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Electrophysiological event-related-potentials & their association with genome-wide-associated risk variants in schizophrenia

A thesis submitted to the University of Dublin
for the degree of Doctor of Philosophy
Department of Psychiatry
University of Dublin

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2012

Declaration

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Statement of Work

This work is the product of the psychosis research group, Dept. of Psychiatry and Institute of Neuroscience, Trinity College Dublin. The clinical recruitment and collection of case samples for DNA was performed by Dr. Liz Cummings, Dr. Morgan Savage and Dr. Susan Moore and was overseen by Prof. Aiden Corvin. The collection of control samples for DNA was performed by the author.

Genotyping of rs1344706 (ZNF804A), rs6490121 (NOS1) and rs12807809 (NRGN) was performed by Emma Quinn, Andreia Costa, Róisin Judge and Ciara Fahey of the Neuropsychiatric Group, Trinity College Dublin and was overseen by Dr. Derek Morris.

The collection and analysis of all EEG data was undertaken by the author.

Abbreviations

ERP	Event-related-potential
TCIN	Trinity College Institute of Neuroscience
EEG	Electroencephalogram
SZ	Schizophrenia
GWAS	Genome-wide-association-studies
SNP	Single-nucleotide-polymorphism
A	Adenine
G	Guanine
T	Thymine
C	Cytosine
RNA	Ribonucleic acid
DNA	Deoxyribonucleic acid
CNV	Copy-number-variation
NRXN1	Neurexin-1
PGC	Psychiatric GWAS Consortium
ISC	International Schizophrenia Consortium
MHC	Major histocompatibility complex
MGS	Molecular genetics of schizophrenia
DZ	Dizygotic
MZ	Monozygotic
MRI	Magnetic-resonance-imaging
PET	Positron emission topography
BOLD	Blood-oxygen-level-dependent
NO	Nitric oxide
CPT	Continuous performance task
VNTR	Variable-number-tandem-repeat
DTNBP1	Dysbindin
ERN	Error related negativity
MMN	Mismatch negativity
PPI	Pre-pulse inhibition
IgE	Serum immunoglobum E levels
PHF11	PHD finger protein 11
SWAT	Switching-attention task
EF	Executive functioning
CNTRICS	Treatment Research to Improve Cognition in Schizophrenia
PFC	Pre-frontal cortex
ACC	Anterior cingulate cortex
CANTAB	Cambridge Cognition Test Battery
SCID	Structured Clinical Interview for DSM
SAPS	Scale for the Assessment of Positive Symptoms
SANS	Scale for the Assessment of Negative Symptoms
ISI	Inter-stimulus-interval

CMS	Common mode sense
DRL	Driven right leg
WCST	Wisconsin Card Sorting Task
NOS1	Nitric oxide synthasase-1 gene
SWM	Spatial working memory
cGMP	Cyclic guanosine monophosphase
NMDA	N-Methyl-d-Aspartate
GABA	Gamma-aminobutyric-acid
nNOS	Neuronal nitric oxide
WAIS	Wechsler Adult Intelligence Scale
WMS	Wechsler Memory Scale
ZNF804A	Zinc-finger protein gene
ANT	Attentional Network Task
HLA	Human leukocyte antigen
LTP	Long-term-potentiation
CaMKII	Ca^{2+}/calmodulin-dependent-protein-kinase-II
MANOVA	Multi-variate analysis of variance
DAOA	D-amino-acid-oxidase-activator
PP1R1B	Protein-phosphate-1-regulatory-inhibitor-subunit-IB
ApoE4	Apolipoprotein E

Summary

This thesis describes the use of electrophysiological event-related-potentials as a method for understanding, at the cortical level, the functional significance of putative schizophrenia susceptibility genes identified in recent genome-wide-association-studies.

This thesis is presented in two sections. Section one concerns the rationale for using event-related-potentials (ERPs) as intermediate or endophenotypes in schizophrenia genetics and reviews the various ERPs in terms of the criteria for endophenotypes originally set out by Gottesman & Gould (2003). The first chapter outlines the evidence for these ERPs as useful endophenotypes and how they have already been applied to the study of candidate schizophrenia susceptibility genes. Chapter two focuses on a potential ERP which may index executive functioning deficits in schizophrenia. As yet, there is no robust electrophysiological component which indexes executive functioning, a well known cognitive deficit in schizophrenia. Chapter 2 deconstructs the sub-components of executive-functioning and concentrates on which aspects are most deficient in schizophrenia. It then goes on to test in a case and control sample whether ERPs during the performance of an executive-functioning task, reliably distinguish between groups.

Section two presents three studies that employ the P1 and the P300 ERPs to characterize the role of candidate susceptibility genes at the level of summated neuronal activity. The P1 measures visual sensory processing whilst the P300 reflects

memory and attentional processing. Chapter three presents data on the P1 and its association with a NOS1 gene variant previously identified in the O' Donovan et al. (2008) genome-wide-association-study. It also looks at how the P1's association with NOS1 may be mediated by top-down processing as measured by a spatial-working-memory task. Chapter four and five presents data on the P1 and the P300 and their association with risk variants in ZNF804A and NRGN. Finally, chapter six summarises the results of these studies and provides a discussion of how these results contribute to our understanding of the mechanisms by which these genes may be increasing disease risk. It also addresses the limitations of this work and future directions.

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Chapter 1

Electrophysiological event-related-potentials in schizophrenia genetics

1.1. Introduction

There is a burgeoning literature on the use of intermediate phenotype or 'endophenotypes' in schizophrenia genetics. As originally conceived, the use of endophenotypes was proposed as a strategy for reducing the genetic complexity of the broader illness phenotype that would allow greater power for identifying genes of small effects. Since then, the intermediate phenotype strategy has moved away from gene discovery (as first envisaged by Gottesman & Gould, 2003) and has instead focused on confirming the effects on individual brain systems of variants showing statistical association with illness. Among those approaches discussed, including neurocognitive, neuroimaging, and electrophysiological approaches, much attention has been placed on establishing whether individual paradigms meet the criteria for intermediate phenotypes of being associated with illness, show evidence of heritability, and show relative stability over time. In the case of visual and auditory evoked potentials studied in EEG paradigms, several reviews have focused on comparing the heritability of different evoked potentials (e.g. P50, P300, mismatch negativity) in the intermediate phenotypes approach. To date however, no review has been undertaken of individual genes whose function has been investigated using evoked potentials.

