical regions connected by these areas of the CC.

A MRI study of people experiencing their first episode of schizophrenia and who were medication naive found a decrease in CC areas involved in information transfer between the temporal, prefrontal, and inferior parietal cortices, which

suggests possible transfer abnormalities between these brain regions, and indicates that these difference are part of the disease process, and not due to medication effects (Keshavan, et al., 2002). Associations have been found between decreased anterior callosal size and reductions in total CC volume and 'fibre integrity' (a vague and imprecise term often used in the literature to describe differences found in white matter) and the severity of auditory hallucinations (David, Minne, Jones, Harvey, & Ron, 1995; Knöchel, et al., 2012). Moreover, posterior CC decreases in fractional anisotropy (FA) have been correlated with poorer clinical outcomes (Mitelman et al., 2007).

Investigations into the integrity of the white matter of the CC in people with schizophrenia using FA have found decreased white matter FA bilaterally in the CC (Mitelman, et al., 2007), with specific decreases found in the genu, isthmus and splenium (Knöchel, et al., 2012; Price et al., 2007). A meta-analysis of diffusion tensor imaging (DTI) studies found a significant decrease in the splenium, but no significant difference in the genu of the CC between the control group and people with schizophrenia (Patel et al., 2011), indicating variability in the findings in the literature.

4. Altered Cerebral Asymmetries

4.1. Reduced Physical Asymmetry in the Brain

Cerebral physical asymmetry can be observed in several parts of the brain. In the normal population the brain displays asymmetry with larger right hemisphere prefrontal and frontal regions, and larger left hemisphere occipitoparietal, occipital, and sensorimotor regions (Falkai, Schneider, Greve, Klieser, & Bogerts, 1995; Sharma et al., 1999). These asymmetries have been found to be reduced or absent in

people with schizophrenia and their first degree family members (Bilder et al., 1994; Falkai, et al., 1995; Sharma, et al., 1999; Sommer, André, Ramsey, Bouma, & Kahn, 2001; Turetsky et al., 1995). Moreover, reduced frontal and temporal asymmetry, as measured by volume, has been linked with early onset schizophrenia (Maher, Manschreck, Yurgelun-Todd, & Tsuang, 1998). Reductions in right prefrontal activation have been correlated with cognitive disorganisation and deficits in working memory in people with schizophrenia (Perlstein, Carter, Noll, & Cohen, 2001), and bilateral reductions in prefrontal cortex activation have been found in medication naive people with schizophrenia (Barch et al., 2001).

The role of the temporal lobe in schizophrenia has been of interest in the study of schizophrenia as direct stimulation has been demonstrated to invoke auditory hallucinations (Penfield & Perot, 1963). Reductions in the volume of the left superior temporal gyrus have been reported in people with schizophrenia (Flaum et al., 1995; Shenton, et al., 2001; Shenton et al., 1992). Also, the volume of the left superior temporal gyrus has been significantly correlated with the severity of auditory hallucinations (Barta, Pearlson, Powers, & Tune, 1990; Levitan, Ward, & Catts, 1999), thought disorder, and reductions in verbal fluency (Vita et al., 1995). The planum temporale, which is part of Wernicke's area in the left temporal gyrus, is involved in language processing and is larger in the left hemisphere than in the right hemisphere in the normal population (Eckert et al., 2008; Loftus et al., 1993). This asymmetry in the planum temporale occurs early in development and has been observed in 80% of foetuses at 29 weeks gestation (Wada, Clark, & Hamm, 1975). A meta-analysis of 10 studies found people with schizophrenia had reduced left PT asymmetry (Sommer, André, et al., 2001).

4.2. Functional Asymmetry in the Brain

Further cerebral asymmetry can be observed in the functional specialisation of each hemisphere. This is demonstrated in the lateralisation of language to the left hemisphere in more than 90% of right-handers (Springer et al., 1999), 85% of ambidextrous people, and 73% of left-handers in the normal population (Knecht et al., 2000). People with schizophrenia have been found to have decreased cerebral lateralisation of language. Using fMRI one study has shown that during semantic decision and verb generation tasks people with schizophrenia had the same degree of left hemisphere activation as control participants, but they also had increased right hemisphere activation. This was positively correlated with hallucination symptom severity (Sommer, Ramsey, & Kahn, 2001). Another fMRI study using a covert verb generation task concluded that the reduced lateralisation of language in schizophrenia was due to higher levels of left-handedness in this population, rather than being a function of schizophrenia itself (Razafimandimby, Tzourio-Mazoyer, Mazoyer, Maïza, & Dollfus, 2011). In contrast, a meta-analysis of handedness, schizophrenia, and language found that the significant decrease in language lateralisation present in people with schizophrenia was only apparent in vowel or fused word tasks, not in all dichotic listening tasks (Sommer, André, et al., 2001). These results imply that cerebral lateralisation of language is altered to some degree in schizophrenia, however, the exact nature of this difference is still unclear.

4.3. Schizophrenia as a By-Product of Cerebral Lateralisation and Language

It has been proposed that schizophrenia should have been selected against during human evolution as it is inherently non-adaptive due to people with schizophrenia having reduced fecundity compared with people without schizophrenia

(Crow, 2000; Haverkamp, Propping, & Hilger, 1982; Nanko & Moridaira, 1993; Svensson, Lichtenstein, Sandin, & Hultman, 2007). However, due to the continued stable incidence of schizophrenia it has been postulated that schizophrenia is linked to genes that are fundamentally involved in the speciation event that led to the evolution of Homosapiens (Crow, 2000). Crow (2002) argues that the translocation of the Xq21.3 gene on the X chromosome onto the Y chromosome (Yp11.2) may have been involved in this event, which led to the development of cerebral lateralisation, and the corresponding development of the phonological output of language as a function of the left hemisphere (Crow, 2002, 2008). Moreover, Crow (2000) proposes that schizophrenia is the result of a failure to develop language dominance in one hemisphere, and cites language defects and reduced cerebral asymmetry in people with schizophrenia as support for this hypothesis. This failure to develop cerebral asymmetries leads to deficits or anomalies in an individual's capacity to distinguish one's own language production from that of language produced by others. This is postulated to be responsible for auditory hallucinations, thought insertion, and thought broadcasting, which are some of the core symptoms of schizophrenia (Crow, 2000).

4.4. Handedness and Cerebral Functional Asymmetry

More evidence for altered asymmetries in the schizophrenia population comes from studies in human handedness. Approximately 90% of the normal population is right-handed (Dragovic & Hammond, 2008; Hardyck & Petrinovich, 1977), which is linked with the functional lateralisation in the cerebral cortex (Corballis, 1991; Springer, et al., 1999). Meta-analyses have found a leftward shift in handedness in people with schizophrenia compared to the normal population (Dragovic &

Hammond, 2005; Satz & Green, 1999). Increased rates of left-handedness have also been reported in children who later develop schizophrenia (Crow, et al., 1996).

Satz and Green (1999) propose that this shift in handedness is due to increased rates of mixed handedness, as opposed to left-handedness, in people with schizophrenia. However, in their meta-analysis Dragovic and Hammond (2005) dispute this and conclude that there is an increase in left-handedness in people with schizophrenia. This alteration in handedness is linked to alterations in cerebral laterality. Non-right-handedness is significantly correlated with reduced left asymmetry in the superior temporal gyrus, in which speech and language areas are located (Deep-Soboslay et al., 2010).

Left-handed people with schizophrenia have higher levels of thought disorder and higher rates of disorganised type schizophrenia, when compared with right-handed people with schizophrenia (Dollfus, Buijsrogge, Benali, Delamilleure, & Brazo, 2002; Manoach, Maher, & Manschreck, 1988). A meta-analysis has found that within the normal population mixed handedness, as opposed to strong right or left-handedness, is associated with higher scores on schizotypy measures (Somers, Sommer, Boks, & Kahn, 2009). Moreover, some studies have found increased rates of non-right-handedness in non-affected family members of people with schizophrenia (Orr, Cannon, Gilvarry, Jones, & Murray, 1999), however, others have not (Deep-Soboslay, et al., 2010; DeLisi, Svetina, et al., 2002; Dragovic, Hammond, Badcock, & Jablensky, 2005). In sum, there appears to be strong support for altered asymmetry in people with schizophrenia in anatomy, cerebral function, and handedness.

5. Left Hemisphere Dysfunction

Left hemisphere dysfunction in people with schizophrenia is evidenced in physiological and behavioural differences. Functional magnetic resonance imaging

(fMRI) has shown people with schizophrenia with prominent negative symptoms have anatomical abnormalities in the left neocortical and limbic regions, and related white matter tracts (Sigmundsson et al., 2001). People with schizophrenia have also been shown to exhibit reduced left hemisphere advantage during a dichotic fused words task, and this was correlated with higher levels of positive symptoms (Bruder et al., 1995). Studies using fMRI found decreased activity in Wernicke's area, an area linked to formal thought disorder, in people with schizophrenia (Kircher et al., 2001).

Further evidence for left hemisphere dysfunction in schizophrenia has come from deficits found in receptive syntax processing (Abi-Dargham et al., 2000). Deficits in left hemisphere functions, such as lexical and semantic processing in language, have been positively correlated with the level of thought disorder people with schizophrenia (Kerns & Berenbaum, 2002; Titone & Levy, 2004). Decreased right-hand force in non-medicated people with schizophrenia has also been proposed as further support for left hemisphere abnormalities in people with schizophrenia (Purdon, Woodward, & Flor-Henry, 2001).

6. Right Hemisphere Dysfunction

Researchers looking at the right hemisphere in people with schizophrenia have also found evidence of differences between the schizophrenia population and the normal population. The right hemisphere is thought to be involved in speech prosody, recognition of facial affect, and the interpretation of metaphors (Brownell, Potter, & Michelow, 1984; Kucharska-Pietura & Klimkowski, 2002; Ross & Monnot, 2008), skills that are often disturbed in people with schizophrenia (Addington, Penn, Woods, Addington, & Perkins, 2008; Kucharska-Pietura & Klimkowski, 2002; Murphy & Cutting, 1990). In addition, people with right hemisphere damage can experience delusional misidentification (Capgras Syndrome) (Förstl, Almeida, Owen, Burns, &

Howard, 1991), break-down of self/other boundaries (Bogousslavsky & Regli, 1988), and loss of will (Coslett & Heilman, 1989), all of which are symptoms of schizophrenia (Cutting, 1994).

Moreover, right hemisphere lesions can result in the loss of the ability to use prosody and emotional gesticulation when speaking (Ross & Marek-Marsel, 1979). Right hemisphere damage is also linked to deficits in the ability to express and perceive emotion (Borod, 1992; Borod, Koff, Perlman, & Nicholas, 1986), and removal of the right hemisphere can result in deficits in perceiving negative emotional expressions, lies, and sarcasm (Fournier, Calverly, Wagner, Poock, & Crossley, 2008). A study of people with schizophrenia with negative symptoms and people with right hemisphere brain damage found both these groups had difficulty identifying facial expressions (Borod, Martin, Alpert, Brozgold, & Welkowitz, 1993). Similarly, people with schizophrenia have been found to exhibit less physical expression (Troisi, Spalletta, & Pasini, 1998), and less non-verbal emotional expression when compared to controls (Gottheil, Paredes, Exline, & Winkelmayer, 1970). In contrast, however, Mattes, Heimann and Birbaumer (1995) found people with schizophrenia in remission produced more sad facial expressions and less happy facial expressions when compared to controls.

7. Electroencephalography and Schizophrenia

7.1. EEG

EEG creates an attenuated view of the synchronous excitatory and inhibitory neuronal post-synaptic potentials in the cerebral cortex (Barlow, 1993; Olejniczak, 2006). Experimentally its basic function is to observe the physiological output, or change in neural activity in the cortex, as a function of different stimuli or behaviour,

thus allowing for the inference of the role of different cortical areas to various sensory or behavioural functions (Lopes da Silva, 2005). The recorded activity is the summation of the electrical activity primarily from groups of pyramidal neurons, which creates a picture of temporal brain activity (Barlow, 1993; Olejniczak, 2006).

The temporal accuracy of EEG data is precise, within the millisecond range (Michel et al., 2001; Mulert, Pogarell, & Hegerl, 2008). The spatial acuity of EEG is much less than that of its temporal one. This is partly due to the electrical activity generated by the cortex being distorted as it passes through the cortex, meninges, and skull. As such, some spatial accuracy is lost. The spatial resolution of the EEG signal is influenced by factors such as the number of electrodes used, source localisation, and noise levels (Im, Gururajan, Zhang, Chen, & He, 2007). Due to the so-called 'inverse problem', it cannot be assumed that the generators of the electrical activity recorded by each electrode lie directly beneath that electrode. This is because the electrical activity in the brain is generated in 3-dimensions, but EEG electrodes only record a 2-dimensional image from the surface of the scull. The reverse reconstruction of the activity into 3-dimensions creates an infinite number of possible generation sources (Im, et al., 2007; Nunez, 1981; Olejniczak, 2006; Pascual-Marqui, Michel, & Lehmann, 1994).

7.2. Medication Effect on EEG

Comparison between studies of people with schizophrenia is confounded by some studies using medicated individuals and others using non-medicated individuals. Furthermore, there exists a range of possible antipsychotic medications available, further confounding comparisons between studies, as participants in different studies

may be medicated differently. There appears to be a lack of recent literature addressing this issue from which to draw upon.

One study looking at the effect of medication on visual evoked potentials (VEPs) of people with schizophrenia found that there was no difference in the amplitudes of auditory and visual P100, N200 and P300 components, despite medication ameliorating psychotic symptoms (Ford et al., 1994). This lack of effect of medication on the P100 has also been replicated by (Ruhrman, Brockhaus, Tendolkar, Pukrop, & Klosterkötter, 2000). The decrease in the P300 amplitude and latency has been reported to have been corrected after six weeks of neuroleptic treatment with haloperidol or remoxipride (Coburn et al., 1998).

A study comparing the resting EEG frequency characteristics between first episode, first time medicated people with schizophrenia and people with chronic, medicated schizophrenia found no significant differences between the two groups (Sponheim, Clementz, Iacono, & Beiser, 1994). In the same study, when compared with control participants both groups of people with schizophrenia were found to have significantly decreased alpha, and increased beta and theta activity. The authors proposed that this demonstrated that long-term medication has little effect on EEG frequency signals, but instead variations between controls and people with schizophrenia are due to the disease process (Sponheim, et al., 1994). Another study looking at EEG power and oscillations in unmedicated people with schizophrenia found significant increases in interhemispheric oscillation coherence measures in the beta and delta bands in the schizophrenia group compared to controls. No difference in absolute power was found between the groups (Nagase, Okubo, Matsuura, Kojima, & Toru, 1992). A later study of medication-naive people with schizophrenia found decreased fast alpha band and increased slow alpha and beta band activity (Omori et

al., 1995). This concurs with findings of increases in the alpha and beta bands in medicated people with schizophrenia (Boutros et al., 2008; Saletu, Küfferle, Anderer, Grünberger, & Steinberger, 1990).

The effect of medication on EEG is a complex issue. As such the influence that it has on EEG signals should be reviewed on a case by case basis.

7.3. Source Localisation of the EEG

One technique for source localisation is 'Low Resolution Electromagnetic Tomography' (LORETA). This creates a three dimensional image of the electrical activity within the cortex from the 2-dimensional scalp recordings (Pascual-Marqui, et al., 1994). This technique creates a topographic map of the EEG oscillations by calculating the smoothest "3-dimensional current distributions" between the oscillations based on the data (Pascual-Marqui, et al., 1994, p. 49). Subsequently, we will reconstruct the current density dynamics from each estimated source. The peak energy at each source (within a particular time window) can then be used as a potentially more accurate estimate of the latency differences between activation of particular areas of the brain.

8. Event Related Potentials (ERPs)

ERPs are the summation of synchronous activation of pyramidal neurons that consist of negative and positive wave forms (Epstein, 2003). They are considered to be the neurobiological response or transient change of regularly occurring wave forms as a function of sensory stimulation or internal event processing (Celesia & Peachey, 2005), and are considered to be indicative of cortical information processing (Pfurtscheller & Lopes da Silva, 2005).

Studies investigating VEPs recorded from the optic tract and proximal to the lateral geniculate neuclei in three Macaque monkeys suggest that VEP activity in the the optic tract and thalamus in the first 50-55ms is directly due to the effect of retinal stimulation (Schroeder, Tenke, Arezzo, & Vaughan Jr, 1989). VEPs recorded 50-55ms after direct retinal stimilation are no longer a direct response to the stimulus. It is postulated that activity after this time reflects the activity of neuronal systems/neuclei within the lateral geniculate neucleus and the cortex. This is supported by Kraut, Arezzo and Vaughan (1985) who recorded Macaque monkey VEPs on the cortical surface and intracortically from the opercular striate cortex. Kraut et al. (1985) concluded that VEP activity after 50ms (i.e., the N75) is produced in cortical lamina IV of the calcarine cortex as a result of excitation from the visual stimulus. They suggest that later VEPs are generated independently from the original stimulus. They infer from their results that in humans early VEPs, such as the P40 are generated subcortically, while the later P100 VEP is generated by inhibitory activity of the thalamo-recipient lamina (Kraut, et al., 1985) in cortical extrastriate areas (Di Russo, Martinez, Sereno, Pitzaliz, & Hillyard, 2001).

A study examining flash evoked potentials in humans postulated that VEPs before 100ms are generated in the visual system, namely the retina and optic tract as a function of stimulus luminosity changes (Pratt, Bleich, & Berliner, 1982). A similar study in eight awake human participants recorded VEPs on the occipital cortical surface and intracortically (Ducati, Fava, & Motti, 1988). The intracortical electrode began recording at the scalp at the posterior occipital area (approximately areas 17 and 18) and continued to record in 5-10 mm increments as it moved towards the nucleus ventralis lateralis thalami. This data supported the hypothesis that the N75-P100 VEP recoded on the scalp is generated in the striate and parastriate cortex. The

polarity of all evoked potentials (EPs) recorded cranially was reversed when the recording electrode passed below the cortex (Ducati, et al., 1988). MRI studies have also supported occipital lobe as the generator of the early P100 component (80-110ms) and researchers have proposed that occipito-temporal cortex is involved in the generation of the later P100 component (110-140 ms) (Bokura, Yamaguchi, & Kobayashi, 2001; Clark, Fan, & Hillyard, 1995; Di Russo, et al., 2001; Martinez, Di Russo, Anllo-Vento, & Hillyard, 2001). The N160 has been suggested to be more difficult to localise as it appears to be generated in more than one cerebral area. These include occipital and parietal lobes (Clark, et al., 1995; Di Russo, et al., 2001) and occipito-temporal lobes (Bokura, et al., 2001; Clark, et al., 1995; Hopf, Vogel, Woodman, Heinze, & Luck, 2002). Despite the aforementioned research, a clear and accurate understanding of the generators of VEPs is not known (Di Russo, et al., 2001; Epstein, 2003). Furthermore, the latencies of VEPs have been linked to the integrity of myelin in the visual system, suggesting that reductions in latencies are indicative of axonal damage or reductions in axon diameter (Klistorner et al., 2008; You, Klistorner, Thie, & Graham, 2011; Yu et al., 2011).