Schizophrenia (SZ) is a chronic, debilitating mental illness with heritability estimates of approximately 80-85% (Cardno & Gottesman, 2000). Schizophrenia is a complex genetic illness, that is, it does not adhere to standard Mendelian patterns of inheritance. Understanding just what the neural and phenotypic mechanisms of genetic variation actually are continues to remain elusive. There are multitudes of variables which contribute to the risk of experience SZ. This includes environmental and genetic factors and consideration of the heterogeneity therein. Regardless of the best approach towards the identification of risk genes in SZ and what way they impact upon brain function and the oft disunity between geneticists and neuroscientists in tackling this matter, there is the further impediment of the mode of identifying the population for study in the first instance at the clinical level. Different methodologies have been employed to deconstruct the genetics of complex psychiatric illnesses, for example, linkage analysis, genome-wide-association studies (GWAS) and candidate gene studies. Firstly however, the different forms of genetic variation will be outlined. There are very subtle differences in the genes of different individuals. It was originally conceived that this variation between individuals occurred every one in one-thousand DNA letters, with the implication that there was 99.9% similarity across the genome. Since then, with ameliorations in technology, it was discovered that there was more variation than that, and that individuals are 99% similar, with variation in 1% of the genome.

1.1.1. Variation

There are different forms of variation by which risk may be increased. One such form of variation is single-nucleotide-polymorphisms (SNPs). A SNP is a DNA sequence variation occurring when a single nucleotide, either A, T, C or G differs between. For example, one individual may have a DNA fragment which reads AAGC[C]TA and another has a fragment which reads AAGC[T]TA i.e., it contains two alleles, C and T. These SNPs may fall into coding sequences of genes, non-coding regions of genes or in the intergenic region between genes. It is impossible for all SNPs to be involved in the protein encoding, but where SNPs are not in a protein-coding region, they may still be involved in gene splicing (chemically cutting DNA using restriction enzymes and combining them to create new DNA), transcription factor binding (transcribing genetic information from DNA to RNA to specific genes) and in the sequencing of non-coding RNA (RNA not translated into a protein).

Since then, the International HapMap Project has found larger pieces of DNA in addition to variance explained by SNPs. These are known as copy-number-variations (CNVs). They are relatively uncommon variants. For CNVs, sometimes they may manifest themselves by repeating once, twice or many times in an individual. Alternatively, an entire gene may be repeated in an individual or may have been deleted entirely. CNVs are somewhat complicated by phenotypically undefined traits, genetic heterogeneity, incomplete or varied penetrance and their interaction with non-genetic factors. Despite these shortcomings, there is growing evidence that CNVs contribute to SZ with

evidence of a duplication of 1.4micro-bases of chromosome 15 (Kirov et al., 2008), and CNVs on the neurexin-1 (NRXN1) gene in SZ (Rujescu et al., 2009; Walsh et al., 2008).

1.1.2. Approaches to psychiatric-genetics: linkage, candidate gene approach, genome-wide association studies

There have been several techniques employed in endeavouring to expound genetic variation. At one time linkage studies prevailed. In linkage analysis, where there is a disease locus i.e., a mutation, any markers located adjacent to this locus segregate together, in families. Linkage is now integrated into candidate gene association studies and is less heavily pursued because few linkage studies on SZ or other complex disease have yielded consistent results (Burmeister, 1999).

Alternatively, candidate gene association studies make *a priori* assumptions about the underlying biology of the illness (e.g., genes that encode protein targets for psycho-active drugs) and then pursue candidate genes associated with this biology or position to examine genetic variation therein (Burmeister, McInnis & Zollner, 2008; Braff & Freedman, 2002). On the other hand, genome-wide-association-studies explore statistically associated markers, across the entire genome, with no emphasis on their known function or potential relationship to brain biology. They are unconstrained by hypotheses about genetic association with the illness (Pearson & Manolio, 2008). They are also more likely to pick up on alleles with lower population frequency than candidate-gene studies which are more

dependent on markers with higher allele frequencies (Risch, 2000).

The candidate gene approach has often been criticized. For example, it attempts to identify candidate risk genes in schizophrenia often without sufficient knowledge of either the robustness of the candidate gene in question or how brain pathways are related to brain pathology (Cowan, Kopmisky & Hyman, 2002; Tabor, Risch & Myers, 2002). Another source of difficulty is the lack of replicability across candidate gene studies (Ioannidis et al. 2003; Munafo, 2006; Sanders et al. 2008; Thaker, 2008) but this is often due to variation in study design and different variants and linkage disequilibrium being associated with different relative risk in differing, heterogeneous populations (Stephens et al. 2001). Association studies are also criticized for finding association across multiple haplotypes on the same gene e.g., Dysbindin (Mutsuddi et al., 2006). However, this may be explained by the relative combined contribution of numerous mutations at the same locus (Gershon, Liu & Badner, 2008).

In addition to the candidate gene approach, another technique employed in identifying risk genes is the genome-wide-association method which has been popularised in recent years (Tabor, Risch & Myers, 2002). GWAS studies are classical case-control studies in many respects. Each individual case and control in the sample is genotyped for a pre-defined set of a million or more genetic markers spaced across the genome. These genetic markers are usually always single-nucleotide-polymorphisms. Each SNP is then tested for association with the

disease i.e., the allele frequencies in cases is compared to controls, with a large case/control difference suggesting a role for a particular SNP or its genomic region. A typical Type I error threshold for genome-wide significance is often taken to be 5 x 10^{-8}. Sample sizes by necessity in GWAS studies must comprise of at least 7,000 cases and controls (Hindorff et al., 2009) if they are to be sufficiently powered. In order to get anywhere near the types of samples required to detect common alleles of small effect, the only option seems to be large institutions pooling data in consortiums e.g., the Psychiatric GWAS Consortium (PGC) and the International Schizophrenia Consortium (ISC).

The GWAS are not without their own noteworthy obstacles. They have huge potential for generating false-positive results, they lack any information on gene function, they require a huge sample size which may contain a sample with a biased selection pattern and they will not pick up on genetic variation due to environmental factors or gene-gene interactions (Pearson & Manolio, 2008). Moreover, it has been suggested that GWAS may not be the best approach where it continues to assume that diagnosis of SZ represents a clear diagnostic entity- SZ is neither a single disease entity nor a definitive syndrome and this biological complexity is a problem GWAS must negotiate (Tandon, Nasrallah & Keshavan, 2009). Another bone of contention is that often identified loci in SZ prove quite difficult to replicate, with each new study bringing new loci to the surface, a problem which does not seem to generalise to other diseases to the same extent e.g., Type II diabetes (Scott et al., 2007). One exception to this might be the replication of association with the zinc-finger ZNF804A (Riley et al 2009; Shi et

al 2009; Steffanson et al., 2009; Steinberg et al., 2010; Williams et al., 2010; Zhang et al., 2010).

As previously outlined, the most recent GWAS studies have individually failed to achieve genome-wide statistical significance but following pooled meta-analysis of European ancestry subjects the samples have become sufficiently powered to identify new regions of interest. There have been seven published GWA of SZ to date (Dudbridge & Gusnanto, 2008; Kirov et al., 2008; Lencz et al., 2007; Mah et al., 2006; O' Donovan et al., 2008; Shifman et al., 2008; Stefansson et al., 2009; Sullivan et al., 2008). Over time, the samples their power to detect small genetic effects becomes greater with increasing numbers of cases and controls. The latest published GWAS employ cutting-edge genotyping techniques coupled with the large cohorts of cases and controls in the identification of candidate loci for disease susceptibility. They have also benefited from the genome-wide haplotypes map of 3.1 million SNPs spanning the genome with whole genome SNP typing platforms (The International HapMap Consortium, 2007).

Through this method, several regions have been supported as being associated with SZ. The first region is located on chromosome six, wherein lies the major histocompatibility complex (MHC). The second region is 6p21.3-22.1, a marker located upstream of the neurogranin gene on 11q24.2 and the third region is marker in intron four of the transcription factor 4 on 18q21.2. These markers were the result of pooled samples from the SGENE consortium led by Kari Stefansson, the Broad Institute of MIT and Harvard led by Pamela Sklar and the

Molecular Genetics of Schizophrenia (MGS) led by Pablo Gejman. These findings were published in *Nature* in 2009 [Stefansson et al., 2009). Since then another body, the Psychiatric GWAS Consortium (PGC) has widely communicated their pre-publication results on pooled psychiatric GWAS data. Their analysis, presented at a session at the World Congress for Psychiatric Genetics in San Diego confirmed previously reported associations with the three regions (MHC, 18q and 11q) and revealed three more at 7p, 8q and 10q.

The various techniques outlined have all identified markers of interest through their association with the broad phenotype i.e., psychosis. However, an approach other than finding association at the macro-disease level has been to examine how these distinct genes could underlie certain endophenotypic traits in SZ e.g., verbal working memory, pre-pulse inhibition, nicotinic receptor functioning. Leboyer et al. (1998) adopt what they call the "candidate symptom approach" from the candidate gene approach. Hereby, illness-related but smaller characteristics are believed to be more greatly associated with the illness genotype, demonstrating a substantially less complex pattern of inheritance. These are called endophenotypes. The rational is that candidate genes in SZ affects the biology of neural mechanisms, arguably with greater penetrance at the neuro-systems level than at the clinical level offering a more direct route to genetic variance (Kendler, 1997; Meyer-Lindenberg & Weinberger, 2006; Thaker, 2008).

1.2. The endophenotypic approach

An endophenotype is a quantifiable characteristic, associated with a disease phenotype with a clear genetic connection; the main assumption surrounding the endophenotype is that it is less genetically complex than the disease phenotype (Gottesman & Gould, 2003). An endophenotype can be any cognitive, neurophysiological, biochemical, endocrinological, neuroanatomical or neuropsychological quantitative trait (Gottesman & Gould, 2003). Assuming that clinical behaviour is, amongst other things, a consequence of alterations to biological brain traits owing to faulty genes, these endophentoypes, in theory, may be a more direct route to the connection between the gene and clinical behaviour and central to this is the assumption that variation in an endophenotype is dependent upon variation in fewer genes than the more complex disease phenotype (Gottesman & Shields, 1972; Walters & Owen, 2007). In short, the endophenotype is genetically simpler and consequently, with the size of the effect between the gene and the phenotype increasing; the endophenotype is intermediate between genotype and disease. These endophenotypes are popular because they are easy to administer and are capable of being collected in large numbers in multiple forms. They are often relatively inexpensive and convenient to record or collect with animal models of these endophenotypes often readily available (Luck et al., 2010).

The concept of 'endophenotypes' was adapted by Gottesman & Shields (1972) from the work of John & Lewis (1966) who studied the small Australian eumastacid grasshopper, the

"Moraba scurra" and how their chromosomal variation related to their geographical distribution. Gottesman & Shields (1972) originally described these "endophenotypes" as internal phenotypes discovered by a "biochemical test or microscopic examination." John & Lewis (1966) found grasshopper distribution was more discernible at the microscopic and internal (the "endo") level than at the obvious and the external (the "exo)" level. Gottesman & Gould (2003) refer to the "exo" as behavioural macros." The use of the term "endophenotype" has been critiqued by Meyer-Lindenberg & Weinberger (2006). They argue that using the term "endophenotype" under-represents the implication of what they call "intermediate phenotypes" as real biological traits which predictably lie on the path from gene to behaviour and are primary rather than secondary phenotypes.

Several endophenotypic criteria were originally suggested by Gershon & Goldin (1986) and Leboyer et al. (1998) and adapted by Gottesman & Gould (2003) to include the following:

- *The endophenotype is associated with illness in the population:* the endophenotype is consistently correlated with the population in question e.g. SZ.
- *The endophenotype is heritable:* Heritability is one of the pivotal requirements for an endophenotype (Gottesman & Gould, 2003). Heritability is the way in which variance within a population is due to genetic variance. This genetic variance is dependent on a number of factors such as the way different alleles influence a trait, the frequency of these alleles, the effect sizes of the variants and the mode of gene action and changes which might occur in any of these factors (Visscher,

Hill & Wray, 2008). Traditionally, in psychiatric genetics, heritability has been heavily dependent on estimated correlations of MZ and DZ twin pairs (Falconer & Mackay, 1996). Hereby, statistics can be estimated based on MZ resemblance, DZ resemblance and overall phenotypic variation. Such measures attempt to understand the genetic component of risk to disease. This is independent of any known environmental factors e.g. stress, nutrition, parental care.

- *The endophenotype is primarily state-independent:* The association between the endophenotype and the illness in question is evident regardless of phase of illness. Hereby, there should be little difference between those experiencing their first episode, and those with chronic SZ, and medication, age or other such factors such not be found to alter the endophenotype outcome.
- *Within families, the endophenotype and the illness co-segregate:* When the endophenotype in question is established to co-segregate within families, these family members are compared to a set of unrelated control participants, and the endophenotype is found to be significantly more prevalent in relatives compared to these controls.
- *The endophenotype is found in unaffected family members at a higher rate than the general population.*
- *The endophenotype has good psychometric properties* e.g., reliability and validity: (Donohoe, Goldberg & Corvin, 2009).
- *The endophenotype reflects a causal pathway from gene to disorder:* This is a criteria which was part and Gottesman & Gould's original concept has been further developed by

Bearden & Freimer (2006) and Waldman (2005) whereby the endophenotype should reflect part of the causal pathway from gene to disorder; the endophenotype should show association with the candidate gene over and above genetic association with the disease. That is, the effects of a gene on a disorder are expressed either fully or in part, through the endophenotype.