There appear to be more studies investigating alterations in VEP amplitude differences than differences in the latencies of the various EPs in people with schizophrenia in the literature. The lack of latency studies may derive from the link between latency and stimulus intensity. However, there is also evidence that amplitudes are impacted on by stimulus intensity (Buchsbaum & Silverman, 1968; Carrillo-de-la-Peña, Rodriguez Holguín, Corral, & Cadaveira, 1999). Using stimuli, such as checkerboards, the same luminance across all trials and both groups, as was done in the current study, should control for this interaction and provide further information about speed of signal transfer within these groups.

8.1.Visual Event Related Potentials

8.1. 1. P100

The P100 is the one of the most reliable and identifiable ERPs in humans that peaks approximately 100-130 ms after the presentation of a visual stimulus (Di Russo, et al., 2001). However, the absence of, or variations in the P100 cannot be used as clinical indicators of cortical abnormality or disease (Epstein, 2003). When the occipital cortex is suppressed by magnetic coil stimulation between 80-100 ms after the presentation of a visual stimulus participants are no longer able to see the stimulus presented (Amassian et al., 1989). This indicates that neural activity occurring at the P100 is important for the processing of visual information (Ameassian, et al., 1989), and may also be involved in orientating attention to task relevant stimuli visual (Luck, Heinzea, Mangun, & Hillyard, 1990; Mangun & Hillyard, 1991). Interestingly, one study has reported that in the normal population woman had an earlier P100 onset in the left hemisphere and males had an earlier onset in the right hemisphere (Johnson, Lowwery, Kohler, & Turetsky, 2005).

The P100 has been demonstrated to be lower in amplitude in people with schizophrenia during visual tasks (Campanella, Montedoro, Verbanck, & Rosier, 2006; Ruhrman, et al., 2000; Vohs et al., 2008; Yeap et al., 2008). Moreover, both people with schizophrenia and controls have been found to have different cortical areas generating the P100. This study used Local Auto-Regressive Average (LAURA) distributed linear inverse source estimation to investigate the location of the generator of the P100 (this provides a visual image of localisation differences, but does not provide data to assess for a statistically significant difference) (Foxe, Murray, & Javitt, 2005). This appeared to point to reduced left occipital P100 in the schizophrenia group during an illusory contour processing task. Although found

globally, one study reported these P100 reductions to be greater over occipital-parieto than occipito-temporal areas (Foxe, Doinger, & Javitt, 2001). However, despite the frequency of the reported reduction in P100 amplitude making this finding appear relatively robust, not all studies have found a reduction in P100 amplitude in people with schizophrenia (Johnson, et al., 2005).

8.1.2. N160

The visual N160 is a negative peak that occurs approximately 160ms after stimulus presentation and is thought to be activated by faces (Bentin, Allison, Puce, Perez, & McCarthy, 1996; Eimer, 2000). A study investigating the N160 in two participants with callosal agenesis found it was absent in the hemisphere ipsilateral to the stimulated visual field. The authors concluded that the N160 in the hemisphere not directly receiving the visual information may be generated in response to trans-callosal information transfer (Rugg, Milner, & Lines, 1985).

During a facial affect processing task people with schizophrenia have longer PN170 latencies (Lee, Kim, Kim, & Bae, 2010) and decreased amplitudes when compared with controls (Turetsky et al., 2007). One study investigating the N170 VEP latencies in schizophrenia found no difference between this group and controls, however they did find a reduction in the amplitude of the N170 (Campanella, et al., 2006). In people with schizophrenia reduced P160 amplitudes have been reported in the right hemisphere, but not the left hemisphere, during a lexical decision task, and this was linked with reduced asymmetry of interhemispheric transfer (Barnett, Kirk, & Corballis, 2007).

Decreases in the N170 amplitude at occipito-temporal sites have been reported in people with schizophrenia and have been positively correlated with higher scores

on the Positive and Negative Syndrome Scale (Campanella, et al., 2006), and with deficits in facial emotion recognition tasks and positive symptoms (Turetsky, et al., 2007). However, a study using illusory contour tasks failed to find a N160 reduction in schizophrenia (Foxe, et al., 2005). This study also performed LAURA source estimation and the authors proposed that the generators of this visual N160 to be in the lateral-occipital and posterior occipital regions.

Source localisation using standardized low-resolution brain electromagnetic tomography (sLORETA) during the presentation of happy, neutral and fearful faces found that the N170 was reduced in the middle frontal gyrus and inferior frontal gyrus in the schizophrenia group compared to the control group in response to fearful faces only (Jung, Kim, Kim, Im, & Lee, 2012). No differences were found between the groups in the P100, N250 and the P300. Moreover, within the schizophrenia group males had a reduction in source activity in the superior temporal gyrus, middle temporal gyrus, insula and inferior frontal gyrus compared to woman with schizophrenia (Jung, et al., 2012). Interestingly, no difference in source activity was found between the genders in the control group. This suggests that gender plays a role in the alteration of VEP activation and localisation in people with schizophrenia.

8.1.3. P300

Aberrations have been reported in the visual P300 of people with schizophrenia. In people with non-paranoid schizophrenia visually generated P300 amplitudes have been observed to become successively smaller when participants were shown images of faces exhibiting affect from negative to neutral and positive. The reverse was observed in people with paranoid schizophrenia and controls, with smaller amplitudes observed for positive affect, which became successively larger

from neutral to negative affect (Ueno et al., 2004). Furthermore, participants in the non-paranoid group had significantly longer P300 latencies than the control and paranoid groups. This reduction was also observed by Lee et al. (2010) in a similar task, however the type of schizophrenia the participants had was not reported. Reductions in the amplitude of the visual P300 have been observed to be correlated with reductions in the right hippocampus (Egan et al., 1994). However, there are some studies that have not observed a reduction in the P300 in people with schizophrenia (Ford, et al., 1994; Mathalon, Ford, & Pfeffrbaum, 2000).

8.1.4. N400

The N400 is considered to be linked to semantic processing in the normal population. It is often larger in amplitude when a stimulus has not been primed, or is incongruous with previous stimuli (Kutas & Hillyard, 1980). Delayed N400 latencies and reduced N400 amplitudes have been observed during a picture semantic matching tasks in people with schizophrenia (Bobes, Lei, Ibáñez, Yi, & Valdes-Sosa, 1996; Mathalon, Faustman, & Ford, 2002). Smaller N400 amplitudes have been positively correlated with the severity of negative symptoms (Olichney, Iragui, Kutas, Nowacki, & Jeste, 1997).

It is clear that there are alterations in the amplitude and latencies of the VEPs in people with schizophrenia. These appear to be linked to alterations in brain structure and function, and contribute to the growing knowledge of alterations in cortical processing in the brains of people with schizophrenia.

8.2. Auditory Evoked Potentials

8.2.1. P50

Deficits in early auditory processing in people with schizophrenia have been found earlier than the P50. Using EEG and Brain Electrical Source Analysis of this component it has been suggested that aberrations in auditory EPs may begin as early as 15ms after stimulus onset, and may represent aberrations in subcortical processing associated with the thalamus and brain stem (Leavitt, Molholm, Ritter, Shpaner, & Foxe, 2007).

The P50 is a preattentive wave form (Boutros, Korzyukov, Jansen, Feingold, & Bell, 2004). The suppression of the second P50 in paired stimulus presentations has been found to be reduced in people with schizophrenia compared to control participants, and is often referred to as a 'gating deficit' (Clementz, Geyer, & Braff, 1997, 1998; Yee, Nuechterlein, Morris, & White, 1998). This has been found in the early stages of the disease. It has been proposed that this failure to gate the second P50 may be linked to difficulty filtering out irrelevant sensory information, which may then flood the cortex (Boutros, Belger, Campell, D'Souza, & Krystal, 1999; Carr & Wale, 1986; Waldo, Adler, & Freedman, 1988). Less suppression of the P50 may be related to frontal and temporal lobe deficits, and is correlated with higher anxiety-depression scores on the Brief Psychiatric Rating scale, and with attention deficits (Erwin, Turetsky, Moberg, Gur, & Gur, 1998; Korzyukov et al., 2007; Yee, et al., 1998). This P50 amplitude reduction has also been found in first-degree family members of people with schizophrenia. The same study reported people with schizophrenia also had N100 amplitude reductions, but first-degree family members did not (Waldo, et al., 1988). Interestingly, the first-degree relatives had larger than normal N100 amplitudes, suggesting a possible compensation for the earlier P50

gating deficit (Waldo, et al., 1988). Antipsychotic treatment with risperidone for three months has been found to improve the gating of the P50 to paired stimuli in people who had recently developed schizophrenia (Yee, et al., 1998). Similarly, another study found people with schizophrenia who were unmedicated displayed a gating deficit and that medicated people with schizophrenia did not (Daskalakis et al., 2002).

8.2.2. N100

The amplitude, but not the latency, of auditory N100 ERPs has been found to be reduced in people with schizophrenia and in their first degree relatives (Boutros et al., 2009; Boutros, et al., 2004; O'Donnell, Vohs, Hetrick, & Shekhar, 2004; Salisbury, Collins, & McCarley, 2010; Turetsky et al., 2008). Boutros et al. (2009) also found a gating deficit in the N100, which was positively correlated with negative schizophrenia symptoms.

8.2.3. P200

Reductions in P200 amplitude and sensory gating, and increases in latency have been demonstrated in people with schizophrenia (Boutros, et al., 2004; Brecher, Porjesz, & Begleiter, 1987; O'Donnell et al., 1993; O'Donnell, et al., 2004; Ogura et al., 1991). This reduction in the auditory N200 amplitude in people with schizophrenia has been correlated with a decrease in the volume of left superior temporal gyrus and bilateral medial temporal lobe structures (O'Donnell, et al., 1993). The N200 amplitude has also been found to be reduced in auditory odd-ball tasks in people with schizophrenia to rare target tones, but not to frequent target tones (O'Donnell, et al., 1993; Ogura, et al., 1991). Moreover, reductions in both the auditory and visual N200 have been found to be correlated with left hippocampal

volume (Egan, et al., 1994). Some earlier studies, however, did not find a reduction in the auditory N200 in people with schizophrenia (Brecher, et al., 1987; Roth, Horvath, Pfeffrbaum, & Kopell, 1980).

8.2.4. P300

The P300 is a positive waveform that is considered to be a part of the neural network involved in updating information regarding task relevant stimuli (Salisbury et al., 1998). Reductions have been found in the auditory P300 amplitude in people with schizophrenia compared to controls (Groom et al., 2008; Jansen, Hu, & Boutros, 2010; Jeon & Polich, 2003; Mathalon, et al., 2000; O'Donnell, et al., 2004; Winterer, Egan, Rädler, Coppola, & Weinberger, 2001). Egan et al. (1994) found a negative correlation between P300 amplitude and the positive symptoms of psychosis as rated by the Psychiatric Symptom Assessment Scale. It has been suggested that this decrease in the P300 amplitude is indicative of left temporal lobe disturbance in schizophrenia as one study found a P300 amplitude decrease over the left, but not right, temporal lobe in people experiencing their first episode of schizophrenia (Salisbury, et al., 1998). A decrease in the left, but not right, posterior superior temporal gyrus volume in chronic schizophrenia has also been linked with a decrease in P300 amplitude (McCarley, Nakamura, Shenton, & Salisbury, 2008; McCarley et al., 2002; McCarley et al., 1993). There appears to be some disagreement in the literature regarding this trait in siblings without schizophrenia, some studies report that non-schizophrenic siblings do not exhibit a reduction in P300 amplitude (Winterer, et al., 2001), whilst other studies report that they do exhibit a P300 amplitude reduction (Groom, et al., 2008).

Increases in the auditory P300 latency have been reported in people with schizophrenia (Jeon & Polich, 2003; O'Donnell et al., 1995). This latency increase is also positively correlated with age, with people with schizophrenia exhibiting a more pronounced latency increase associated with age than is found in the normal population (O'Donnell, et al., 1995). However, not all studies have found an increase in latency in the P300. Despite reporting a decrease in P300 amplitude, McCarley et al. (1993) did not find an increase in the P300 latency in people with schizophrenia.

Source localisation of the P300 in the normal population has reported a wide distribution of generators of the auditory P300, although there was distinct generation over the anterior cingulate cortex. In people with schizophrenia a reduction in the anterior cingulate cortex's generation of the P300 was observed (Sabeti, Moradi, & Katebi, 2011).

The literature on auditory EPs further supports the findings in the literature on visual EPs, that there are alterations in the cortical activity and information processing in people with schizophrenia when compared to the normal population.

9. Interhemispheric Transfer Time

Poffenberger (1912) first clearly described the ability to measure the time taken for information to travel from one hemisphere to the other using retinal stimulation. Poffenberger was able to show that information could be selectively presented to the visual cortex of one hemisphere by only stimulating one retinal visual field. Behavioural response times to these stimuli were observed to be longer when the information was presented to the hemisphere contralateral to the cortical motor area required to action a behavioural response to the stimuli (Poffenberger, 1912). The difference in reaction times when the stimuli was presented to the hemisphere contra- or ipsilateral to motor region in the hemisphere required to perform the behavioural

response was considered the time taken for information to travel from one hemisphere to another, and is called the ‘crossed-uncrossed difference’ (Poffenberger, 1912). It has been demonstrated that EEG EPs provide a measure of the IHTT without the need for behavioural responses (Brown, et al., 1994; Saron & Davidson, 1989). Average evoked potential IHTTs can be calculated by presenting a stimulus to one visual field and subtracting the EP latency generated in the hemisphere ipsilateral to the visual field from the EP latency generated in the hemisphere contralateral to the stimulus presentation. The difference between the latencies is the time taken for interhemispheric transfer.

9.1. Behavioural Differences in Interhemispheric Transfer

People with schizophrenia have been found to have reduced or impaired transfer of information between the cerebral hemispheres. In a tactile discrimination task participants were taught to identify visually hidden objects by touch with one hand. When required to identify the same objects with the opposite hand people with schizophrenia had significant deficits compared with control participants (Green, 1978). The schizophrenia group’s results were similar to those of split-brain monkeys on the same task (Lee-Teng & Sperry, 1966), suggesting abnormal interhemispheric information transfer (Green, 1978).

People with schizophrenia also have reduced accuracy in mirror drawing tasks when compared with first degree relatives and controls. This was observed both before and after 6 weeks of receiving antipsychotic medication (Biswas, Nizamie-Haque, Pandey, & Mandal, 1996; Mandal, Singh, Asthana, & Srivastava, 1992). The results suggest that before and after medication administration people with schizophrenia had significantly less accuracy, but not reaction time, than both control

groups. It is postulated that this may represent corpus callosum information transfer deficits (Biswas, et al., 1996).

In the normal population it has been demonstrated that bilaterally presented visual information is processed faster than information presented to one hemisphere alone (Berger, 1988; Brown, Larson, & Jeeves, 1993; Mohr, Pulvermüller, Cohen, & Rockstroh, 2000; Mohr, Pulvermüller, & Zaidel, 1994). This has been termed 'bilateral advantage' and is considered to be the result of interhemispheric communication (Brown, Jeeves, Dietrich, & Burnison, 1999). In contrast to the normal population, people with schizophrenia do not display an accuracy or reaction time advantage for bilaterally presented words (Barnett, et al., 2007; Mohr, et al., 2000), or unfamiliar shapes (Eaton et al., 1979), suggesting interhemispheric communication deficits in this group. Finally, people with schizophrenia have reduced comprehension of aural information when it is presented to the left ear and bilaterally. This deficit was not found for information presented to the right ear (Green & Kotenko, 1980). The authors postulate that this deficit was due to problems during interhemispheric information transfer.

9.2. Electrophysiological Differences in Interhemispheric Transfer Time

Using both the P100 and the N160 VEPs, investigations into IHTTs have found that in the normal right-handed population IHTT from the right to the left hemisphere is faster than from the L-R hemisphere (Barnett & Corballis, 2005; Brown, et al., 1994; Iwabuchi & Kirk, 2009; Marzi, et al., 1991; Moes, et al., 2007; Norwicka, et al., 1996). People who are left handed and have reduced cerebral asymmetry have been found to have symmetry of transfer times between the hemispheres (Iwabuchi & Kirk, 2009). Moreover, this asymmetry of IHTT is not

found in people with schizophrenia. Instead, this group display no significant difference between the transfer times from the right to the left hemisphere and the left to the right hemisphere (Barnett, et al., 2005; Endrass, et al., 2002). However, not all studies have been able to replicate this finding. Whitford et al. (2011) found no difference in the interhemispheric transfer times between people with schizophrenia and control participants. Moreover, in contrast to the studies cited above, Whitford et al. (2011) found IHTT in both people with schizophrenia and controls was faster from the left to the right hemisphere than the reverse when analysing both the P100 and N160 VEPs. The authors also found a significant correlation between reduced white matter integrity (as measured by FA) and longer IHTTs, and observed that people with schizophrenia did not differ from controls in the integrity of the visual fibres of the corpus callosum. The lack of difference found in white matter FA between the schizophrenia and control group was postulated to be the reason that there was no difference in IHTT latencies between the groups (Whitford, et al., 2011).

It has been proposed that findings of symmetry of IHTT in people with schizophrenia, in contrast to the asymmetry found in the general population, represents callosal dysfunction in schizophrenia (Endrass, et al., 2002), or fewer fast conducting axon fibres originating in the right hemisphere of people with schizophrenia relative to controls (Miller, 1996). Barnett et al. (2005) propose that the IHTT symmetry that they observed in people with schizophrenia adds weight to Miller's hypothesis of right hemisphere white matter aberrations in this group. Furthermore, it would be expected that any CC dysfunction would affect EP amplitudes and speed of signal transfer in both directions (Barnett & Kirk, 2005; Marzi, et al., 1991). Their conclusion is also supported by their finding of reduced right hemisphere N160 amplitude in the schizophrenia group compared to controls,

which was not observed in the left hemisphere, suggesting the presence of right hemisphere dysfunction in schizophrenia. In contrast, Whitford et al. (2011) did not find a difference in the P100 or N160 amplitudes between people with schizophrenia and controls.

There are a limited number of studies investigating EPs and IHTT in people with schizophrenia, with the majority supporting symmetry in speed of signal transfer in this population. Further research is needed to clarify some of the discrepancies reported in the data between these studies.

10. Introduction to the Current Study

The literature reviewed above illuminates the presence of a diverse and complex range of differences in the anatomy and function in the brains of people with schizophrenia. Despite this, there does not appear to be one genetic or biological trait present in all people with schizophrenia that can parsimoniously explain the aetiology of the disease. Thus, schizophrenia is still a topic for debate and further investigation. Although no one theory appears to be able to conclusively provide a comprehensive and parsimonious understanding of the disorder, one of the more convincing and comprehensive theories is Miller's (1996, 2008). Miller (1996, 2008) proposes that left hemisphere language functioning requires processing that is temporally specific. He hypothesises that slower conducting small calibre and unmyelinated axons are able to provide this temporal information. He also proposes that spatial processing in the right hemisphere requires faster myelinated or large calibre axons. This results in the left hemisphere having a smaller white to grey volume ratio than the right hemisphere. Moreover, callosal projections are made up of axons projecting from one hemisphere to the other. Therefore, the greater number of fast conducting axons in the right hemisphere results in faster speed of signal transfer from the right to the left (R-

L) hemisphere, and the greater proportion of slower conducting axons in the left hemisphere result in the inverse, that is, slower speed of signal transfer from the left to the right (L-R) hemisphere. Miller (1996, 2008) proposes that this white matter distribution pattern is global within each hemisphere, rather than being specific to language or spatial processing areas (Miller, 1996).

Evidence that supports Miller's (1996) hypothesis is found in the normal population, which has significantly faster R-L than L-R speed of signal transfer between the hemispheres. Moreover, people with schizophrenia do not display a significant difference in IHTT between the R-L and L-R hemispheres. Miller postulates that it is right hemisphere dysfunction, namely the lack of fast conducting axons in the right hemisphere, that causes this difference in people with schizophrenia, resulting in this population having "two left hemispheres" (Miller, 2008, p. 30). However, he does suggest that this is statement is an oversimplification of his hypothesis, and does suggest his theory is open to expansion (Miller, 2008).

The aim of this thesis was to further investigate the demonstrated IHTT alterations in people with schizophrenia. We were guided by Miller's above stated hypothesis, that the right hemisphere in people with schizophrenia has a rediction in fast conducting axons. We also further explored this idea by looking at *within* (intra) hemisphere VEP latencies as well as absolute latencies within each hemisphere in an attempt to further elucidate altered hemispheric axonal type. EEG provided an ideal instrument to test both these hypotheses due to its fine temporal resolution. In consideration of Whitford et al.'s (2011) suggestion that the investigation of only the N160 by Barnett et al. (2005) in their investigation of altered asymmetry in IHTT in people with schizophrenia was a potential drawback to their findings, we analysed both the P100 as well as the N160. This study also looked at the difference between

the *intra*hemispheric latencies of the P100 and N160 (which we have called intra-HTT) in each hemisphere in an attempt to further elucidate white matter types within each hemisphere. According to Miller's (1996) theory it is likely that *intra*-HTTs and the absolute latencies within each hemisphere would also display a similar temporal pattern to that of IHTT, i.e., latencies within the right hemisphere would be faster than within the left hemisphere (Miller, 2008).

Source analysis was utilised to estimate the bilateral sources underlying the P100 and N160, and to reconstruct the current density dynamics of those sources. These density reconstructions were then used to calculate the latency differences between maximum source current densities (Pascual-Marqui, et al., 1994).

This thesis further investigated and analysed data previously collected by a PhD student. The current study aimed to strengthen the outcome of Barnett et al.'s (Barnett, et al., 2005; Barnett & Kirk, 2005) findings by bootstrapping the data and applying source analysis to the data, as well as investigating *intra*-HTT and the absolute latencies of the P100 and the N160.

All participants were male for greater subject homogeneity, and to avoid confounds related to sex (Bachmann et al., 2003; Panizzon et al., 2003; Witelson, 1989), and possible differences between brain structure deficits in male and female people with schizophrenia (Salem & Kring, 1998). Due to the possibility of the existence of several subtypes of schizophrenia, which may have different cerebral laterality profiles, participants were selected who had a symptom profile of predominantly negative symptoms (Gruzelier, 1999) in order to further reduce confounds in the data. The participants fell broadly into the DSM-IV-TR diagnosis: 295.60 Schizophrenia, Residual Type. This type is defined as having previously met

criteria for an episode of schizophrenia, however, the person no longer has prominent positive symptoms, but continues to have some negative symptoms (APA, 1994).

Participants in the schizophrenia group had not been hospitalised for six months prior to testing. They were high functioning, and most were working or studying at university level. The task was designed so both groups (people with schizophrenia and controls) would be able to perform at a similar level. Both groups were right-handed and were matched for handedness using the Edinburgh Handedness Inventory (Oldfield, 1971). This inventory assesses laterality and provides scores that range from -100, reflecting extreme left-handedness to +100, reflecting extreme right-handedness. A score of 0 represents ambilaterality. This ensured, as best as possible, that language laterality was in the left hemisphere for both groups, as left-handers have an increased rate of bilateral or right-sided language representation (Knecht, et al., 2000).

In short, based on Miller's hypothesis of axonal lateralisation in the normal and schizophrenia populations, it was expected that the control group would have faster transfer from the right to the left hemisphere than from the left to the right hemisphere in both the P100 and N160 components. It was expected that the schizophrenia group would have no difference in transfer time for either IHTT direction (right to left, left to right) in the P100 and N160 components. It was expected that the control group would have faster P100 and N160 latencies in the right hemisphere than in the left hemisphere, and that within the schizophrenia group there would be no difference between the P100 and N160 component latencies between the hemispheres. It was also expected that the control group would have faster P100 and N160 latencies in the right hemisphere than the schizophrenia group, and similar latencies in the left hemisphere.

Finally, for intra-HTT within each group it was expected that the control group would have a shorter lag between the latencies in the right hemisphere than in the left hemisphere. Within the schizophrenia group it was expected that there would be no difference in the onset of the P100 and N160 latencies between the right and left hemispheres. It was also predicted that the control group would have a shorter lag between these latencies in the right hemisphere than the schizophrenia group, and that there would be no difference in this lag between the groups in the left hemisphere.

Method

Participants

Participants comprised two groups of males, 13 with schizophrenia and 13 age matched controls. The mean age of the group with schizophrenia was 31.5 years old (*SD* = 8.3), and for controls was 30.8 years old (*SD* = 7.4). All schizophrenia group participants were taking standard atypical antipsychotics at the time of testing (chlorpromazine equivalent 400 mg). The mean number of years that individuals in the schizophrenia group had experienced schizophrenia was 7.8 years (*SD* = 3.3). Control group participants were excluded if they had a history of mental illness, neurological disorder, drug or alcohol abuse, or had a first-degree relative with schizophrenia.

Procedure

Research approval was granted by The Auckland District Health Board Ethics Committee. The control participants were recruited through recruitment notices posted at the University of Auckland. Participants with schizophrenia were recruited through notices placed in mental health outpatient units.

Each participant was informed of the research goals and the experimental procedure and gave written consent. Each member of the schizophrenia group underwent a semi-structured psychological interview lasting approximately an hour to confirm a DSM-IV-TR diagnosis of schizophrenia. The Positive and Negative Symptoms Scale (Kay et al., 1987) was used to assess the symptom profile displayed by the participants. The results indicated that all participants with schizophrenia had predominately negative symptoms (Mean negative = 22.1, *SD* = 2.8; Mean positive = 15.9, *SD* = 3.2). The two groups were matched for handedness using the Edinburgh

Handedness Inventory (Oldfield, 1971). There were no significant differences between the groups for laterality quotient (p = .082), or age (p = .989).

Stimuli

Stimuli were circular checkerboards with a diameter of 1.4° of visual angle. The checkerboards consisted of alternating black and white squares, with an average luminance equal to that of the light grey background, and appeared for 100 ms with their innermost edge 4° to the left (LVF), right (RVF), or on both (BVF) sides of central fixation. The BVF condition was added for reasons not pertinent to the aims of this thesis. Data were segmented and averaged for each of the three conditions (i.e., LVF, RVF, BVF). Catch trial conditions, where no stimuli were presented, were discarded. Catch trials were included to ensure attention was maintained throughout the procedure and that participants did not press the space bar at random time intervals.

The experiment was conducted in a quiet electrically-shielded Faraday chamber where participants were monitored via a closed-circuit camera. Participants sat 57cm from the stimulus display screen (so that 1cm corresponded to 1° of visual angle). Stimuli were presented on a 15" SVGA monitor (640x480 pixel resolution).

Participants were asked to press the keyboard spacebar immediately upon seeing a stimulus appear in any position on the screen. They were asked to make no response if no stimulus was presented (i.e., catch trials). An ‘Anticipation Error’ message appeared if responses were made before stimulus onset. Stimuli were preceded by a variable inter-stimulus time interval (550, 750, or 950 ms) and a central fixation of 1000 ms. Trials in which participants failed to respond within 3 seconds, or made an anticipation error, were re-run so that 380 trials were available for analysis from each subject.

Four blocks of trials were presented. Two blocks were performed with the right hand and two with the left hand in a randomly assigned counterbalanced order (i.e., Right (R)-Left (L)-L-R or L-R- R-L). There was a short practice with each hand before the experimental trials began. Each block consisted of 30 LVF, 30 RVF, 30 BVF, and 5 catch trials. In total there were 380 trials across the four blocks. A randomised trial list was generated for every participant and a brief break separated each block.

Apparatus

The EEG data were acquired (250-Hz sampling rate) with Electrical Geodesics amplifiers (200kΩ input impedance) using a 128-channel Ag/AgCl electrode net (see Appendix A) and the data were amplified (100MΩ input impedance). The data acquisition software was run on a Macintosh GA with 16-bit analogue-to-digital conversion card. The impedances of electrodes ranged from 40kΩ to 60kΩ (average = 43kΩ) which is recommended for this EEG set-up. The EEG data were acquired using a common vertex (Cz) reference and later re-referenced to the off-line nasion electrode. Recordings contaminated by eye movements were rejected according to a criterion of 70μV activity recorded in eye channels.

Statistical Analysis

The data was subjected to two main analyses, an averaged evoked potential (AEP) analysis and a source analysis. As the data were examined with source analysis it was 'bootstrapped' before being submitted to statistical analysis. Source analysis is performed using a set of grand average -1 waveforms from the data. This produces a set of virtual subjects in which the subjects are the grand average of all subjects minus 1 (the excluded subject is different in each virtual subject). This 'bootstrapping'

reduces the variation in the AEP signals from individual differences in the placement of electrodes on the scalp, and individual variation in cranial shape and size. It also reduces signal noise. Bootstrapping thus provides a version of the data that is appropriate for source analysis whilst still retaining individual variation, so it is also appropriate to use in analysis of variance and other statistical methods (Miller, Patterson, & Urlich, 1998).

Average Evoked Potential Analysis

All data was analysed using The Statistical Package for the Social Sciences (SPSS, v.18). Effects were considered significant at alpha < .05. Pairwise comparisons were conducted using a Bonferroni correction to the alpha level. Both the P100 and the N160 latencies from each subject in each condition were recorded from occipito-parietal electrodes bilaterally (OP60 and OP85). An 'in house' AEP viewing programme was used for calculating the approximate median point of both components. Also, both P100 and N160 were determined using the nasion electrode (electrode 17). The P100 was determined as the greatest positive amplitude wave in the data occurring between 80-140 ms, and the N160 was determined as the greatest negative amplitude wave in the data occurring between 140-220 ms (Norwicka & Fersten, 2001).

The data for each of the components were then analysed separately using ANOVA. The direction of the calculated interhemispheric transfer time (IHTT) (right-to-left or R-L, and left-to-right or L-R) was used as the within-subjects factor, and group (controls, schizophrenia) as the between- subjects factor. The R-L IHTT was calculated from the right hemisphere median P100 minus the left hemisphere median P100 when the visual stimulus was presented to the LVF. The L-R IHTT was

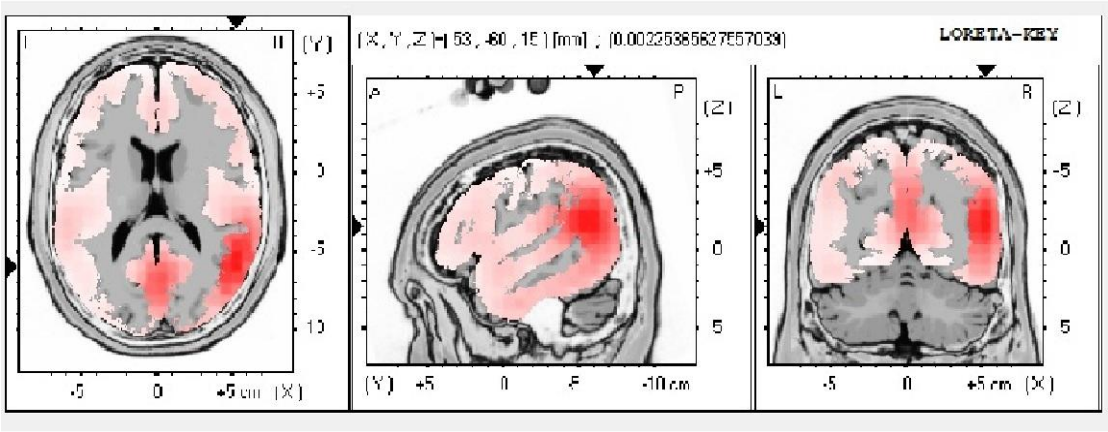
calculated from the left hemisphere median P100 minus the right hemisphere median P100 when the visual stimulus was presented to the RVF. The same procedure was used to calculate the IHTT for the N160 component.

Intrahemispheric latencies were also examined. The difference between the onset time of the P100 and the subsequent onset of the N160 (intra-HTT) in the right hemisphere was compared to the difference in onsets in the left hemisphere. This was explored in each group. The difference between the intrahemispheric P100 and N160 latencies (N160 minus P100) was also examined in each hemisphere in both groups. These latencies were calculated by subtracting the latency of the P100 from the N160 within (as opposed to between) each hemisphere. The latencies of the individual components were analysed within and between the two groups.

Source Localisation

Source localisations were performed using low-resolution electromagnetic tomography (LORETA; Pascual-Marqui et al., 1994). Using all 129 electrodes, source estimations were performed on a window including the time-point at which the potential was maximal for a particular component (e.g., N160). The LORETA solutions were obtained using a minimally regularised version that guaranteed stable solutions (Pascual-Marqui et al., 1994), after which the time course and magnitude of the source current activation was constructed (see figure 1 below). IHTT was then calculated from the latencies of the maximal reconstructed P100 and N160 source activation for each cerebral hemisphere.

A



B

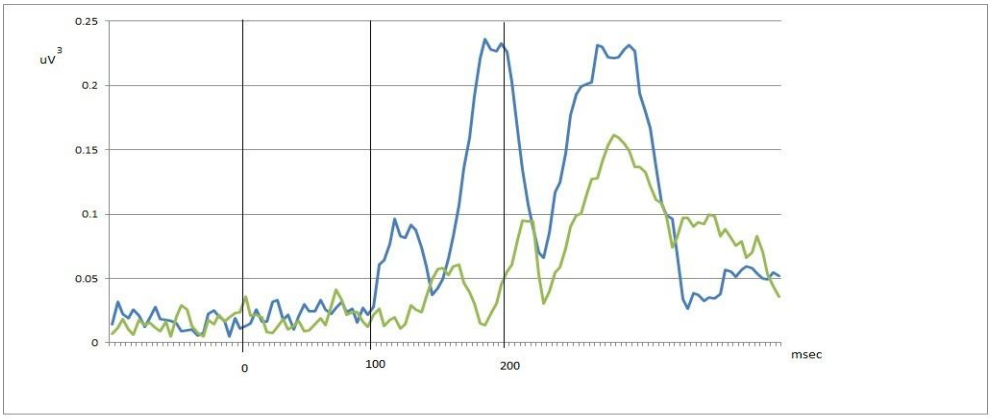


*Figure 1.*Temporal profile of current densities from maximally activated voxels identified by LORETA source estimation.

A. LORETA source estimation for a left visual field stimulus showing maximal activation (at the N160 peak) in right parietal area.

B. Current density reconstruction for the maximally activated right parietal voxel (blue) and the homologous left parietal voxel (green). Absolute latencies are taken from the appropriate peaks in the reconstructed current density over the same time course as that taken for the raw AEP.

Results

Raw AEP Data

P100 IHTT

AEP data for the P100 were analysed using a split-plot ANOVA with direction (R-L, L-R) as the within-subjects factors, group (control, schizophrenia) as the between-subjects factor, and inter-hemispheric transfer time (IHTT) in milliseconds as the dependent variable. IHTT was calculated for each component (P100, N160) as the difference in the peak of the latency from the hemisphere contralateral to stimulus presentation minus the latency of the same component in the hemisphere ipsilateral to stimulus presentation. The analysis revealed significant main effects of direction ($F_{(1, 24)} = 29.07$, $p < .001$) and group ($F_{(1,24)} = 347.41$, $p < .001$), and a significant interaction between direction and group ($F_{(1,24)} = 22.51$, $p < .001$). The main effect of direction indicated that for both groups R-L transfer was faster ($M = 32.77$, $SD = 2.12$) than L-R ($M = 40.46$, $SD = 5.04$). The main effect of group indicated that the control group showed faster IHTT ($M = 21.69$, $SD = 4.07$) than the schizophrenia group ($M = 51.54$, $SD = 4.07$).

For the significant interaction, simple effects tests with Bonferroni adjustment revealed that, as predicted, the control group had significantly faster R-L IHTT ($M = 14.46$, $SD = 3.13$; $p < .001$) than L-R IHTT ($M = 28.92$, $SD = 7.13$; $p < .001$). Also as predicted, the schizophrenia group did not show a significant difference between R-L IHTT ($M = 51.08$, $SD = 2.99$) and L-R IHTT ($M = 52.00$, $SD = 7.13$, $p = .651$). Pairwise comparisons between groups showed the control group had significantly faster R-L IHTT ($M = 14.46$, $SD = 2.99$) than the schizophrenia group (M = 51.08, $SD = 2$ .99, $p < .001$), and this also fits with the predictions of this thesis. The same

trend was observed for the L-R direction, with the control group having significantly faster IHTT (M = 28.92, SD = 7.13) than the schizophrenia group (M = 52.00, SD = 7.13, $p < .001$). This is shown in Figure 2.