Any notion of endophenotypes ever being genetically simpler than the disease itself has been subject to much criticism and given that it rests very much as an assumption this somewhat qualms excessive resolution regarding the merits of the endophenotype (Flint & Munafo, 2007). For example, there is a probably a low probability that any of these traits, like the disease phenotype, will be associated with one particular gene (Bearden & Freimer, 2006; Walters & Owen, 2007). Moreover, the assumption that an endophenotype lies on the causal pathway between genes and the disorder is an inference commonly made which has yet to be fully substantiated (Bearden & Freimer, 2006; Gottesman & Gould, 2003; Gould & Gottesman, 2006; Waldman, 2005; Reus & Freimer, 1997).

So, the argument is whether the gene is involved in SZ, or whether the gene is involved in cognitive deficits, which in turn, cause SZ. This is further complicated by the possibility that any phenotypic trait could be entirely epiphenomenal i.e., does not occur as a direct consequence of any genetic variant. It remains to be seen whether endophenotypes sufficiently meet their criteria and become widespread in association studies towards the elucidation of gene-disease pathways (Walters & Owen,

2007). Recently, the use of endophenotypes to study the functional consequence i.e., gene mechanisms, of risk genes has been popularized (Meyer-Lindenberg & Weinberger, 2006) and commentators concur that if the endophenotype is associated with a disease, meets the criteria for an endophenotype, and is associated with the presence of an already identified risk-allele then this, by all appearances, is evidence that it may actually lie "on the disease pathway" (Walters & Owen, 2007:889).

1.3. Event related potentials as endophenotypes

Event Related Potentials (ERPs), voltage fluctuations in the electroencephalogram (EEG) time-locked to internal or external events have been proposed as suitable endophenotypes for SZ genetics. Post-synaptic graded potentials from pyramidal cells create electrical dipoles between the body of the neuron and the dendrites causing differences in electrical potentials. Hereby, large populations of active neurons produce electrical activity which is then recordable at the head surface using EEG measures. Different brain waves signal brain electrical activity according to electrode placement and functioning in adjacent brain regions. Essentially, ERPs are significant voltage fluctuations resulting from evoked neural activity which may be provoked by either an internal or an external stimulus. The evoked potential in EEG is strictly phase-locked to the onset of an experimental condition e.g. stimulus onset, whereas oscillations are a result of any sensory event. Unlike magnetic-resonance-imaging (MRI) or positron emission topography (PET), which are highly spatially specific, EEG is temporally specific. The blood-oxygen-level-dependent (BOLD) signal from MRI reflects a

stimulus-induced hemodynamic response and is typically delayed in the order of two seconds during which time blood must travel from arteries to capillaries and draining veins (Kwong et al., 1992). Therefore, it is more reflective of long-duration changes, rather than brief, temporally accurate changes in neuronal activity accounted for by the ERP (Luck, 1999). The BOLD signal in MRI typically reflects local field potentials which are a combination of post-synaptic and pre-synaptic activity at multiple neurons. The ERP results from synchronized post-synaptic-potentials in cortical pyramidal neurons which are aligned perpendicular to the scalp with large dipoles between the dendrites and the soma of these neurons whereas a much broader set of neural processes leads to the changes in the BOLD signal (Luck et al., 2010). Because of these differences, MRI is much better at capturing anatomical sites of brain responses to stimuli and in the determination of neural responses whereas ERPs are excellent at capturing changes in neural activity at a milli-second to milli-second basis, linked to very specific aspects of neural activity (Luck et al., 2010). ERP models have also been found cross-species in studies of pharmacology and genetic manipulations in SZ (Ehrlichman, Maxwell, Majumndar & Siegel, 2008; Javitt, Spencer, Thaker, Winterer & Hajos, 2008; Metzger, Maxwell, Liang & Siegel, 2007).

So, what is the evidence that these ERPs, as endophenotypes in SZ have fulfilled their promise as being a useful measure for understanding the impact of SZ genetic risk variants on brain function? Outlined below is the evidence for the P50, P1, P300, ERN MMN and PPI meeting of the criteria of an endophenotype as and their evidence of association with risk genes in SZ. ERP

measures of smooth-pursuit-eye-movement-dysfunction (SPEMD) and antisaccade eye movement will not be included in the current chapter. Although there is evidence that it is a promising SZ endophenotype (see Calkins & Iacono, 2000; Holzman, 2000; Levy, Holzman, Matthysse & Mendell, 1994 for recent reviews) the current review discusses solely brain ERPs.

1.3.1. P300 as an endophenotype

1.3.1.1. *What does the P300 measure?* The P300 is a sensitive measure of impaired attention across a number of disorders, and has been extensively researched on account of the ease with which is may be elicited (Duncan et al. 2009). In SZ, P300 amplitude reduction between patients and controls has been repeatedly demonstrated, with the reduction occurring primarily over mid-line electrodes (Bharath, Gangadhar, & Janakiramaiah, 2000; Renoult et al., 2007). Evidence suggests the P300 relates to higher cognitive processes including memory and attention in conscious processing of an event, though it must be acknowledged that the specific mechanisms of the P300 are yet to be definitively elucidated. The P300 onset occurs at approximately the same latency as the participant's response, suggesting that this component commences after the stimulus has been sufficiently processed and has been sufficiently perceived to enable response (Kutas et al. 1977; McCarthy & Donchin, 1981).

The oft-noted attentional deficit found in SZ (Cornblatt & Keilp, 1994) is thought to be reflected in P300 amplitude differences between controls and patients especially where an auditory

P300 is the eliciting stimulus (Bruder et al., 1996). A recent study found that P300 asymmetry in SZs correlated with the severity of positive symptoms and worse global functioning (Renoult et al. 2007). The P300 deficit at parietal regions is possibly reflective of underlying structural and volume deficits in these regions in SZ (McCarley et al., 2002; McCarley et al., 1993). Convergent evidence from intracranial investigation, studies with patients with focal brain injuries and functional neuroimaging studies suggests that a widespread cortical network may be involved (Soltani & Knight, 2000). This includes the temporo-parietal junction, medial temporal cortex and the lateral prefrontal cortex are all areas involved in the generation of the P300. Injuries to the temporal-parietal region have been associated with impaired P300s (Knight, Scabini, Woods & Clayworth, 1989; Yamaguchi & Knight, 1991, 1992). A correlation was found between P300 amplitude reduction in SZ and volume reduction in such structures as the superior-temporal-gyrus, Heschl's area, and the planum temporale. These are all areas involved in language generation and understanding, and in auditory processing. A study by Halgren, Marinkonic & Chauvel (1998) used intracranial recordings using stereotactically placed electrodes to explore the underpinnings of the P300.