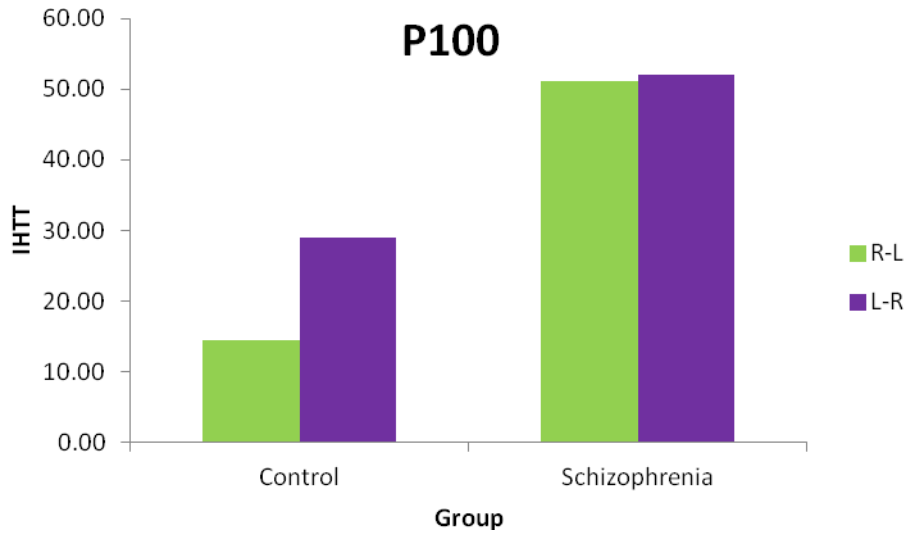


Figure 2. Bar graph showing the raw AEP P100 as a function of IHTT direction

N160 IHTT

The AEP data for the N160 were analysed using a split plot ANOVA with direction (R-L, L-R) as the within-subjects factors, group (control, schizophrenia) as the between-subjects factor, and IHTT as the dependent variable. The analysis revealed significant main effects of direction ($F_{(1, 24)} = 74.84$, $p < .001$), group ($F_{(1, 24)} = 266.41$, $p < .001$), and a significant interaction between direction and group ($F_{(1, 24)} = 49.87$, $p < .001$). The main effect of group indicated that, overall, the control group showed faster IHTT (M = 21.69, SD = 4.50) than the schizophrenia group (M = 50.615.54, SD = 4.50). The main effect of direction indicated that for both groups R-L transfer was faster (M = 28.62, SD = 5.04) than L-R transfer (M = 43.69, SD = 3.82).

For the significant interaction, simple effects tests with Bonferroni adjustment revealed that, as predicted, the control group had significantly faster R-L IHTT (M = 8.00, SD = 7.13, p < .001) than L-R IHTT (M = 35.39, SD = 5.40, p < .001). The schizophrenia group did not show a significant difference between R-L IHTT (M = 49.23, SD = 7.13, p = .27) and L-R IHTT (M = 52.00, SD = 5.40, p = .27), which was also as expected.

Pairwise comparisons between groups showed the control group had significantly faster R-L IHTT (M = 8.00, SD = 7.13) than the schizophrenia group (M = 49.23, SD = 7.13, p < .001), as would be expected. In the L-R direction the same trend was observed. The control group had significantly faster IHTT (M = 35.39, SD = 5.40) than the schizophrenia group (M = 52.00, SD = 4.50, p < .001). It was predicted that there would be no difference between the groups for this comparison. This is shown in Figure 3.

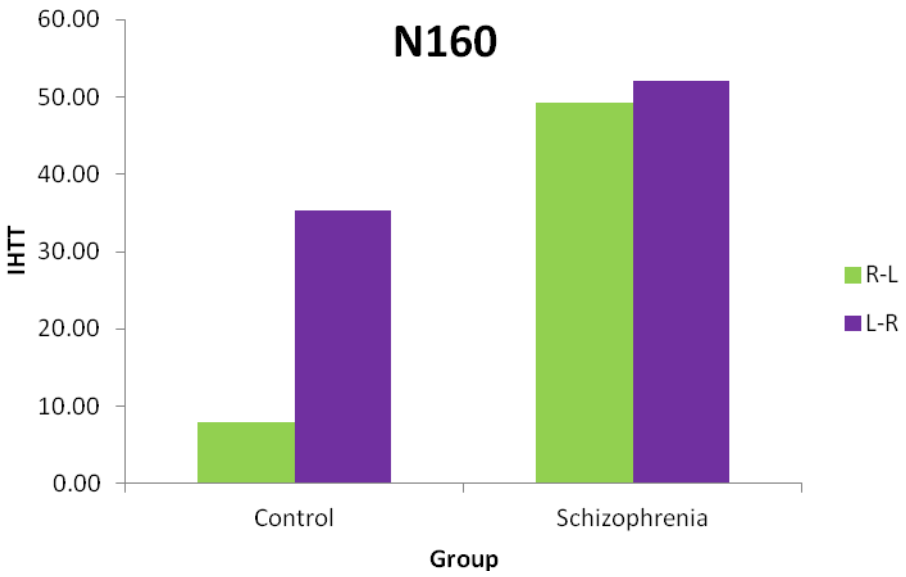


Figure 3. Bar graph showing the raw AEP N160 as a function of IHTT direction.

Intrahemispheric Transfer Time (intra-HTT)

A follow-up ANOVA was performed using the difference between the intrahemispheric P100 and N160 latencies (N160 minus P100), which we have termed intra-HTT, as the dependent measure, hemisphere (right, left) as the within participants factor, and group (control, schizophrenia) as the between-subjects factor.

A significant main effect of group ($F_{(1,24)} = 107.83$, $p < .001$) was observed. There was also a significant interaction effect between hemisphere and group ($F_{(1,24)} = 8.12$, $p = .009$). The main effect of group indicated that overall the control group had longer intra-HTT ($M = 66.46$, $SD = 4.21$) when compared to the schizophrenia group ($M = 49.23$, $SD = 3.21$).

Simple effects tests were performed on the significant interaction. Surprisingly, in the right hemisphere controls ($M = 68.92$, $SD = 6.08$, $p < .001$) showed longer intra-HTTs than did the schizophrenia group ($M = 46.46$, $SD = 6.08$, $p < .001$). Again, in the left hemisphere controls ($M = 64.00$, $SD = 6.52$, $p < .001$) showed longer intra-HTT latencies than the schizophrenia group ($M = 52.00$, $SD = 6.52$, $p < .001$), which was also unexpected (see Figure 4 below).

Also, for the controls, the intra-HTT was marginally greater in the right hemisphere ($M = 68.92$, $SD = 6.08$) compared to the left hemisphere ($M = 64.00$, $SD = 1.81$) however, this only approached significance ($p = .070$). In contrast, for the schizophrenia group, intra-HTT was significantly greater in the left hemisphere ($M = 52.00$, $SD = 6.52$) compared to the right hemisphere ($M = 46.46$, $SD = 6.08$, $p = .043$), this is the inverse of what was expected.

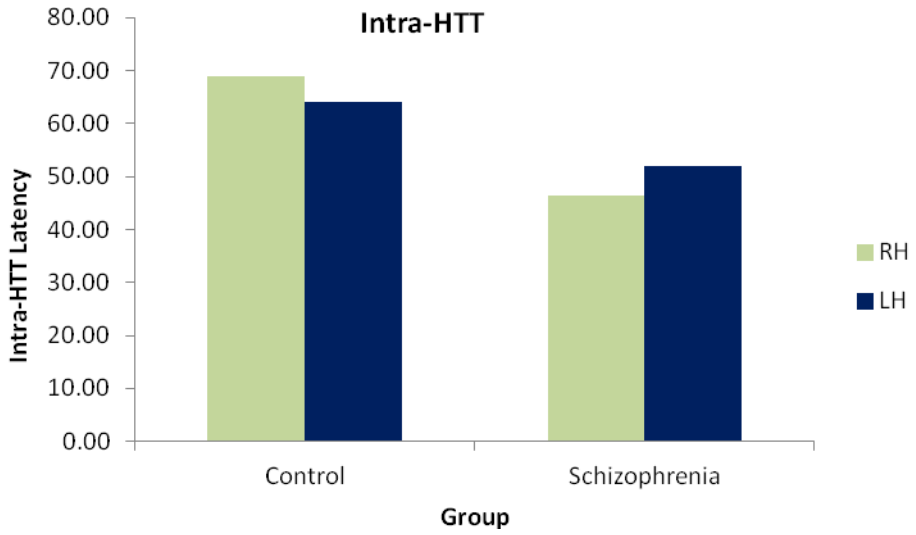


Figure 4. Bar graph showing intra-HTT raw AEP latencies as a function of group and hemisphere.

P100 and N160 Absolute Latencies

This analysis investigated differences between the hemispheres by evaluating the latency of each component and comparing the two *within* (as opposed to between) each hemisphere. This aimed to elucidate the conduction velocity for transmission of action potentials within each hemisphere and to further investigate hemispheric white matter integrity, and possibly white matter type. An ANOVA was performed with component (P100, N160) and hemisphere (right, left) as the within-subjects factors and group (control, schizophrenia) as the between-subjects factor and the time latency of these components as the dependent variable. Significant main effects of component ($F_{(1,24)} = 4446.95$, $p < .001$), hemisphere ($F_{(1,24)} = 132.27$, $p < .001$), and group ($F_{(1,24)} = 57.93$, $p < .001$) were observed. Significant two–way interaction effects between component and group ($F_{(1,24)} = 98.64$, $p < .001$), and hemisphere and group ($F_{(1,24)} = 29.29$, $p < .001$), were observed. A significant three–way interaction effect between component, hemisphere and group ($F_{(1,24)} = 9.76$, $p = .005$) was also observed.

The main effect of component indicated that, as would be expected, the P100 latency (M = 123.31, SD =1.55) was faster overall when compared to the N160 latency (M = 181.15, SD = 2.80). The main effect of hemisphere indicated that across both groups AEPs were faster in the left hemisphere (M = 147.00, SD = 2.23) than the right hemisphere (M = 157.46, SD = 3.28). The main effect of group indicated that, overall, the schizophrenia group had faster AEP latencies (M = 148.77, SD = 2.30) than the control group (M = 155.69, SD = 2.30) (see Figure 5 and Figure 6 below).

Simple effects tests were performed on the significant three-way interaction. For the P100, controls had faster latencies (M = 116.00, SD = 3.28, p = .005) than people with schizophrenia (M = 120.00, SD = 3.28, p = .005) in the left hemisphere, no significant difference was observed between the groups in the right hemisphere (controls: M = 128.92, SD = 2.74; people with schizophrenia: M = 128.31, SD = 2.74, p = .57). Surprisingly, for the N160, people with schizophrenia had significantly faster latencies (M = 174.77, SD = 7.20, p < .001) compared with controls (M = 197.85, SD = 7.20, p < .001) in the right hemisphere. This was also observed in the left hemisphere (people with schizophrenia: M = 172.00, SD = 3.28; controls: M = 180.00, SD = 3.28, p < .001).

As expected, pairwise comparisons further showed that within the control group the P100 latency (M = 128.92, SD= 2.74, p < .001) was significantly faster than the N160 (M = 197.85, SD = 7.20, p < .001) in the right hemisphere and the left hemisphere (P100: M = 116.00, SD = 3.28, p < .001; N160: M = 180.00, SD = 3.28, p < .001). Within the schizophrenia group the same trends were observed with the P100 latency (M = 128.31, SD = 27.36, p < .001) being significantly faster than the N160 (M = 174.77, SD = 7.20, p < .001) in both the right hemisphere and the left

hemisphere (P100: *M* = 120.00, *SD* = 3.28; N160: *M* = 172.00, *SD* = 3.28, *p* < .001), as would be expected.

Finally, surprisingly, pairwise comparisons showed that for the control group the P100 latency was significantly slower in the right hemisphere (*M* = 128.92, *SD* = 2.74) than the left hemisphere (*M* = 116.00, *SD* = 3.28). This was also observed for the N160. That is, the right hemisphere latencies (*M* = 197.85, *SD* = 7.20, *p* < .001) were significantly slower than the left hemisphere latencies (*M* = 180.00, *SD* = 3.28, *p* < .001), the inverse of what was predicted. For the schizophrenia group, P100 latencies were observed to be significantly slower in the right hemisphere (*M* = 128.31, *SD* = 2.74, *p* < .001) than the left hemisphere (*M* = 120.00, *SD* = 3.28, *p* < .001). However, in the schizophrenia group no significant differences were found in the N160 latencies between the right hemisphere (*M* = 174.77, *SD* = 7.20, *p* = .219) and left hemisphere (*M* = 172.00, *SD* = 3.28, *p* = .219), as was predicted.

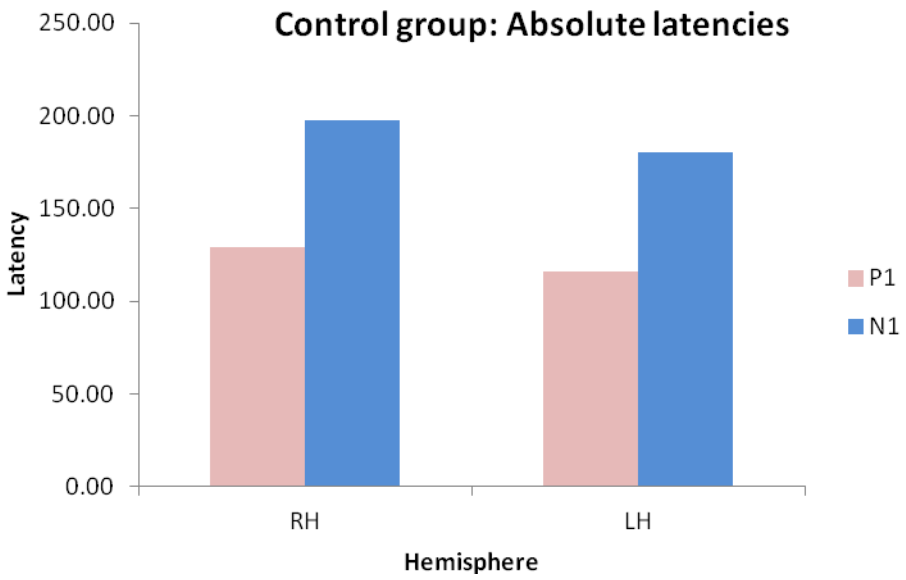


Figure 5. Bar graph showing the P100 and N160 raw AEP absolute latencies in the control group as a function of cerebral hemisphere.

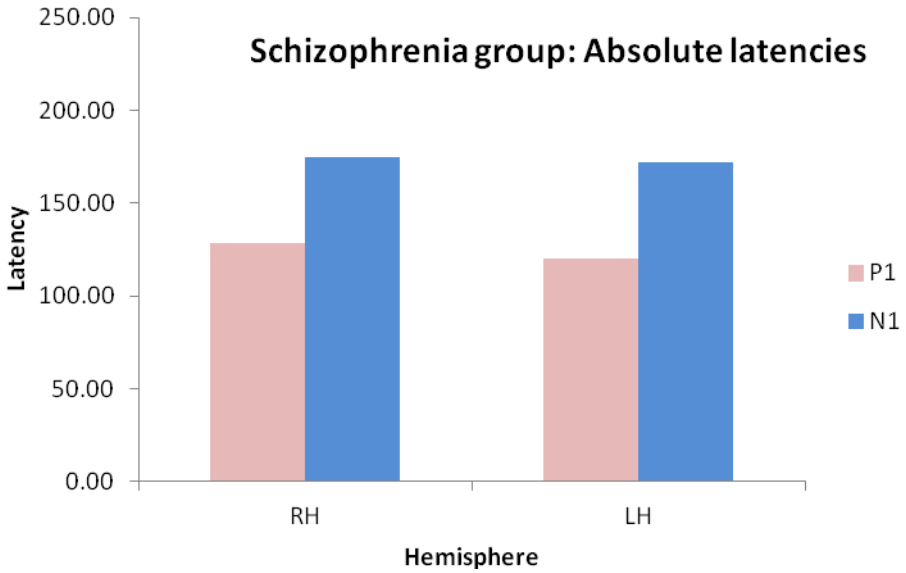


Figure 6. Bar graph showing the P100 and N160 raw AEP absolute latencies in the schizophrenia group as a function of cerebral hemisphere.

LORETA Source Estimation Data

The same procedure used analyse the AEP data was used to analyse the source localised data.

P100 IHTT

The AEP data for the P100 were analysed using a split plot ANOVA with direction (R-L, L-R) as the within-subjects factors, group (control, schizophrenia) as the between-subjects factor and inter-hemispheric transfer time (IHTT) in milliseconds as the dependent variable. The analysis revealed significant main effects of direction ($F_{(1, 24)} = 10.48$, $p = .004$) and group ($F_{(1,24)} = 1053.64$, $p < .001$), and a significant interaction between direction and group ($F_{(1,24)} = 55.62$, $p < .001$). The main effect of group indicated that, overall, the control group showed faster IHTT ($M = 19.08$, $SD = 2.38$) than the schizophrenia group ($M = 49.39$, $SD = 2.38$). The main

effect of direction indicated that, for both groups, R-L transfer was faster (*M* = 32.46, *SD* = 2.27) than L-R (*M* = 36.00, *SD* = 2.84).

Simple effects tests with Bonferroni adjustment, for the significant interaction, revealed that, as expected, controls had significantly faster R-L IHTT (*M* = 13.21, *SD* = 3.24) than L-R IHTT (*M* = 24.92, *SD* = 4.03, $p < .001$). However, the schizophrenia group had significantly faster L-R (*M* = 47.08, *SD* = 4.03) than R-L (*M* = 51.69, *SD* = 3.24) IHTT ($p = .006$). Comparisons between groups showed the control group had significantly faster R-L IHTT (*M* = 13.21, *SD* = 3.24) than the schizophrenia group (*M* = 51.70, *SD* = 3.24, $p < .001$). The same trend was observed for the L-R direction with the control group having significantly faster IHTT (*M* = 24.92, *SD* = 4.03) than the schizophrenia group (*M* = 47.08, *SD* = 4.03, $p < .001$). This is shown in Figure 7 below.