No ERP have been more investigated than the P300 as an endophenotype and whether it is associated with candidate SZ genes. There may be several reasons for this. Firstly, as already noted the P300 is very easily elicited - it does not require great concentration on behalf of the individual as it is usually very readily elicited by standard odd-ball paradigms. The P300 also

benefits from being an easily identified, large component and requires only a small number of electrodes to measure it.

1.3.1.2. *What is the evidence of stability, co-segregation:* There is evidence that the P300 is stable and co-segregates with illness (Frangou et al., 1997; Roxborough, Muir, Blackwood, Walker, & Blackburn, 1993; Schreiber, Stolz-Born, Kornhuber, & Born, 1992; Weisbrod, Hill, Niethammer, & Sauer, 1999). The P300 deficit in SZ is evident before treatment has commenced (Hirayasu et al., 1998) and at first-episode of SZ (McCarley et al., 2002; Salisbury et al., 1998). Ozgurdal et al. (2008); Van der Stelt, Lieberman & Belger (2005) and vanTricht et al., (2010) found that patients at the prodromal phase of the illness or at high risk of developing psychosis, demonstrated auditory P300 abnormalities akin to patients at both recent and chronic stages of the illness. In the vanTricht et al., (2010) study, the P300 was in fact the biggest predictor of developing first psychotic episode in the ultra-high-risk group. Bramon et al. (2008) found that those with an at-risk mental state demonstrated significantly reduced amplitude measures compared with controls.

1.3.1.3. *What is the evidence of heritability of the P300?* Weisbrod et al. (1999) compared monozygotic twins concordant and discordant for SZ on P300 measures. Compared to healthy controls, P300 amplitudes were significantly smaller in affected twins as well as non-affected twins. That P300 amplitudes were reduced not only in twins with a diagnosis of SZ, but also non-affected twins of discordant pairs was interpreted as strongly supporting the genetic transmission of P300 abnormalities in SZ. Bestelmeyer et al. (2009) found that auditory P300 amplitudes

were significantly correlated in monozygotic twins, this being significantly bigger than for dizygotic twins. Van Beijsterveldt (van Beijsterveldt & van Baal, 2002) pooled five studies reporting mono-zygotic and dizygotic correlations in a meta-analysis (O' Connor, 1994; Katsanis et al. 1997; Polich & Burns, 1987; Rogers & Deary, 1991; van Beijsterveldt et al. 1998b & Wright et al. 2001). These studies showed evidence for the influence of genetic factors i.e. identical twin correlations significantly exceeding fraternal twin correlations. Across studies, the estimated heritability of the P300 was 60% and for P300 latency, it was 51%. For example in the study by Wright et al. (2001), the monozygotic correlations for P300 amplitude ranged from 0.5 to .64 and were approximately double those for dizygotics which ranged from .24 to .33. Other evidence of heritability comes from Katsanis et al. (1997) and Yoon et al. (2006).

Blackwood et al. (1991) investigated a large pedigree of adults consisting of siblings and relatives of patients with SZ, and compared them to controls. P300 amplitudes and latency of both relatives and patients were significantly smaller and longer compared to controls. Roxborough et al. (1993) examined P300 measures in first and second degree relatives of SZ patients, the patients themselves, and controls, and found a significant P300 amplitude reduction and latency delay for the relatives and patient groups compared to control groups. Bramon et al. (2005) pooled 472 relatives and 513 controls in a meta-analysis, finding that P300 amplitudes were significantly reduced in relatives and the P300 latency was significantly delayed in patients. Collectiveiy this evidence support the heritability of P300

abnormalities in SZ (Cannon et al. 2000, Toulopoulou et al. 2007).

Blackwood et al. (2001) investigated a family with a translocation at chromosome 1q42, the chromosomal region involving the DISC1 gene. Within the family, members who carried the translocation presented with a wide range of major psychiatric disorders, including SZ and major depression. Significantly, the only phenotype common to all carriers (irrespective of clinical phenotype) was an abnormal P300 response. Asymptomatic translocation carriers showed similar P300 amplitude reductions as was found in translocation carriers who were diagnosed with a range of major psychiatric disorders (Blackwood & Muir, 2004). Again in support of the usefulness of the P300 as an endophenotype, this data suggests that the P300 was the only phenotype bar none that was carried by all translocation carriers, clinically affected or not.

1.3.1.4. *What is the evidence of molecular genetic association with the P300 tested in relation to a number of candidate SZ genes*

i) Association has also been reported between Neuregulin-1 and the P300 (Bramon et al. 2008). NRG1 has many functions in the brain, particularly neurodevelopment and the regulation of neural functioning and plasticity, for example, in regulating the expression of ion-channel receptors or the release of excitatory and inhibitory transmitters in the synapse (Buonanno & Fischbach, 2001; Falls, 2003; Ozaki, 2001). It has also been found to regulate axonal signalling (Michailov et al., 2004) whereby reduced NRG1 expression caused hypomyelination and reduced

nerve conduction in mutant-mouse models. Bramon et al. (2008) examined the effect of a single nucleotide polymorphism (SNP) SNP8NRG221533 and two microsatellite markers in Neuregulin-1 which were previously associated with risk for schizophrenia, on P300 amplitude and latency. Association was found between latency and the NRG-1 SNP. There was no association found between P300 amplitude measures and any of the NRG1 markers considered. Since then, NRG1 has been associated with changes in prefrontal cortical activations (Hall et al, 2006) and white matter integrity (McIntosh et al, 2008). These data reflect the liklihood that not all illness associated molecular variants will be associated with any one intermediate phenotype.

ii) More recently, association has been found between the P300 and NOS1, another gene associated with SZ (Reif et al., 2006). Nitric Oxide (NO) is generated from arginine after glutamate activation of NMDA receptors and calcium influx. NMDA receptors allow calcium ions to enter the neuron. After calcium influx, neuronal NOS is activated and arginine is converted to NO (Bredt & Snyder, 1989). A large body of evidence has found that inhibitors of NO e.g. nitroarginine, block the generation of LTP (Haley, Wilcox, & Chapman, 1992; O'Dell, Hawkins, Kandel, & Arancio, 1991). Reif et al. (2006) grouped patients according to genotype and found that, in relation to a P300 ERP from a continuous performance task (CPT), shorter latencies were associated with those carrying an identified variable number tandem repeat polymorphism (VNTR). It was also found that those homozygous for a GG allele exhibited longer peak latencies, indicating that the A allele on SNP1 (G-84A in exon 1c) positively affected pace and accuracy of cognitive processing. Reif et al.