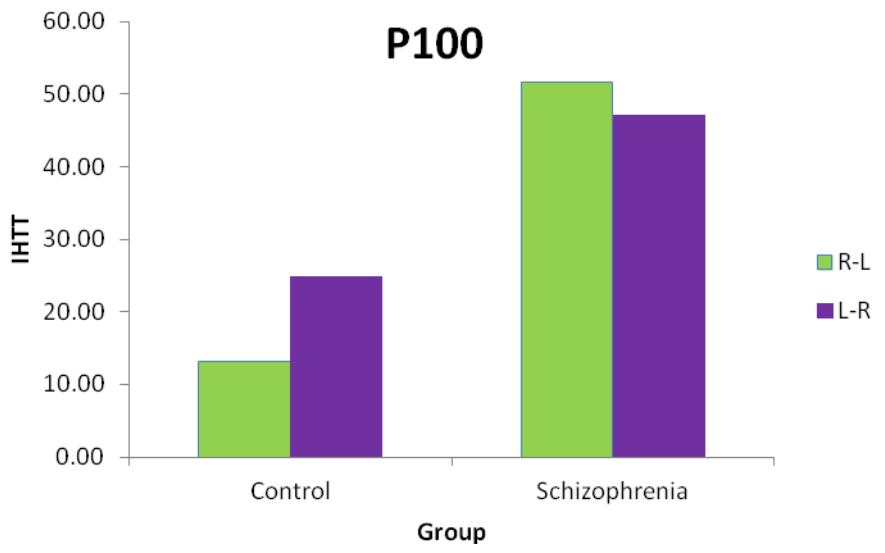


Figure 7. Bar graph showing the source localised P100 as a function of IHTT direction.

N160 IHTT

The AEP data for the N160 were analysed using a split plot ANOVA with direction (R-L, L-R) as the within-subjects factors, group (control, schizophrenia) as the between-subjects factor, and IHTT as the dependent variable. The analysis revealed significant main effects of direction ($F_{(1, 24)} = 5.88$, $p = .023$), group ($F_{(1, 24)} = 65.24$, $p < .001$), and a significant interaction between direction and group ($F_{(1, 24)} = 6.24$, $p = .02$). The main effect of group indicated that, overall, the control group was faster ($M = 18.15$, $SD = 10.44$) than the schizophrenia group ($M = 51.23$, $SD = 10.44$). The main effect of direction indicated that, for both groups, R-L transfer was faster ($M = 29.69$, $SD = 2.27$) than L-R ($M = 39.69$, $SD = 14.62$).

Simple effects tests with Bonferroni adjustment, for the significant interaction, revealed that controls had significantly faster R-L IHTT ($M = 8.00$, $SD = 3.28$) than L-R IHTT ($M = 28.31$, $SD = 20.67$, $p = .002$), as predicted. And as expected, the schizophrenia group did not show a significant difference between R-L IHTT ($M = 51.39$, $SD = 3.24$) and L-R IHTT ($M = 51.08$, $SD = 20.67$, $p = .958$). Comparisons between groups showed the control group had significantly faster R-L IHTT ($M = 8.00$, $SD = 3.24$) than the schizophrenia group ($M = 51.39$, $SD = 3.24$, $p < .001$), as expected. In the L-R direction the same trend was observed. The control group had significantly faster IHTT ($M = 28.31$, $SD = 20.67$) than the schizophrenia group ($M = 51.08$, $SD = 20.67$, $p = .010$). This is shown in Figure 8.

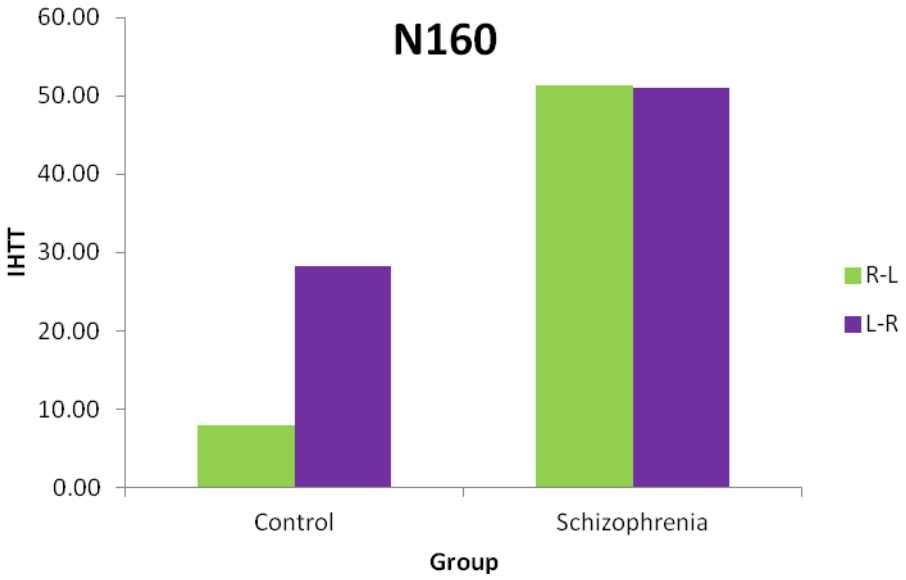


Figure 8. Bar graph showing the source localised N160 as a function of IHTT direction.

Intrahemispheric Transfer Time (intra-HTT)

A follow-up ANOVA was performed using the difference between the intrahemispheric P100 and N160 latencies (N160 minus P100), which we have termed intra-HTT, as the dependent measure, hemisphere (right, left) as the within-subjects factor, and group (control, schizophrenia) as the between-subjects factor.

A significant main effect of hemisphere ($F_{(1,24)} = 4.85$, $p = .037$) and group ($F_{(1,24)} = 479.06$, $p < .001$) was observed. There was also a significant interaction effect between hemisphere and group ($F_{(1,24)} = 24.14$, $p < .001$). Surprisingly, the main effect of group indicated that, overall, the control group had longer intra-HTT latencies ($M = 66.92$, $SD = 2.52$) when compared to the schizophrenia group ($M = 45.23$, $SD = 2.52$). The main effect of hemisphere indicated that overall the right hemisphere had longer intra-HTT latencies ($M = 57.08$, $SD = 2.41$) when compared to the left hemisphere ($M = 55.08$, $SD = 2.45$), this was also surprising.

Simple effects tests were performed on the significant interaction. For the right hemisphere, controls (M = 70.15, SD = 3.38, $p < .001$) showed longer intra-HTT than the schizophrenia group (M = 44.00, SD = 3.38, $p < .001$). This trend was repeated in the left hemisphere, where controls (M = 63.69, SD = 3.46, $p < .001$) showed a longer intra-HTT than the schizophrenia group (M = 46.46, SD = 3.46, $p < .001$) (see Figure 9 below).

Also, for the controls, intra-HTT was significantly greater in the right hemisphere (M = 70.15, SD = 3.38, $p < .001$) compared to the left hemisphere (M = 63.69, SD = 3.46, $p < .001$), the inverse of what was predicted. In contrast, in the schizophrenia group, the difference between the intra-HTTs in the left hemisphere (M = 52.00, SD = 4.25) and the right hemisphere (M = 46.46, SD = .3.46) only approached significance (p = .067).

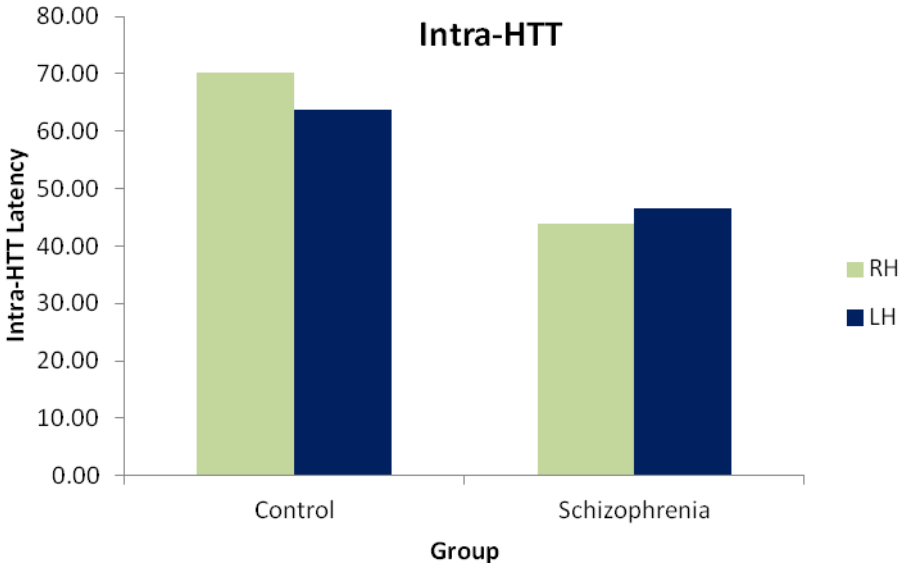


Figure 9. Bar graph showing source reconstructed intra-HTT as a function of group and hemisphere.

P100 and N160 Absolute Latencies

This analysis investigated differences between the hemispheres by evaluating the latency of each component and comparing the two *within* (as opposed to between) each hemisphere. This aimed to elucidate the conduction velocity for transmission of action potentials within each hemisphere and to further investigate hemispheric white matter integrity, and possibly white matter type. An ANOVA was performed with component (P100, N160) and hemisphere (right, left) as the within-subjects factors and group (control, schizophrenia) as the between-subjects factor and the time latency of these components as the dependent variable.

Significant main effects of component ($F_{(1,24)}$ = 12805.81, p < .001), hemisphere ($F_{(1,24)}$ = 199.00, p < .001), and group ($F_{(1,24)}$ = 131.76, p < .001) were observed. Significant two–way interaction effects between component and group ($F_{(1,24)}$ = 479.06, p < .001), and hemisphere and group ($F_{(1,24)}$ = 123.44, p < .001) were also observed. Finally, a significant three–way interaction effect between component, hemisphere and group ($F_{(1,24)}$ = 24.144, p < .001) was observed.

The main effect of component indicated that the P100 latency (M = 122.46, SD = 1.51) was faster overall when compared to the N160 latency (M = 178.54, SD = 1.22), as would be expected. The main effect of hemisphere indicated that across both groups AEPs were faster in the left hemisphere (M = 146.15, SD = 1.76) than the right hemisphere (M = 154.85, SD = 1.19). The main effect of group indicated that, overall, the schizophrenia group had faster AEP latencies (M = 147.23, SD = 1.44) than the control group (M = 153.77, SD = 1.44) (see Figure 10 and Figure 11 below).

Simple effects tests were performed on the significant three-way interaction. For the P100, controls had faster latencies (M = 114.15, SD = 3.42, p < .001) than people with schizophrenia (M = 123.08, SD = 3.42, p < .001) in the left hemisphere,

but surprisingly, no significant difference was observed between the groups in the right hemisphere (controls: M = 126.46, SD = 2.84; people with schizophrenia: M = 126.15, SD = 2.84, p = .787). For the N160, people with schizophrenia had significantly earlier latencies (M = 170.15, SD = 1.80, p < .001) compared with controls (M = 196.62, SD = 1.80, p < .001) in the right hemisphere. This was also observed in the left hemisphere (people with schizophrenia: M = 169.54, SD = 2.63; controls: M = 177.85, SD = 2.63, p < .001). Both these findings were the inverse of what was predicted.

As expected, pairwise comparisons further showed that within the control group the P100 latency (M = 126.46, SD = 2.84, p < .001) was significantly faster than the N160 (M = 196.62, SD = 1.80, p < .001) in the right hemisphere and the left hemisphere (P100: M = 114.15, SD = 3.42, p < .001; N160: M = 177.85, SD = 2.63, p < .001). Within the schizophrenia group the same trends were observed with the P100 latency (M = 126.15, SD = 2.84, p < .001) being significantly faster than the N160 (M = 170.15, SD = 1.80, p < .001) in both the right hemisphere and the left hemisphere (P100: M = 123.08, SD = 3.42; N160: M = 169.54, SD = 2.63, p < .001), as predicted.

Finally, pairwise comparisons also showed that in the control group the P100 latency was significantly slower in the right hemisphere (M = 126.46, SD = 2.84) than the left hemisphere (M = 114.15, SD = 3.42, p < .001). This was also observed for the N160. That is, the right hemisphere latencies (M = 196.62, SD = 1.80, p < .001) were significantly slower than the left hemisphere latencies (M = 177.85, SD = 2.63, p < .001). Both these findings are the inverse of what was predicted. In the schizophrenia group, P100 latencies were observed to be significantly slower in the right hemisphere (M = 126.15, SD = 2.88,) than the left hemisphere (M = 123.08, SD = 3.42, p = .027), as would be predicted. Surprisingly, however, in the schizophrenia group no

significant differences were found in the N160 latencies between the right hemisphere (M = 170.15, SD = 1.80, p =. 449) and left hemisphere (M = 169.54, SD = 2.63, p = .449).

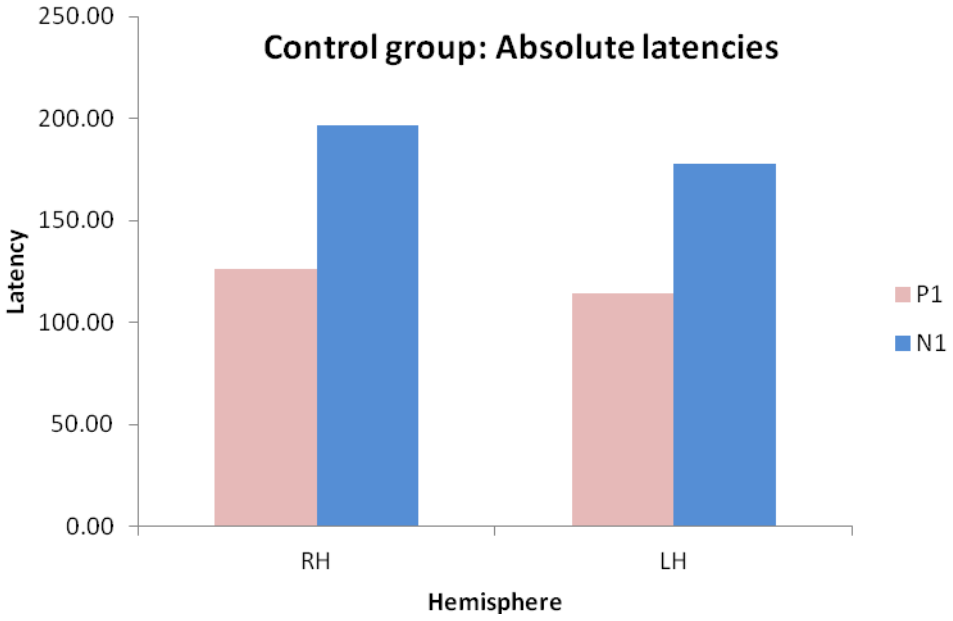


Figure 10. Bar graph showing the P100 and N160 source localised absolute latencies in the control group as a function of cerebral hemisphere.

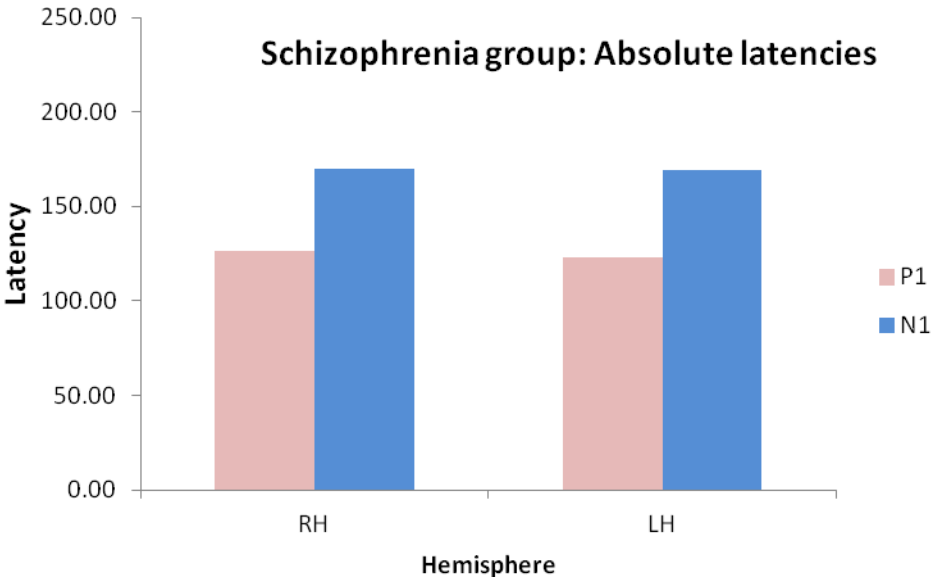


Figure 11. Bar graph showing the P100 and N160 source localised absolute latencies in the schizophrenia group as a function of cerebral hemisphere.

Discussion

A 128-channel EEG and the Poffenberger task were used to investigate the IHTTs between the hemispheres (R-L, L-R) in the normal population and in people with schizophrenia. The intra-HTT within and between each group were also investigated as were the absolute latencies of each of the P100 and N160 components within and between each hemisphere of each group. LORETA source reconstruction was used to reconstruct the current density dynamics believed to underlie each of the visual AEP components under question. The experiment was guided by Miller's (1996, 2008) hypothesis that states that within the normal population there is an asymmetrical distribution between the right and left hemispheres of fast and slow conducting axons. Miller (1996, 2008) has suggested the right hemisphere has a greater ratio of fast conducting axons and the left hemisphere has a greater ratio of slow conducting axons. He proposes that this asymmetry of hemispheric axonal distribution allows for the specialised functions of each hemisphere, namely, fast parallel processing of visuospatial information in the right hemisphere and temporally precise processing of language in the left hemisphere. This distribution of white matter, Miller (1996, 2008) proposes, results in asymmetrical transfer of information between the cerebral hemispheres (faster R-L than L-R) in the normal population. Furthermore, Miller (1996, 2008) proposes that a developmental anomaly results a reduction of fast conducting fibres in the right hemisphere in people with schizophrenia, leading to a symmetrical distribution of white matter between the two hemispheres, and symmetry of IHTT. Specifically, this experiment aimed to test these hypotheses and add to findings of IHTT differences in both people with schizophrenia and the normal population.

1. AEP Data: Interhemispheric Transfer Time

The P100 and the N160 IHTT data collected in this study appear to add further support to Miller's (1996, 2008) hypothesis that there is a reduction of fast conducting axons in the right hemisphere in people with schizophrenia. Overall, in both the P100 and N160 components, the control group had faster IHTTs than the schizophrenia group, indicating the control group had faster overall communication between the hemispheres. Interestingly, in both the P100 and N160 components, the main effect of group indicated that overall IHTT was faster from the R-L than L-R.

Within the control group IHTT was faster from R-L than from L-R in both the P100 and N160 components. Within the schizophrenia group there was no significant difference in the IHTT from the R-L and the L-R in either component. This is the result expected by Miller's (1996, 2008) hypothesis.