(2009) genotyped 167 controls for NOS 1 VNTR on a go/no-go CPT and found that the no-go centroid, a measure of medial pre-frontal cortex activity during cognitive response-controls (Fallgatter & Strik, 1999) was localized significantly more posteriorly in carriers of the short NOS 1 VNTR allele, suggesting that there is a diminishment of the anterior-cingulate-cortex in short-allele-carriers and consequently an impaired cognitive-control of initiated responses i.e. impulsivity.

iii) A polymorphism in the COMT gene results in the substitution of the amino acid value for methionine at codon 158 and it is understood that carriers of the Met variant of the COMT gene may have higher DA levels in the PFC, resulting in optimal working memory performance for Met/Met and Val/Met carriers versus Val/Val carriers because Val/Val homozygotes degrade DA more rapidly than their Met/Met counterparts (Meyer-Lindenberg et al. 2005). Furthermore, treatment with anti-psychotics, acting on DA is found to improve cognitive performance, particularly working memory in Met/Met homozygous patients over Val/Val homozygous patients (Bertolino et al. 2004; Egan et al. 2001; Weickert et al. 2004; Woodward, Jayathilaka & Meltzer, 2007). The same genotype has been examined in relation to the P300 (Gallinat et al., 2003). During an oddball task condition, Met/Met homozygotes had lower frontal P300 amplitude than Val/Val homozygotes. Golimbet et al. (2006) also found significant association between Met/Met genotype and higher P300 amplitudes in relatives of SZ patients. Likewise, Gallinat et al. (2003) found lower frontal P300 amplitudes in Met/Met carriers, reflecting reduced cortical noise levels. Ehlis et al. (2007) found that Met/Met homozygous

patients had increased fronto-central P300 amplitudes compared with Val carriers on a Go/No-Go task.

iv) Sinkus et al., (2008) has also found a significant effect of 2bp deletion in exon6 of CHRFAM7A (cholinergic receptor, nicotinic, alpha 7, exons 5-10, family with sequence similarity 7A, exons A-E) on P300 latency. CHRFAM7A is in close proximity to the alpha-7-nicotinic receptor CHRNA7 gene which is located on chromosome 15 and is a region associated with SZ. The alpha-7-nicotinic receptor locus has been associated with P50 deficits also (Freedman et al. 1997).

Table 1.1. The evidence for P300 as an endophenotype

Measure	Study	Sample	Co-segregates with illness	State-independence	Identified in 1st degree relatives; heritability	Associated with risk genes in SZ (gene)
P300	Frangou et al. (1997)	SZ=33 R=57 C=32	+			
	Roxborough (1993)	SZ=30 C=30	+			
	Schreiber et al. (1992)	HighRiskSZ=21 C=21	+			
	Hirayasu et al. (1998)	SZ (neuroleptic-free)=45 SZ(drug free)=56 C=73		+		
	McCarley et al. (2002)	SZ=15 C=16 AffectivePsychosis=16		+		
	Salisbury et al. (1998)	1st episodeSZ=14 C=14 1st episode AffPsy=14		+		
	Bestelmeyer et al. (2009)	SZ MZ =14 SZ DZ = 14			+	
	Katsanis et al. (1997)	MZ ©=30 DZ © = 34			+	
	Yoon et al. (2006)	Males © = 578 Females © = 674			+	
	Ozgurdal et al. (2008)	Prodromal = 54; 1st episode SZ = 31 chSZ=27; C=54	+	+		
	Hall et al. (2009)	MZdiscordantBPD=10 MZconcordantBDP=6 MZcontrols=43 DZcontrols=33 BipolarDisorderfamilies=31 C=39	+		++	
	Van der Stelt et al. (2005)	Prodromal = 10 Recent onset = 10 Chronic = 14 C=14		+		
	Weisbrod et al. (1999)	MZ discordant SZ= 8 MZ concordant SZ = 5 MZ controls = 9			++	
	O'Connor (1994)	MZ = 59 DZ = 39			++	
	Polich & Burns (1987)	MZ=10 C=20			+	
	Wright et al. (2001)	Twin pairs = 335 Siblings = 39			++	
	Van Beijsterveldt et al. (1998)	Twin pairs = 213			++	
	Blackwood et al. (1991)	SZ=31 C=33			+	
	Bramon et al. (2005)	SZ=30 Rel=40 C=40			++	
	Roxborough et al. (1993)	SZ=30 C=30	+			
	Bramon et al. (2008)	SZ=64 Rel=97 C=35				+ (Neuregulin-1)
	Reif et al. (2006)	SZ=48				+ NOS 1 (VNTR)
	Ehlis et al. (2007)	SZ=56				+ (COMT)
	Blackwood & Muir (2004)	R(carriers)=12 R(noncarriers)=10 otherSZ=20 C=26				+ (DISC1)
	Fallgatter et al. (2006)	C=48				+ (Dysbindin)
	Golimbet et al. (2006)	SZ=44 R=35				+ (Relatives only: COMT)
	Gallinat et al. (2003)	SZ=49 C=176				+ (COMT)
	Reif et al. (2009)	C=167				+ NOS 1 (VNTR)
	Shaikh et al. (2008)	SZ/SZAff=76 1stDegR=124 C=37				+ (2bp deletion CHRFAM7A)

C=controls ; AffPsy=Affective psychosis; chSZ=chronicSZ; MZ=monozygotic; DZ=dizygotic; Rel=relatives; SZAff=Szaffective
++ distinguishes a familial study from a twin study (+)

1.3.2. The P1 as an endophenotype

1.3.2.1. *What does the P1 measure?* The initial P1 peak is an automatic sensory response elicited by visual stimuli regardless of the task the subject is currently engaged. It peaks at around 100milliseconds following stimulus onset and is one of the most robust components of the visual evoked potential (Yeap et al., 2006). It has a bilateral occipital distribution (Yeap, Kelly, Thakore, & Foxe, 2008) and is believed to be mediated predominantly by magnocellular connections from the lateral geniculate nucleus to the visual cortex, with knock-on consequences from impaired magnocellular streams to parvocellular streams (Doniger, Foxe, Murray, Higgins, & Javitt, 2002). This distinction between magnocellular and parvocellular streams in mediating the visual P1 has been shown in paradigms where the stimuli are manipulated to stimulate the magnocellular and parvocellular streams separately, with the result that the parvocellular stream is largely spared (Butler et al., 2007; Kveraga, Boshyan & Bar, 2007; Lalor, Yeap, Reilly, Pearlmutter & Foxe, 2008; Schecter et al., 2005).