One possible explanation for the decreased IHTT in the schizophrenia group could be aberrations in white matter, leading to reduced speed of interhemispheric communication. Moreover, the absence of faster R-L IHTT in the schizophrenia group may reflect a decrease in right hemisphere white matter myelination, calibre, or integrity in people with schizophrenia (Miller, 1996). IHTT has been linked with white matter integrity (Whitford, et al., 2011), which further supports Miller's (1996, 2008), Barnett and Kirk's (2005), and Barnett et al.'s (2005) hypotheses, and the interpretation of the IHTT data from this thesis, that the difference between the control group and schizophrenia group IHTT data are evidence of white matter abnormalities in the schizophrenia population. This also fits with reported bilateral differences in temporal and parietal lobe white matter, and CC white matter reported in people with schizophrenia (Bersani, et al., 2010; Knöchel, et al., 2012; Lim et al., 1999; Mori et al., 2007; Walterfang, et al., 2009; Walterfang, et al., 2008).

This study investigated IHTT in both the P100 and N160, unlike Barnett et al. (2005) and Barnett and Kirk (2005) who used the N160, but not the P100 to measure IHTT. The findings of the IHTT data from the P100 and N160 in this thesis supports the growing body of evidence that in the normal population IHTT is faster from the R-L than from the L-R, and that there are alterations in this asymmetry in the schizophrenia population (Barnett & Corballis, 2005; Barnett, et al., 2005; Barnett & Kirk, 2005; Brown, et al., 1994; Marzi, et al., 1991; Moes, et al., 2007; Norwicka, et al., 1996). Moreover, symmetry of IHTT in people with schizophrenia has also been found for linguistic and auditory stimuli (Barnett & Kirk, 2005; Endrass, et al., 2002), suggesting that this finding is not confined to VEP data.

1.1. Intrahemispheric Transfer Time (intra-HTT)

The intra-HTT latencies were investigated in an attempt to ascertain if there were differences in the time between the onsets of each component within each hemisphere of each group. However, an important point to consider when interpreting the intra-HTT data is our inability to decisively conclude that we are measuring serial activations within a single network within a hemisphere. This confound is discussed further in section 2.1 below.

Miller's hypothesis (1996, 2008) would suggest that in the normal population intra-HTT latencies in the right hemisphere may be shorter than in the left hemisphere, as he proposes that the left hemisphere has fewer fast conducting axonal fibres. It is postulated here that this would result in faster transfer from the location of the P100 generator in the occipital lobe to the location where the N160 is generated in the occipital and parietal/temporal areas (Bokura, et al., 2001; Clark, et al., 1995; Di Russo, et al., 2001; Hopf, et al., 2002). Furthermore, Miller's (1996, 2008) hypothesis

would suggest that within the schizophrenia group there would be no difference between the hemispheres in intra-HTT due to a reduction in fast conducting fibres in the right hemisphere, resulting in 'two left hemispheres' (Miller, 2008, p. 30).

Surprisingly, the control group had longer intra-HTT latencies in both the right hemisphere and the left hemisphere when compared to the schizophrenia group, suggesting slower axonal conduction times between the occipital and parietal and/or temporal lobes of both hemispheres (Bokura, et al., 2001; Clark, et al., 1995; Di Russo, et al., 2001; Hopf, et al., 2002). This aspect of the data appears to be contrary to what would be predicted by Miller's (1996, 2008) hypothesis. It is possible that this may indicate some kind of processing advantage or aberrant processing in the schizophrenia group.

Surprisingly, within the control group the difference between the intra-HTT latencies in the right hemisphere and in the left hemisphere only approached significance, with longer times observed between the latencies in the right hemisphere. Within the schizophrenia group the intra-HTT in the right hemisphere was found to be shorter than the intra-HTT in the left hemisphere, when it would be predicted by the AEP IHTT data (and Miller's (1996, 2008) hypothesis) that no significant difference would be observed. Although significance was not reached in the control group, this pattern of findings are in line with what would be predicted by the observed greater left than right white matter FA and parallel diffusion in the occipital and temporal lobes of the left hemisphere in the normal right-handed male population (Iwabuchi et al., 2011), but appears contrary to what would be predicted by Miller (1996). Certainly, it would appear that the difference between the controls and those with schizophrenia on this measure suggests that a different process or system is involved.

1.2. P100 and N160 Absolute Latencies

Further analysis of the absolute latencies of the two components in the AEP data found that people with schizophrenia had faster latencies overall when compared with the control group. This may reflect differences in ascending pathways via the thalamus for example, rather than any difference in neocortical processing. However, there may be a contribution of neocortical registration of ascending input at the neocortex. To the extent that the differences in absolute latencies are due to such differences in neocortex, the direction of the group difference would be surprising. Miller's hypothesis (1996, 2008) would predict that the control group would have faster latencies overall, as he suggests people with schizophrenia have a slowing in right hemisphere axonal conduction. It might, therefore, be predicted that this would result in an increase in the mean of the schizophrenia group's latencies. However, the absolute latency data does fit with the finding that overall, people with schizophrenia had shorter intra-HTT AEP latencies than the control group. Again we conclude that different systems underlie the differences between control and schizophrenia groups.

Moreover, overall, the latencies of both components in both groups were faster in the left hemisphere than in the right hemisphere. Miller's (1996, 2008) hypothesis would predict the inverse finding, due to his hypothesis of greater numbers of fast conducting axons in the right hemisphere in the normal population. However, the data found in this study does fit with the asymmetry of white matter distribution found by Iwabuchi et al. (2011), who observed that the left occipital and temporal lobes had greater FA and parallel diffusion than the right hemisphere. Again, we might suggest that the ascending system – including the occipital to parietal cortex projection— differs qualitatively in controls from that of the parietal IHTT system; interestingly,

the difference between controls and those with schizophrenia is in a different direction on these measures.

1.2.1. P100

Controls had faster P100 AEPs in the left than in the right hemisphere, and the same pattern was observed in people with schizophrenia. This is surprising as Miller's (1996, 2008) hypothesis would predict that the control group would have faster latencies in the right hemisphere and that there would be no difference in the latencies between the hemispheres in people with schizophrenia. However, this finding in the control group is in line with Iwabuchi et al.'s (2011) data, and suggests that people with schizophrenia have the same pattern of axonal myelination in both hemispheres as the normal population, although this is at odds with Miller's (1996, 2008) hypothesis. This however, does not appear to fit with the above reported IHTT data. As noted above, this may suggest that the generators of the absolute latencies and those that project to the CC are impacted differently in the people with schizophrenia.

The control group had faster P100 latencies in the left hemisphere than the schizophrenia group, while there was no significant difference in the P100 latencies between the groups in the right hemisphere. Again, this aspect of the data is the reverse of what would be predicted by Miller (1996, 2008). If it is assumed that the AEP and source analysis patterns displayed by the control group are 'normal', the data suggests that there is a slowing in the P100 latency in the left occipital lobe of the schizophrenia group (Ducati, et al., 1988; Pratt, et al., 1982). This may reflect several possible axonal alterations in the left hemisphere in the schizophrenia group, including aberrations in the optic tract, in thalamic axons projecting to the striate and parastriate cortex, and/or deficits in the striate and parastriate cortex itself, (Di Russo,

et al., 2001; Ducati, et al., 1988). It is difficult to speculate as to the meaning of this result as the subcortical and cortical generators of the P100 are not completely understood. But, this finding does appear to reflect alterations in the left occipital white matter in people with schizophrenia.

1.2.2. N160

The control group had slower N160 AEP latencies in both hemispheres when compared to the schizophrenia group. This aspect of the data is surprising given Miller's (1996, 2008) hypothesis of a reduction in right hemisphere white matter in people with schizophrenia. It would be expected that the control group would have faster right hemisphere N160 latencies than people with schizophrenia and have the same latency within the left hemisphere. As VEP latencies have been demonstrated to be linked to axonal size and myelination, it must be suggested that this is due to a larger diameter or myelinated axons in the schizophrenia group in the occipital and temporal/parietal lobes compared with the control group, as this is the logic that is being applied to the interpretation of shorter latencies in the control group. However, this is surprising as people with schizophrenia have been demonstrated to have an overall decrease in white matter FA, possibly due to a decrease in myelination, when compared to the normal population (Kanaan et al., 2009; Minami et al., 2003; White et al., 2011).

Within the control group the N160 was earlier in the left hemisphere than the right hemisphere in both the AEP and source analysis data. This suggests that within the control group there are faster conducting axons in left occipital and temporal and/or parietal lobes than the right hemisphere (Bokura et al., 2001; Clark et al., 1995; Di Russo et al., 2001; Hopf et al., 2002). Although this aspect of the data does not

appear to fit with Miller's hypothesis (1996, 2008) or the IHTT data, it does fit with Iwabuchi et al.'s (2011) observed greater FA and parallel diffusion in the left than right occipital and temporal lobes in the normal right handed male population.

Finally and to reiterate, it seems that there are at least two patterns of data in the control population. That relating to ascending systems to, and intrahemispheric projections from, the occipital lobe, and that relating to interhemispheric transfer of information. It seems that those in the schizophrenia group differentially differ from controls on measures that potentially access these two systems.

2. Source Reconstructed Data: Interhemispheric Transfer Time

The analysis of the source reconstructed (source current density) data provided very similar results to the AEP data. However, there were some differences found between the raw AEP and source reconstructed results. These are discussed below in the sections relevant to those particular results.

Overall, for calculations based on both the P100 and N160 components, the control group had faster IHTTs than the schizophrenia group, indicating faster overall speed of signal transfer between the hemispheres in the control group, as would be expected (Miller, 1996). Interestingly, the main effect of group indicated that overall IHTT was faster from the R-L than L-R. Within the control group IHTT was faster from R-L than from L-R in both the P100 and N160 components, as was expected and this fits with Miller's (1996, 2008) hypothesis.

One difference observed between the AEP and source data was faster L-R than R-L IHTT in the P100 component source reconstruction data in the schizophrenia group. No significant difference between R-L and L-R IHTT was found in the AEP data and no significant difference was found within the schizophrenia group in IHTT from the R-L and L-R hemisphere in the N160 component. Interestingly, this faster

left to right P100 IHTT is still slower than both the right to left and left to right IHTT latencies in the control group. This finding may point to a reduction in fast conducting axons in both the right hemisphere and left hemisphere occipital lobe in schizophrenia when compared with the control group, which fits with Miller's (2006; 2008) hypothesis. Changes in white matter in both the right and left occipital lobes have been reported in people with schizophrenia, which may be linked to these findings (Agartz, Andersson, & Skare, 2001; Lim, et al., 1999; Shenton, et al., 2001).

Another recent study has reported faster L-R IHTT in people with schizophrenia (Whitford, et al., 2011). This study investigated IHTTs of the visual evoked P100 and N160 using current source density analysis. Interestingly, IHTTs in both the control group and in the schizophrenia group were observed to be faster from the L-R hemisphere in both the P100 and N160. This is very surprising as there is strong evidence from other studies that suggest that in the normal population IHTT is faster from the R-L than the L-R hemisphere (Barnett & Corballis, 2005; Brown, et al., 1994; Iwabuchi & Kirk, 2009; Marzi, et al., 1991; Moes, et al., 2007; Norwicka, et al., 1996) . Moreover, Whitford et al. (2011) found no significant difference between the IHTT of the normal population and people with schizophrenia. Whitford et al. (2011) used DTI-derived FA to investigate the integrity of the visual fibres of the CC in both their control and schizophrenia group. They observed that IHTTs were positively correlated to FA, and found no difference in FA between the two groups. Whitford et al. (2011) suggested that their use of current source density may provide a more accurate measure of VEP latencies than looking at the raw VEP latencies. Interestingly, the only data from this thesis that is in line with Whitford et al.'s (2011) findings is the faster L-R IHTT in the P100 observed in people with schizophrenia. The rest of the data from the current study are in conflict with Whitford et al.'s

findings. Namely, the IHTT in the control group of the current data was faster in the R-L direction in both components. Moreover, in the schizophrenia group in this study in the N160 AEP and source localised components demonstrated no difference in the IHTTs from the R-L and the L-R hemispheres. Lastly, LORETA source reconstructed latencies are arguably more accurate than current source density (Pascual-Marqui, et al., 1994). This adds robustness to the findings reported here and elsewhere that in the controls there will be faster R-L IHTT.

Unlike the present study, Whitford et al. (2011) included female participants in both their schizophrenia and control group. This presents a significant possible confound in their study, and may partly explain their findings. Women have been found to have different latencies and amplitudes in different VEP components when compared with males (Lee, et al., 2010), and have shorter IHTTs (Moes, et al., 2007) and less asymmetry in IHTT than men (Norwicka & Fersten, 2001). Moreover, woman with schizophrenia been found to have greater CC density than males with schizophrenia (Highley et al., 1999); and have a different disease presentation and course, including age of onset, which may indicate a possible sex hormone interaction with the disease (Häfner, Behrens, Vry, & Gattaz, 1991; Häfner, et al., 1993; Salem & Kring, 1998).

Whitford et al.'s (2011) failure to find difference between the control group and schizophrenia group could be linked to the inclusion of women in their participant groups. It is possible that the lack of WM alterations in either group is linked to the their failure to find a difference in IHTT between the groups, as IHTT is linked to white matter integrity (Whitford, et al., 2011). Lastly, Whitford et al. (2011) do not appear to have used a group of people with schizophrenia from a sub-group with homogenous symptoms. This may also add a further confound to their findings as, as

reported above, there appears to be strong evidence to suggest that different symptom subtypes have different neurobiological presentations (Gruzelier, 1999). To avoid this confound the current study used a group of people with schizophrenia with a homogenous symptom profile: predominantly negative symptoms.

2.1. Intrahemispheric Transfer Time (intra-HTT)

Several differences were found between the AEP and the source reconstructed data in the intra-HTT results. The control group had longer intra-HTT latencies overall when compared to the schizophrenia group. The main effect of hemisphere observed in the source analysis data was not found in the AEP data. This main effect in the source reconstructed data found that across both groups intra-HTT was longer in the right hemisphere than the left hemisphere. As LORETA reconstructed source data is arguably more accurate than raw AEP latencies this finding is considered to more accurate than the lack of significance found in the raw AEP data. Although this aspect of the data is not in line with Miller (1996), this pattern would be predicted in the normal population by the greater left than right occipital and temporal white matter distribution in the normal population found by Iwabuchi et al. (2011).

Surprisingly, the control group had longer intra-HTT latencies in both the right hemisphere and the left hemisphere when compared to the schizophrenia group.

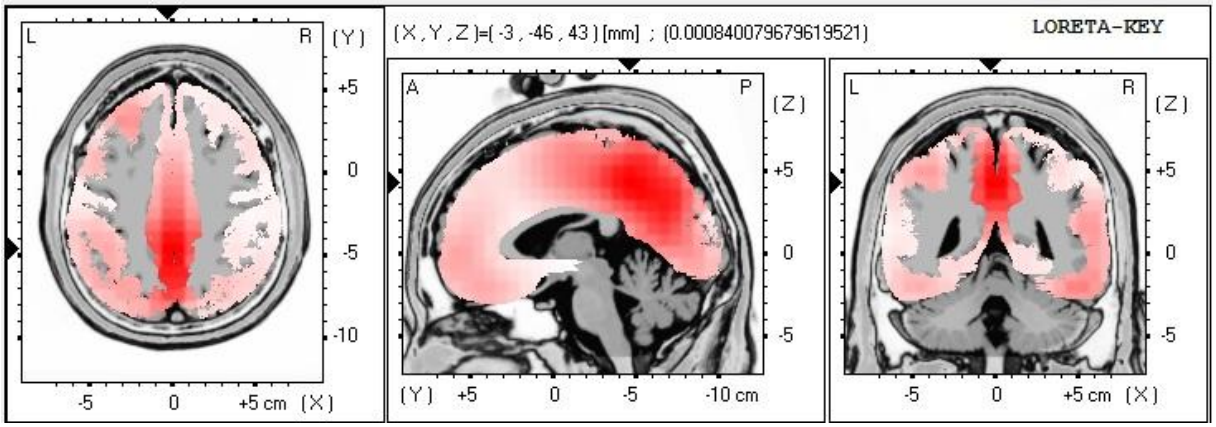
Within the control group the intra-HTT latencies were longer in the right hemisphere than the left hemisphere. This difference only approached significance in the AEP data. Both the AEP and source reconstructed data's pattern of intra-HTT difference was in the same direction. These findings in the control group are in line with what would be predicted by the observed greater left than right white matter FA and parallel diffusion in the occipital and temporal lobes of the left hemisphere in the

normal right-handed male population (Iwabuchi, et al., 2011), but does not appear to fit with Miller's (1996) prediction.

Within the schizophrenia group the difference between the intra-HTTs in the right and the left hemisphere only approached significance, with shorter intra-HTT in the right hemisphere than the left hemisphere. This is in contrast with the raw AEP data which found the intra-HTT in the right hemisphere to be significantly longer than in the left hemisphere. The LORETAs more accurate latencies are in line with the symmetry of white matter between the hemispheres postulated by Miller (1996, 2008).

An important point to consider when interpreting the intra-HTT data is our inability to decisively conclude that we are measuring intra-HTT. This confound is highlighted by the source estimations in figure 12 below.

A



B

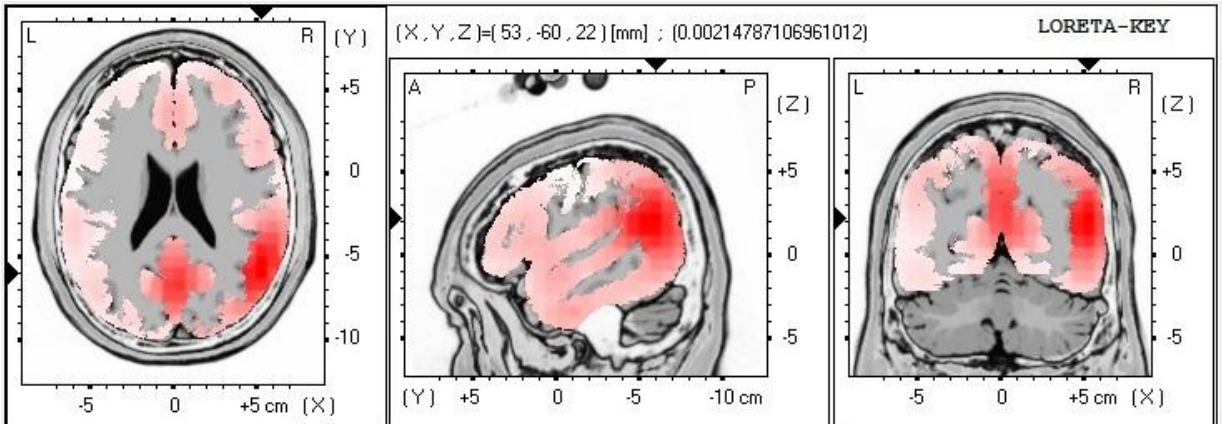


Figure 12. Source estimations of the largest extra striate energy for the P1 (A) and N1 (B) potentials evoked by a left visual field stimulus.
(Note that the P1 secondary source is medioparietal, and the N1 secondary source is laterotemporal).