1.3.2.2. *What is the evidence of stability and co-segregation with illness:* A P1 deficit has been shown to differentiate between patients and controls (Butler et al., 2001; Chen et al., 1999; Doniger, Foxe, Murray, Higgins & Javitt, 2002; Foxe, Doniger & Javitt, 2001; Green, Nuechterlein, Breitmeyer, & Mintz, 1999; Haenschel et al., 2007; Schechter et al., 2005; Schwartz & Evans, 1999; Yeap, Kelly, Sehatpour et al., 2008; Yeap et al., 2006). In 2008, Yeap, Kelly, Thakore & Foxe found evidence that the P1 is a potential trait, rather than state-marker. They compared

bilateral occipital electrodes between those experiencing first-episode psychosis and controls. The anticipated difference was found between patient and control amplitudes, suggesting that there may be visual sensory functioning deficits before the main onset of the illness and this is independent of illness-state. Similarly, Koychev, El-Deredy, Haenschel & Deakin (2010) found significantly reduced P1 amplitudes in a high schizotype group when compared with healthy controls.

1.3.2.3. *What is the evidence for heritability of the P1?* There is evidence of heritability with respect to the P1 also, though thus far, the classic comparisons between monozygotic and dizygotic twins has not taken place, as is the case with many endophenotypes in psychosis (Tan, Callicott & Weinberger, 2008). Yeap et al. (2006) examined the P1 component amongst relatives of individuals with SZ, with a view to this reflecting a genetic predisposition to a disease rather than the disease process itself. A P1 deficit for both the patient group and their relatives had a very large effect size and this deficit was most prominent in midline parieto-occipital scalp regions.

1.3.2.4. *What is the evidence of molecular genetic association with the P1 tested in relation to a number of candidate SZ genes?* Dysbindin is another risk gene in SZ which is located on one of the most investigated susceptibility loci in SZ linkage studies. Specifically, evidence suggests that Dysbindin (DTNBP1) might influence exocytotic glutamate release via upregulation of the molecules at the pre-synaptic stage (Numakawa et al. 2004). In terms of an association with an ERP endophenotype, Donohoe et al. (2008) found that there was a 50% decrement in visual

evoked potentials in those in a risk-haplotype carrying patient group with SZ compared to a non-risk-haplotype carrying patient group. Dysbindin (DTNBP1) has also elsewhere been associated with Go/No-Go anteriorisation (measured using the P300) and healthy controls (Fallgatter et al., 2006).

Table 1.2. Evidence for the P1 as an endophenotype

Measure	Study	Sample	Co-segregates with illness	State-independence	Identified in 1st degree relatives;	Associated with risk genes in SZ (gene)
P1	Chen et al. (1999)	SZ=20 Rel=24 C=20			++	
	Green et al. (1999)	SZ=11 C=11	+			
	Schwartz et al. (1999)	SZ=23 C=16	+			
	Yeap et al. (2008)	SZ=52 C=26		+		
	Yeap et al. (2006)	SZ=15 C=26 Rel=25			++	
	Donohoe et al. (2008)	SZ=26				+ (Dysbindin)

++ distinguishes a familial study from a twin study (+)
Rel=relatives; C=controls

1.3.3. The P50 as an endophenotype

1.3.3.1. *What does the P50 measure?* The P50 is elicited by paired clicks, usually separated by an interval of 500msecs. This leads to a brain response approximately 50msecs post-stimulus (Patterson et al. 2008). If a second stimulus is presented not long after the first, the second response is suppressed by inhibitory mechanisms which have been stimulated by the first click (Adler et al. 1999). What is measured is the decrease of the P50 wave to the second click compared with the 1st click. Diminished inhibition to the second click in SZ has been correlated with deficits in sustained attention and word recognition performance (Cullum et al. 1993; Vinogradova et al. 1996).

1.3.3.2. *What is the evidence for state independence and co-segregation?* Patterson et al. (2007) examined 84 studies comparing P50 gating ratios between SZ and controls. P50 gating ratios (i.e., stimulus 2: stimulus 1) for SZ groups ranged from 56-158% with a range of 9-73.4% for controls. In 45 out of 46 studies, the P50 gating ratios were larger for SZ than control subjects (Adler et al., 1982; Boutros et al., 1993; Braff & Geyer, 1990; Erwin et al., 1991; Freedman et al., 1987; Jin et al., 1997; Judd et al., 1992; Martin et al., 2007; Yee et al., 1998). There has been some evidence that the P50 gating increases, and thereby improves, during the post-acute phase of illness (Devrim-Ucok, Keskin-Ergen & Ucok, 2008) and that some anti-psychotic medications may ameliorate the gating deficit, though it has been suggested that the evidence thus far only supports clozapine's improving the deficit (Adler et al., 2005).

1.3.3.3. *What is the evidence of heritability of the P50?* Hall et al. (2007) investigated the heritabilities of 3 ERP components (P50, P300 and Mismatch Negativity) using 40 MZ and 30 DZ twin pairs, finding that P50 heritability was around 68%. Myles-Worsley (2004) investigated families with a high prevalence of SZ in the Republic of Palau, an isolated island in Micronesia, ideally suited to this type of research, as atypical anti-psychotics have not reached its shores yet and many do not take any medication whatsoever. It was found that auditory P50 gating, as measured by the P50 ratio, was similarly impaired in medicated and unmedicated SZ patients. This impairment was also in evidence in first degree relatives who demonstrated significantly higher P50 ratios than controls. This supports earlier work by Siegel et al. (1984) who found P50 gating deficits amongst

relatives of those with SZ. Likewise, Waldo et al. (1994) examined 6 pedigrees, chosen because of a high prevalence of SZ in this family, finding a familial association with the deficit and others have had similar findings (Clementz et al. 1998; Waldo et al. 2000).

1.3.3.4. *What is the evidence for molecular association with the P50?*

i) P50 deficits in SZ have been genetically linked to the locus of the alpha-7-nicotinic receptor gene on chromosome 15q14 (Freedman et al. 1997) 9 families with 104 members were studied and association was found between markers on this chromosome and members with a diagnosis of SZ.

Xu et al. (2001) genotyped three polymorphic markers D15S1360, D15S165 and L76630 localised in the alpha-7-nicotinic receptor gene in families with members who were affected and unaffected by SZ. Significant association was found between L76630 and SZ in these families. This same region (L76630), in addition to another genetic marker (D15S1360) in the 15q14 region was genotyped in a Swiss cohort (Stassen et al. 2000), with the finding of significant differences between patients and controls in the allelic distribution of both markers. De Luca et al. (2004) found evidence of association between the D15S1360 marker and smoking risk, suggesting that the high incidence of smoking amongst those with SZ may stem from self-medicating or correction of this deficit. The finding that smoking, and consequently nicotine absorption improves sensory gating in SZ is believed to be due to increase in glutamate activation of alpha-7 subunit receptors (Gray et al. 1996; Leonard et al. 1996;

Vidal & Changeux, 1993), where inhibitory responses to the second stimulus may be mediated by the hippocampus. In a "proof of concept" study, Olincy et al., (2006) found that inhibition of the P50 response increased during the absorption of an alpha-7-nicotinic agonist in a SZ sample.

ii) Martin et al. (2007) split SZAffective, SZ and control groups depending on whether they were carriers of common CHRNA7 alleles or variant alleles, with the prediction that carriers of the variant alleles would have impaired sensory gating. Regarding the SZ group, variant allele carriers were indistinguishable from common allele carriers on P50 gating ratios. Conversely, variant allele carriers with SZAffective disorder, or who were controls, had higher mean P50 ratios compared to controls with common alleles.

iii) Lu et al. (2007) examined P50 gating based on COMT genotyping in 42 SZ and 25 controls and found that Val homozygous individuals exhibited the greatest gating deficit, with the COMT genotype accounting for 17% of the gating variance in patients but a non-significant 4% in controls.