The observation that the P100 secondary source is medioparietal, and the N160 secondary source is laterotemporal is consistent with suggestions by Foxe et al. (2001; 2005) that the P100 represents activations in early dorsal stream, while the N160 represents activations in early ventral stream. This is inconsistent with our idea that the P100 and N160 represent serial activations within a single network within a hemisphere. It may be more likely that the P100 and N160 represent activations of

neurones in relatively independent networks. It is unlikely therefore, that the latency difference between N100 and P160 is a measure of intra-hemispheric transfer.

2.2. P100 and N160 Absolute Latencies

The data from the source reconstructed absolute latencies had the same pattern as the results as those from the AEP data. It was found that overall people with schizophrenia had faster latencies within both hemispheres when compared with the control group. Also, overall, the latencies in the control group were faster in the left hemisphere than the right, this aspect of the data is the inverse of what would be predicted by Miller (1996, 2008).

2.2.1. P100

The control group had faster P100 latencies in the left than right hemisphere, the same pattern was observed for people with schizophrenia. Once again, this aspect of the data is the reverse of what would be predicted by Miller's (1996, 2008) hypothesis, which would predict faster latencies in the right hemisphere of the control group than the schizophrenia group, and no difference in the latencies between the two groups in the left hemisphere. However, these findings are in line with Iwabuchi et al.'s (2011) data.

The control group had faster P100 latencies in the left hemisphere than the schizophrenia group, however, no difference was observed in the P100 latencies between the two groups in the right hemisphere. Miller (1996, 2008) would expect the opposite pattern: earlier right hemisphere latencies in the control group than in the schizophrenia group. The later left hemisphere P100 in the schizophrenia group is interesting as it may account for the slower L-R than R-L P1 IHTT observed in the

schizophrenia group in the source reconstructed data. As stated above in the AEP P100 absolute latencies section, these results may suggest that there are aberrations in the axons ascending to the left occipital lobe, or aberrations in left occipital lobe white matter of the schizophrenia group (Di Russo, et al., 2001; Ducati, et al., 1988; Pratt, et al., 1982).

2.2.2. N160

Surprisingly, the control group had slower N160 latencies in both hemispheres when compared to the schizophrenia group. As suggested above, EP latencies have been demonstrated to be linked to axonal size and myelination, this may indicate that people with schizophrenia have occipital and temporal/parietal regions with greater ratios of fast conducting axons compared with the normal population. However, this is at odds with reported an overall decrease in white matter FA, possibly due to a decrease in myelination, in people with schizophrenia (Kanaan, et al., 2009; Minami, et al., 2003; White, et al., 2011).

Within the control group the N160 was earlier in the left hemisphere than the right hemisphere. This aspect of the data does not appear to fit with Miller's (1996, 2008) hypothesis and also appears contrary to the control group's IHTT data. But, as noted above, does fit with Iwabuchi et al.'s (2011) observed greater left than right occipital and temporal lobe white matter in the normal population. Within the schizophrenia group there was no significant difference in the N160 latencies between the hemispheres, which is consistent with Miller's (1996, 2008) theory of symmetry between the right and left hemispheres. This is also consistent with the symmetry to IHTT in the N160.

When considered in isolation the P100 and N160 absolute latencies within the control group appear to fit with Iwabuchi et al.'s (2011) observation that there is greater left than right hemisphere parallel diffusion in the occipital and temporal lobes of the normal population, but do not appear to fit Miller's (1996, 2008) hypothesis. Moreover, when viewed in isolation, the N160 absolute latency data from the schizophrenia group fits Miller's (1996, 2008) hypothesis, but the P100 data does not. However, interestingly, the schizophrenia group P100 data are in line with Iwabuchi et al.'s (2011) findings in the normal population. However, when the results of the *between groups* comparisons are viewed, they provide a greater challenge for a simple and parsimonious interpretation of the data. There are significant differences between the groups in both components in the left hemisphere; and between the N160—but not in the P100—in the right hemisphere. A pattern is difficult to uncover in relation to the results from the other analyses published in the literature. The differences between the control group and the schizophrenia group do indicate that people with schizophrenia have aberrations or alterations in white matter regions compared with the normal population, as suggested by Miller (1996, 2008), just not in the way suggested by Miller (1996, 2008). Further investigation is needed to interpret these results, including a study into the FA and parallel and perpendicular diffusion in each lobe and hemisphere in people with schizophrenia.

3. Summary

In summary, the data support the existence of alterations in the white matter of people with schizophrenia, but not completely in the way predicted by Miller (1996, 2008), as there appear to be alterations in both the right and left hemispheres of people with schizophrenia. However, they do appear to reflect altered cortico-cortico connections in people with schizophrenia, as proposed by Miller (1996, 2008).

The results from this thesis generally support Miller's (2006; 2008) hypothesis by finding evidence of alterations in IHTT and therefore inferring alterations in cerebral laterality of axonal type in people with schizophrenia compared with the normal population. The control group's IHTT latencies were clearly congruent with Miller's hypothesis. Within the schizophrenia group the IHTT findings also appear to fit with Miller's hypothesis. The observed faster L-R P100 source reconstructed IHTT is not considered to be in conflict with Miller. The IHTT in this component is slower the IHTT within the control group; indicating a reduction in fast conducting axons in people with schizophrenia.

The intra-HTT data provides an interesting picture of latencies. However, there is a confound inherent in the interpretation of this data as it is not clear that latency differences between P100 and N160 actually reflect serial activations within a single network within a hemisphere. This data set is less clear in its support for Miller (1996; 2008). The Schizophrenia group data support Miller's hypothesis in that there is no significant difference between the two hemispheres in people in this group in the raw or source reconstructed data. The control group data do not appear to fit the pattern expected; with longer latencies in the right hemisphere than the left in the source data, and no significant difference between the two hemispheres in the raw data.

The P100 absolute latency data show a pattern that is less clearly in support of Miller (1996; 2008), both between and within the two groups. Within the schizophrenia group the shorter P100 in the left hemisphere than the right hemisphere is not the symmetry predicted. Within the control group, the data suggest a pattern that does not fit with Miller's hypothesis.

The N160 absolute latency between group data do not support Miller's (2006; 2008) hypothesis. Within the schizophrenia group the data support Miller's hypothesis. Within the control group the data the data is not in support of Miller, with shorter latencies in the LH than the right hemisphere. The between groups comparison does not support Miller's hypothesis, with the N160 longer in both the right hemisphere and left hemisphere in the control group than the schizophrenia group.

Moreover, there appear to be at least two different subsystems differentially affected in those with schizophrenia. The latencies examined represent the building blocks of sensory perception. Dysfunction or altered timing at this level may have a knock-on or cascade effect on later processing, which would almost certainly impact on consciousness, sensation and perception. The substrate of this disconnection/dysconnection may be diffuse, from chemical messengers to cells and white and grey matter (Stephan, Friston, & Frith, 2009). The subsequent mechanism by which this directly maps onto behavioural dysfunction/alteration/aberration still requires further research. There is clear evidence of diffuse white matter anomalies in people with schizophrenia; it is possible that changes in myelination may be involved in these white matter aberrations.

Factors that may be influencing the ability to interpret the current data and create a cohesive picture of the raw AEP and localisation data, and marry these with patterns of white matter alterations in people with schizophrenia reported in the literature, are possible errors or influence of some unknown factor in the neuroimaging data. This is due to the fact that the neuroimaging tools used to obtain and interpret the data are not directly recording from the axons within the brain. As such, the findings are inferred from remote recording of neurophysiology. EEG VEP and source localisation data are only estimations or the best approximation of the

brains internal processes and although considered accurate, are not exact (Lantz et al., 1997; Michel et al., 2004; Pascual-Marqui, et al., 1994). Furthermore, linking the findings from EEG VEP and LORETA data analysis to white matter changes observed in other neuroimaging techniques considered to have good spatial resolution provides another way to unravel the information provided by temporally precise neuroimaging, such as EEG. However, this itself is not a perfect solution as methods such as DTI and MTR also have shortcomings and provide information that is inferred rather than a direct measurement from the brain tissue itself, and as such have inherent limitations (Huang, Zhang, van Zijl, & Mori, 2004; Kubiki et al., 2007; Lori et al., 2002; Schmierer, Scaravilli, Altmann, Barker, & Miller, 2004)

4. Potential Mechanisms for Results

4.1. Callosal Dysfunction

Altered IHTT has several possible causes including abnormalities in the CC. Interhemispheric transfer of information obviously necessitates that information crosses the CC. People with schizophrenia demonstrate reductions in CC size (Highley, et al., 1999; Woodruff, et al., 1995). This reduction in callosal size, rather than dysfunction within the hemispheres, has been hypothesised to affect interhemispheric transfer of information by some researchers (Mandal, et al., 1992; Westerhausen et al., 2006).

Significant negative correlations have been found between the occipital P100 IHTT and white matter density in posterior CC regions, this correlation was not found for the N160 (Westerhausen, et al., 2006). It was postulated that this may have been due to the N160 representing the first stage of visual processing that moves beyond the striate cortex (Westerhausen, et al., 2006). This may indicate that IHTT is not

completely dependent on the CC, but is also a function of cortical region and the type of cortical processing generating the EP.

A meta-analysis of DTI studies of the CC in schizophrenia reported that abnormalities are most frequently observed in the posterior CC (splenium) (Patel, et al., 2011), although fractional anisotropy (FA) reductions have also been reported in the genu (Mori, et al., 2007). Reductions in white matter FA in the CC, specifically in the splenium (Agartz, et al., 2001), and other posterior white matter tracts may contribute to alterations in EP latencies as the CC is organised topographically to connect regions that lie in close proximity to it (Jarbo, et al., 2012; Witelson, 1989). Furthermore, if the CC consists of fibres projecting from one hemisphere to the other (Miller, 1996, 2008), this could also indicate alterations in posterior cortical regions, such as the parietal and occipital lobes, which could be linked to reductions in posterior CC size. In support of this idea, a DTI study using a large sample size of 76 people with schizophrenia found reduced FA in medial temporal-occipital lobes, which the authors proposed corresponded to the inferior longitudinal fasciculus. However, they were not able to exclude the possibility that the inferior fronto-occipital fasciculi, splenium of the CC, and optic radiations were influencing the data (Kanaan, et al., 2009).

If people with schizophrenia do have deficits in the CC, it would be expected that they would have increased IHTTs in both directions (R-L, L-R), which would maintain the asymmetry of transfer. This is not indicated by the current data and the literature (Barnett, et al., 2005; Marzi, et al., 1991). Further, in support of this hypothesis people with agenesis of the CC demonstrate increased IHTT in both directions, when compared to the normal population (Forster & Corballis, 1998; Marzi, et al., 1991).

It has been suggested that asymmetry of interhemispheric transfer in the normal population is due to higher numbers of callosal fibres projecting from the right to the left hemisphere than the reverse (Marzi, et al., 1991). Miller (1996, 2008) proposes that these CC fibres are made-up of axonal projections from each hemisphere. The current data point to the possibility that callosal defects may have a role in the difference between the IHTTs observed in people with schizophrenia and the control group, but as a reflection of altered white matter in the hemisphere that the callosal fibres are made up of, rather than a deficit originating in CC itself. The reduced right hemisphere N160 amplitude in people with schizophrenia reported by Barnett and Kirk (2005) suggests that alterations in hemispheric white matter may be the cause of differences in interhemispheric transfer, namely reduced R-L IHTT. This may be due to reduced numbers of fast conducting axons in the right hemisphere in people with schizophrenia compared to the normal population, rather than a deficit in the CC (Barnett, et al., 2005; Barnett & Kirk, 2005). Moreover, deficits in the CC would not account for differences observed in the *intra*- HTT P100 and N160 latency differences between the control and schizophrenia groups observed in the data.

4.2. White Matter Alterations

If differences in hemispheric myelination are involved in the aetiology of schizophrenia it is likely that this may be visible in asymmetries in cerebral white matter. Greater overall left than right white matter has been reported using magnetization transfer (Silver, Barker, MacManus, Tofts, & Miller, 1997), however another study using magnetization transfer did not find any bilateral differences in white matter between the hemispheres (Mehta, Pike, & Enzmann, 1995). Greater FA of white matter in the normal population has been observed in the cingulum bundle;

superior cerbellar peduncal; arcuate fascicle; and optic radiation of the left hemisphere and greater right hemisphere FA has been observed in the anterior limb of the internal capsule; the anterior limb's prefrontal regions; inferior parietal lobe and superior longitudinal fasciculus (Büchel et al., 2004; Park et al., 2004). Greater FA in regions such as the left arcuate fascicle have been linked with the language functions of that hemisphere (Büchel, et al., 2004). Iwabuchi et al. (2011) recently specifically investigated bilateral regional differences in asymmetry of white matter, and employed FA together with parallel and perpendicular diffusion for a more comprehensive picture of white matter distribution. Their results suggest that within the right-handed normal population the right hemisphere has a rightward asymmetry of white matter in the frontal and parietal lobes and a leftward asymmetry in the temporal and occipital lobes. These findings do not appear to fit with Miller's (1996, 2008) hypothesis a greater ratio of fast conducting axons in the entire right hemisphere compared with the left. However, Iwabuchi et al.'s (2011) data appear to fit with Miller's hypothesis (1996, 2008) in the frontal and parietal lobes, but not in the occipital and temporal lobes.

The findings of increased right hemisphere white matter density in the parietal lobe regions of the left-handers in normal population (Büchel, et al., 2004; Iwabuchi, et al., 2011) may account for the faster R-L IHTT observed in the normal population, by facilitating faster conduction of EPs across the CC than the parietal lobe of the left hemisphere. This fits with the N160 IHTT being faster in the R-L direction. However, for the faster R-L P100 IHTT some explanation is still needed, as it is generated in the right occipital lobe, which Iwabuchi et al. (2011) suggests is less myelinated than the left occipital lobe.

In people with schizophrenia a reduction of right hemisphere white matter has been observed in the parts of the right occipital region (Agartz, et al., 2001) and right internal capsule (Velakoulis et al., 2002). Reduced intervoxel coherence has been reported in the right superior temporal region; anterior transversal temporal region; anterior part of the external capsule; anterior superior longitudinal fascicle; anterior occipitofrontal fascicle (Federspiel et al., 2006). It was proposed that these reductions indicate reduced white matter connectivity within the right hemisphere of people with schizophrenia relative to the normal population. It is possible that this could account for reduced R-L AEP IHTT, and faster L-R source reconstructed IHTT.

Widespread bilateral change in the white matter of people with schizophrenia has also been reported in the literature and may play a role in understanding the current data (Iwabuchi, et al., 2011; Kanaan, et al., 2009; Lim, et al., 1999; Minami, et al., 2003; White, et al., 2011). A reduction in white matter FA globally, and specifically in the prefrontal cortex, external capsule, occipital lobes, uncinate fascicule, cingulum, frontal, temporal, parietal lobes have also been reported in people with schizophrenia (Agartz, et al., 2001; Lim, et al., 1999; Mori, et al., 2007; White, et al., 2011). These findings indicate that in people with schizophrenia the right hemisphere may not have a lower ratio of myelinated axons than the left hemisphere across the entire hemisphere, instead different regions across both hemispheres may have aberrant levels of myelination.

Magnetization transfer ratio (MTR) imaging of people with schizophrenia– another method of investigating myelin integrity and axon density—has found aberrations bilaterally in the frontal and temporal lobes (Foong et al., 2000; Foong et al., 2001), corpus callosum, fornix, right internal capsule, superior occipito-frontal fasciculus, the right posterior cingulum bundle (Kubicki et al., 2005) and in the

fasciculus uncinatus (left greater than right) (Bagery et al., 2003). Interestingly, and possibly not in line with Miller's (1996) predictions, increased mean MTR has been found in the right uncinate fasciculus in people with schizophrenia (Mandle et al., 2010). However, a study by Biernacka-Antosik et al. (2006) found no significant MTR changes within people with schizophrenia, although they did find a trend towards reductions in the left superior temporal gyrus, right occipital cortex, and left periventricular white matter.

These white matter aberrations appear to play a significant role in the disease presentation. Reductions in cerebral white matter connectivity have been positively correlated with clinical measures of psychosis (Camchong, MacDonald III, Bell, Mueller, & Lim, 2011; Ho et al., 2003). It is possible that these changes impact bilaterally on diffuse cortico-cortico white matter input between anterior and posterior brain regions. The current data indicates different patterns of EPs within each hemisphere within the schizophrenia group, and between the schizophrenia group and control group. This further suggests that there may be differences between the two hemispheres in areas of white matter abnormalities.

Further evidence for the role of white matter aberrations in schizophrenia comes from the physical examination of the brains of people with schizophrenia from autopsy and biopsy. These investigations have found abnormalities in oligodendroglia and glia in people with schizophrenia (Cotter, Mackay, Landau, Kerwin, & Everall, 2001; Hoff et al., 2003; Miyakawa et al., 1972; Uranova et al., 2007). Moreover, reduced expression of genes coding for white matter has also been observed in people with schizophrenia (Hakak et al., 2001).

Alterations in the connections in the default mode network, the brain's pattern of activation when at rest, have been reported in people with schizophrenia.

Specifically in the medial frontal and the temporal lobes, which also display reductions in white matter organisation (Camchong, et al., 2011; Ellison-Wright & Bullmore, 2009). The parietal lobes are also part of the default mode network (De Luca, Beckmann, De Stefano, Matthews, & Smith, 2006; Shulman et al., 1997), and have been reported to have altered activation during the brains resting state in people with schizophrenia. It is possible that aberrations in the frontal areas of the default mode network may disturb other areas involved in this network, such as the parietal and occipital regions, in which the P100 and N160 are generated (Clark, et al., 1995; Di Russo, et al., 2001).

Furthermore, alterations in 'effective connectivity' (the influence one region has over another) may arise from aberrant connections between brain regions rather than a reduction in connections, which has been termed 'dysconnectivity' (Pettersson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011). As such, the presence of 'normal' FA may not preclude the possibility of 'dysconnection' at the level of another substrate or an aberration in connectivity without the presence of structural aberrations. A reduction in effective connectivity in the right hemisphere between hippocampus and the frontal lobes has been reported in people classified with an at risk mental state for schizophrenia and people with first episode schizophrenia during a visual processing task (Benetti et al., 2009). Moreover, in the right and the left hemispheres reduced connectivity between the temporal cortex and anterior cingulate has been reported during a self/other speech identification task in people with schizophrenia (Mechelli et al., 2007). This may play a role in psychotic symptom formation, such as auditory hallucinations.

Interestingly, symptoms of schizophrenia have been reported in people with diseases that have white matter demyelination as a symptom. These include people

with frontal and temporal demyelination due to multiple sclerosis (Honer, Hurwitz, Li, Palmer, & Paty, 1987; Reischies, Baum, Bräu, Hedde, & Schwindt, 1988) and people with metachromatic leukodystrophy (Alves, Pires, Guimarães, & Miranda, 1986; Finelli, 1985; Fukutani et al., 1999). This may further support the hypothesis that reductions in myelination are involved in the aetiology of schizophrenia, and responsible for the altered AEP latencies observed in the current study.

EEG has the ability to provide information about the timing of processing occurring in areas or regions that do not show structural differences. Although white matter aberrations may not be observable, other neural functions may be altered.

4.3. Global Brain Changes and Symptoms

In schizophrenia, rather than global reductions in white matter in the right hemisphere or aberrations exclusively within right hemisphere white matter, a pattern of bilateral regional differences appears to be emerging from investigations of volume and size of different brain regions. Areas often cited with bilateral structural aberrations are the frontal, medial and temporal lobes, parietal lobes and subcortical regions (Shenton, et al., 2001). An alteration in language lateralisation in people with schizophrenia is evidenced in increased bilateral cerebral language representation (Sommer, Ramsey, et al., 2001; Weis et al., 2006). This indicates that there are alterations in right hemisphere activity. Increased right hemisphere activation in verb generation and semantic decision tasks may be evidence of reduced left hemisphere inhibition of the right hemisphere, or of a right hemisphere compensation for left hemisphere deficits (Pugh et al., 2001; Sommer, Ramsey, et al., 2001). Due to differences in cerebral functional lateralisation in the normal population, it is possible that structural and neural aberrations may have a different effect on each hemisphere

or that alterations in one hemisphere may affect the functioning of the other. For example, it has been suggested that the left hemisphere may become overactive in people with schizophrenia to compensate for right hemisphere dysfunction linked to the aetiology of the disease (Rotenberg, 1994).

Smaller brain volume in the right frontal lobe has been observed in schizophrenia (Turetsky, et al., 1995) and reduced activation of the right dorsolateral prefrontal cortex has been correlated with negative symptoms, but not positive symptoms (Wolkin et al., 1992). Specifically, negative or 'withdrawal' emotions have been linked to the right frontal lobe (Davidson, 1992).

4.4. Coherence

It might be expected that aberrations in white matter may impact on coherence measures in people with schizophrenia. It has been proposed that coherence may be linked to two types of cortical connections, one based on local short range axon connections (mainly in grey matter) and the other based on long range coritco-cortical white matter connections (Thatcher, Krause, & Hrybyk, 1986). Reduced alpha band coherence, a frequency associated with attention, between hemispheres in people with schizophrenia has been reported. This reduction was due to less coherence in right hemisphere parietal electrodes (Shaw, Colter, & Resek, 1983). This finding fits with reduced alpha-band coherence in the right hemisphere between prefrontal and occipital regions and prefrontal and temporal regions in people with schizophrenia (Hoffman et al., 1991). The same study also reported a reduction in alpha band between left prefrontal and left anterior parietal regions (Hoffman, et al., 1991). Reduced alpha and interhemispheric coherence was correlated with negative schizophrenia symptoms when the brain was in a resting state. This was also linked

with a decrease in coherence between the right frontal and parietal lobes (Merrin & Floyd, 1996). This correlation was not found in the left hemisphere. Moreover, during a visual imagery task, within the normal population, left-handed individuals were observed to have reductions in alpha band coherence, whilst right-handers had increased alpha band coherence (Shaw, O'Connor, & Ongley, 1977). The increased rate of left-handedness in people with schizophrenia (Dragovic & Hammond, 2005; Satz & Green, 1999; Sommer, André, et al., 2001) indicates altered or reduced laterality, which may be linked to altered or disrupted coherence within this population.

Reduced coherence has been reported between different areas of the frontal cortex in schizophrenia in the delta and theta bands. Additionally, decreased coherence in the two of the frontal delta bands was correlated with a higher score on the Positive and Negative Syndrome Scale (Tauscher, Fischer, Neumeister, Rappelsberger, & Kasper, 1998). Decreased alpha band coherence between right prefrontal regions and between right occipital and posterior-temporal regions of the cortex have been reported in people with schizophrenia during a visual perception task (Hoffman, et al., 1991). The authors suggest this right fronto-parietal coherence decline is linked to impairment in attention networks. In a left hemisphere activating task, schizophrenic participants were found to have a decrease in alpha coherence in contrast to controls, who had increases in coherence (Michelogiannis, Paritsis, & Trikas, 1991).

Decreases in coherence have also been found in the beta and gamma bands in people with schizophrenia in a study comparing wake and sleep periods (Higashima et al., 2007). Decreases in these two bands were only found during waking periods between central and frontal regions. Moreover, when symptoms abated with

treatment, coherence was found to increase. Changes in coherence have been linked to specific schizophrenia symptoms, for example, decreased coherence between frontal and temporal lobes has been correlated with reality distortion. However, this was only found in male and not in female participants (Norman et al., 1997).

People with schizophrenia that is treatment resistant display higher alpha and delta coherence between frontal regions and decreased delta band coherence between frontal and temporal regions when compared with controls and people with treatment responsive schizophrenia (Ramos, Cerdan, Guevara, Amezcua, & Sanz, 2001). Reduced frontal-temporal coherence has been linked to genetically related but unaffected siblings, indicating a genetic link to coherence disturbance (Winterer, Coppola, Egan, Goldberg, & Weinberger, 2003). These findings of different cerebral coherence between groups of people with schizophrenia with different symptom subtypes further suggest that there may be different outcomes in studies, depending on the subtypes of schizophrenia experienced by the participants in the schizophrenia group. The findings may also indicate that there are alterations in cortical connectivity in the people with schizophrenia.

4.5. Visual Spatial Disturbances

There is evidence to suggest that working memory processing of visuospatial information is predominantly lateralised to the prefrontal cortex and parietal lobe of the right hemisphere in the normal population (D'Esposito et al., 1998; Smith, Jonides, & Koeppe, 1996; Walter et al., 2003). Increased FA of white matter has been observed in the parietal lobe of the right hemisphere (Iwabuchi, et al., 2011). Miller (1996) proposed that in the normal population the right hemisphere has more fast conducting axons for fast visuospatial processing, but that these fast conducting right

hemisphere fibres are reduced in people with schizophrenia. In people with schizophrenia reduced right dorsolateral prefrontal cortex activation has been reported during a visual task (Pomarol-Clotet et al., 2008). Moreover, people with schizophrenia also have deficits in processing visual information, specifically spatial frequency, motion, and trajectory information (Kéri, Antal, Szekeres, Benedek, & Janka, 2000; O'Donnell et al., 1996; Schwartz, Satter, O'Neill, & Winstead, 1989). People with schizophrenia also demonstrate deficits in detection of targets with feature conjunction. Furthermore, a reduction in the P300 over the right parietal lobe of people with schizophrenia during this task further suggests altered right hemisphere functioning (Alain, Bernstein, He, Cortese, & Zipursky, 2002). Lastly, decreased blood flow over the right temporoparietal lobe was observed in a case of Alzheimer's disease with psychotic symptoms (Matsuoka et al., 2010), further linking deficits in the right parietal lobe to psychosis.

4.6. Facial Emotion Recognition Deficits and Reductions in Emotion Expression

Reduced or disrupted white matter networks in the right hemisphere, as indicated by the IHTT of the current data, may contribute or play a role in facial emotion recognition deficits and reductions in non-verbal emotion expression observed in people with schizophrenia (Borod, 1992; Fournier, et al., 2008). It may also contribute to negative psychotic symptoms such as delusional misidentification (Förstl, et al., 1991), break-down of self/other boundaries (Bogousslavsky & Regli, 1988), and loss of will (Coslett & Heilman, 1989). Deficits in using prosody, a right hemisphere language function, observed in people with schizophrenia (Murphy & Cutting, 1990), add further weight to this argument.

5. Altered Latencies in Other Diseases

5.1. Attention-deficit/hyperactivity disorder

Attention-deficit/hyperactivity disorder (ADHA) is hypothesised to be linked to right hemisphere dysfunction (Casey et al., 1997; García-Sánchez, Estévez-González, Suárez-Romero, & Carme, 1997; Stephanatos & Wasserstein, 2001), possibly due to right hemisphere hypoarousal (Sheppard, Bradshaw, Mattingley, & Lee, 1999). Interestingly, this group also demonstrates alterations in IHTT, with people with ADHD-inattentive type displaying slower R-L IHTT when compared to controls during a lateralised reaction time task using the Poffenberger paradigm (Rolfe, Kirk, & Waldie, 2007). It has been proposed that the CC is composed of axonal projections from each hemisphere (Miller, 1996, 2008). The right hemisphere hypoarousal and reduced IHTT from the R-L hemisphere observed in people with ADHA may indicate reduced axonal projections from the right hemisphere, or reduced numbers of fast axons in the right hemisphere. This further links right hemisphere aberrations to reduced R-L IHTT.

5.2. Dyslexia

As has been found in people with schizophrenia, people with developmental dyslexia have higher rates of schizotypy, left-handedness/ambidextrality, are more frequently male, and frequently show altered asymmetry of the planum temporale (Eglinton & Annett, 1994; Richardson & Stein, 1993; Saugstad, 1999; Shapleske, Rossell, Woodruff, & Davis, 1999). Also, people with mild learning disabilities have a nearly three-fold increased incidence of schizophrenia (Doody, Muir, Johnstone, & Owens, 1996). It has been argued that these characteristics represent late or delayed neurodevelopment in these two groups (Saugstad, 1999). Furthermore, people with

reduced brain size and asymmetry do not read as well as people with greater cerebral asymmetry (Leonard et al., 2008), pointing to a possible alteration of cerebral asymmetry in dyslexia. People with Dyslexia have also been found to have deficits in visuospatial skills and to have impaired responses to objects in the left visual field, indicating a right hemisphere deficit (Stein, 1991).

Dyslexia can be divided into two subtypes: phonological and non-phonological dyslexia (Annett, Eglinton, & Smythe, 1996). It has been proposed that phonological dyslexia (dysphonetics), which is characterised by difficulty reading non-words, i.e., converting graphemes to phonemes, is related to left hemisphere deficits and reduced cerebral asymmetry. The other group, referred to as dyseidetics, have difficulty with visual memory for words, but can sound out phonemes from graphemes. This is considered to be linked to right hemisphere deficits (Annett, et al., 1996). However, bilateral reductions in the N1 amplitude have been observed in dysphonetics, possibly suggesting some aberration in both hemispheres (Wimmer, Hutzler, & Wiener, 2002). It has been proposed that people with dyslexia have difficulty rapidly sequencing stimuli, which is related to right parietal deficits (Hari & Renvall, 2001). Stein (1991) argues that reading requires the right hemisphere's visuospatial skills to accurately sequence written words, and that a genetically driven lack of hemispheric specialisation and cerebral lateralisation interferes with this process in people with dyslexia. There are clear similarities in findings from people with schizophrenia and people with dyslexia. This may suggest alterations in cerebral white matter myelination asymmetry in the aetiology of one or both dyslexia types.

5.3. Autism spectrum disorder

Another group that appear to have axonal aberrations and right hemisphere deficits are people with autism. It has been proposed that Autism Spectrum Disorder is the result of reduced long-range cortico-cortico connectivity and increased short-range connectivity, which alters cognitive processing. This altered configuration enables superior processing of details, but results in a poorer ability to attend to global components of stimuli (Happé & Frith, 2006; O'Connor & Kirk, 2008). Behavioural examples of this altered connectivity in people with autism is evidenced in this group having increased interest in parts, rather than the whole, of objects (APA, 2000; Happé & Frith, 2006; O'Connor & Kirk, 2008). It has also been proposed that autism is linked to aberrations in cerebral growth and neuronal pruning, and that neural (including axonal) organisation and connections are disturbed, leading to a disconnection between frontal regions and the rest of the brain (Courchesne, 2004; Courchesne & Pierce, 2005). Autistic individuals often display similar deficits as people with schizophrenia that are linked with right hemisphere functions. These include prosody and emotional expression, interpersonal deficits, and hemineglect (Meililllo & Leisman, 2009; Nyden, Carlsson, Carlsson, & Gillberg, 2004; Ozonoff & Miller, 1996; Perry et al., 2001; Weintraub & Mesulam, 1983). Altered cerebral asymmetry, evidenced by increased levels of non-right-handedness, has also been reported in this population (McManus, Murray, Doyle, & Baron-Cohen, 1992; Tsai, 1982). Reduced or altered right hemisphere axonal myelination or changes in the regional patterns of axonal myelination may also be involved in the pathology/aetiology of autism spectrum disorders. This could reduce the ability of different brain regions to communicate via myelinated axons, or possibly create an altered ratio of axon type (slow/fast conducting). Deficits in white matter FA have

been reported in people with autism (Barnea-Goraly et al., 2004), including reduced CC FA, which was associated with reduced processing speed (Alexander et al., 2007). It has also been proposed that there is a deficit in interhemispheric communication in people with autism (Nyden, et al., 2004).

The above discussed findings from other mental disorders indicate that right hemisphere dysfunction, altered cerebral asymmetry, and deficits in white matter are able to create discrete psychological deficits or syndromes.

6. Musicians

Another group that displays alterations in IHTT are musicians. Using EEG EPs this group has been found to have symmetry of transfer times between the two cerebral hemispheres (Patston, Kirk, Rolfe, Corballis, & Tippett, 2007). It was proposed that this was due to alterations in cerebral white matter distribution due to musical training. This symmetry of transfer was found to be the result of faster L-R IHTT in musicians compared to controls (Patston, et al., 2007). In this same study, controls had longer N160 latencies in the right hemisphere than the left hemisphere. Musicians did not display a difference in the N160 latencies between the hemispheres. This supports the theory that alterations in hemispheric white matter can impact on IHTT and EP latencies.

Increased CC size and levels of myelination have been found in musicians compared to non-musicians (Schlaug, Jancke, Huang, Staiger, & Steinmetz, 1995). Higher levels of cerebral FA were positively correlated with the number of hours the musician had spent practicing their instrument during their life span (Bengtsson et al., 2005). These findings suggest that during development it is possible to alter hemispheric asymmetries through behaviour, in this case musical training. As the axons travelling through the CC have been proposed to originate within each

hemisphere (Miller, 1996), it can be deduced that musicians have an increase in left hemisphere myelination, relative to non-musicians. This results in increased IHTT speed from the L-R. These findings further support the hypothesis that people with schizophrenia have decreased levels of myelinated axons in the right hemisphere, which result in decreased N160 amplitude in the right hemisphere and symmetry of IHTT in this group (Barnett & Kirk, 2005).

General Conclusion

This thesis explored one aspect of Miller's (1996, 2008) comprehensive hypothesis on the cause of schizophrenia, specifically Miller's theory regarding laterality of cerebral axonal type within the normal population and people with schizophrenia. Miller (1996, 2008) proposes that in the normal population the right hemisphere has a greater ratio of fast conducting axons than the left hemisphere, and that this laterality is not present in people with schizophrenia due to a reduced number of fast conducting axons in the right hemisphere. The results from this thesis partly support his hypothesis by finding evidence to support alterations in IHTT and cerebral laterality of axonal myelination type in people with schizophrenia compared with the normal population. However, although differences were found between the control group and schizophrenia group, not all of the findings fit with Miller's (1996, 2008) hypothesis.

Recent work by Iwabuchi et al. (2011) may provide some explanation for some of the findings from this thesis that were not in line with Miller's (1996, 2008) hypothesis. They suggest that there is greater white matter coherence, as measured by FA and parallel diffusion, in the temporal and occipital lobes of the left hemisphere and in the frontal and parietal lobes of the right hemisphere in normal right handed males. This supports Miller's (1996, 2008) theory of greater ratios of myelinated right hemisphere white matter in the right frontal and parietal lobes, but does not fit with Miller's hypothesis in relation to the right occipital and temporal lobes. Indeed, the finding that within the control group the N160 was earlier in the left hemisphere than the right hemisphere is in contrast to what would be expected by Miller (1996, 2008), but fits with what would be predicated by Iwabuchi et al.'s (2011) findings. However, Miller (1996, 2008) and Iwabuchi et al.'s (2011) work do not appear to fit or explain

the current data completely. For example, within the schizophrenia group the intra-HTTs in the right hemisphere were found to be shorter than in the left hemisphere, when the inverse would be predicted by Miller's (1996, 2008) theory and Iwabuchi et al.'s (2011) findings. However, we concede that intra-HTT may not represent serial activations within a single network within a hemisphere.

While the emphasis of this thesis is Miller's (1996, 2008) hypothesis, it appears unlikely—considering the breadth of aberrations in the brain found in the many areas of research on schizophrenia—that *global* changes in the right hemisphere and its ratio of fast to slow conducting axons alone are the root of the enduring underlying abnormal psychological traits observed in people with schizophrenia (although it should be stressed that this is not the sum of Miller's (1996, 2008) hypothesis). Moreover Miller (2008) does suggest his theory is open to elaboration. The wide bilateral distribution of white matter alterations in the brain also supports this conclusion (Kanaan, et al., 2009; White, et al., 2011). Moreover, as the hemispheres work in concert, any change in one hemisphere is likely to impact on the other.

The current data may suggest the existence of two different cerebral subsystems for signal transmission of action potentials. One comprising of the neocortical processing region receiving input from the thalamus and its handling or registration of this ascending information, and one that is involved in interhemispheric communication. It is possible that these two systems are regulated by two different genetic mechanisms that are impacted differentially in some manner in people with schizophrenia. It seems that people in the schizophrenia group differ from controls on measures that potentially access these two systems.

Future directions for research that may shed further light on the data from this thesis, and the distribution of white matter in people with schizophrenia in general, would be an investigation into white matter FA, diffusion and cohesion as done by Iwabuchi et al. (2011) using participants with schizophrenia, controlling for disease presentation type, and medication. Future research that would be of importance and add to our understanding of inter- and intra- hemispheric communication, and patterns of white matter distribution within the brain would include EEG investigations of the P100 and N160 as in the current study, in conjunction with a DTI investigation in the manner Iwabuchi et al. (2011) in other groups, including right handers; Woman; other clinical groups, for example people with Dyslexia and Autism Spectrum Disorder; and groups known to have alterations in white matter distribution, e.g. musicians.

In conclusion, this thesis adds to the increasing body of evidence of an alteration in cerebral structure and function in people with schizophrenia. This includes alterations in cortical white matter myelination and distribution when compared to the normal population. It also adds to evidence of alterations in functional asymmetries. These differences are likely to affect the functions of these regions of the brain and how they communicate with each other, which, ultimately, is likely to impact on cognition.

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APPENDIX A

Geodesic Sensor Net 128-Channel EEG