Table 1.3. Evidence for the P50 as an endophenotype

Measure	Study	Sample	Co-segregates with illness	State-independence	Identified in 1st degree relatives; heritability	Associated with risk genes in SZ (gene)
P50	Clementz et al. (1998)	SZ=44 Rel=60 C=45			++	
	Siegel et al. (1984)	SZ=15 Rel=15			++	
	Myles-Worsley (2007)	SZ=85 Rel=83 C=29			++	
	Freedman et al. (1997)	N=97 (x9 families)				+ (α7-nicotinic receptor gene)
	Hall et al. (2007)	MZconcordantSZ=16 MZdiscordantSZ=9 C=78			+	
	Devrim-Ucok et al. (2008)	SZ=16 C=24		-		
	Boutros et al. (1993)	SZ=11 C=11	+			
	Adler et al. (1982)	?	+			
	Braff & Geyer (1990)	?	+			
	Erwin et al. (1991)	SZ=47	+			
	Freedman et al. (1983)	?	+			
	Judd et al. (1992)	SZ=20 C=20	+			
	Jin et al. (1997)	SZ=16 C=16	+			
	Martin et al. (2006)	SZ=37 SZAffective=17 C=149				+ (SZAff only: CHRN17)
	Lu et al. (2007)	SZ=42 C=25				+ (COMT)

++ distinguishes a familial study from a twin study (+)
C=controls; Rel=relatives; ?=unknown

1.3.4. The N1 as an endophenotype

1.3.4.1. *What does the N1 measure?* The N1 is an event related potential with a negative deflection which peaks between 100-200msecs. The first peak is between 100-150msecs and is anteriorally located, whilst the second peak is at 150-200msecs and is more posteriorally located (Luck, 2005). It is found to measure discrimination processing (Ritter et al. 1982; Vogel & Luck, 2000).

1.3.4.2. *What is the evidence that the N1 is state-independent and co-segregates with illness?* Numerous studies have found N1

deficits amongst patients with a diagnosis of SZ (Boutros et al. 2004; Connolly, Manchanda, Gruzelier & Hirsch, 1985; Kayser et al. 2001; Kessier & Steinberg, 1989; Saletu, Itil & Saletu, 1971). Salisbury, Collins & McCarley (2010) compared chronically ill SZ patients, those experiencing their first episode and controls. The task involved counting binaurally presented target tones among standard tones. Both first episode and chronic SZ showed significantly reduced amplitudes compared to controls, but the effect size was larger for chronics.

1.3.4.3. *What is the evidence of heritability of the N1?* Anokhin et al. (2007) compared 48 MZ twins with 40 DZ twins and found heritability estimates to be between 71-76%. Likewise, Force, Venables & Sponheim (2008) compared patients with SZ, their first degree relatives and controls and found that both those with SZ and their first degree relatives exhibited reduced N1 amplitudes in comparison to control participants. Similarly, Turetsky et al., (2008) relatives, patients and controls and found that both SZ and 1st degree relatives exhibited reduced N1 amplitude in comparison to control participants. This has not been supported elsewhere; Magno et al. (2008) found that first degree relatives' MMN was unaffected.

1.3.4.4. *What is the evidence of molecular genetic association with the N1?* As yet, there are no association studies regarding N1 and risk genes for SZ.

Table 1.4. Evidence for the N1 as an endophenotype

Measure	Study	Sample	Co-segregates with illness	State-independence	Identified in 1st degree relatives; heritability	Associated with risk genes in SZ (gene)
N1	Boutros et al. (2004)	SZ=27 C=22	+			
	Connolly et al. (1985)	SZ=10 C=10				
	Kayser et al. (2001)	SZ/SZAff=66 C=32	+			
	Kessler & Steinberg (1989)	?	+			
	Saletu et al. (1971)	?	+			
	Salisbury et al. (2009)	1st episodeSZ=55 ChronicSZ=56 C=108		+		
	Anokhin et al. (2007)	MZ=48 DZ=40			+	
	Force et al. (2008)	SZ=19 Rel=37 C=36			++	
	Turetsky et al. (2008)	Rel=14 C=20			++	

++ distinguishes a familial study from a twin study (+)
C=controls; Rel=relatives; ?=unknown

1.3.5. Error-Related-Negativity as an endophenotype

1.3.5.1. *What does Error Related Negativity measure?* Error related negativity (ERN) is a negative-going deflection at frontal and central electrodes after a response has been elicited which is known to be erroneous (Falkenstein et al. 1991; Gehring et al. 1993). It has also been found to be elicited where someone observes an error being made by another (van Schie et al. 2004). With the use of MRI, the ERN has been found to occur in the anterior-cingulate-cortex (Alain et al. 2002; Dehaene, Posner & Tucker, 1994; Holyroyd et al. 2004) and the dorso-lateral-prefrontal cortex (Mathalon, Jorgensen, Roach & Ford, 2009).

1.3.5.2. *What is the evidence that ERN co-segregates with illness and is state-independent?* Reduced ERNs have been found in SZ (Alain et al. 2002; Kim et al. 2006; Kopp & Rist, 1999; Mathalon et al., 2002). However, evidence suggests that the ERN may be more state rather than trait dependent in a study by Bates,

Liddle, Kiehl & Ngan (2004) whereby participants performed a go/no-go task during the early stages of an acute phase of SZ and following six weeks of treatment with anti-psychotics. It was found that the ERN was significantly reduced in SZ compared with controls during the acute phase, but this increased significantly following treatment. The sample size in this study was quite small however.

1.3.5.3. *What is the evidence of heritability of the ERN?* The only study thus far exploring the heritability of the ERN is from Anokhin, Golosheykin & Heath (2008) which, although did not consist of a sample of patients with SZ, found amongst healthy MZ and DZ twins that heritability estimates were in the region of 40-60%. In contrast, heritability estimates following the pooling of five studies found heritability estimates of the P300 to be in the region of 60-64%.

1.3.5.4. *What is the evidence of molecular genetic association with the ERN?* Thus far, there is no evidence of association between ERN and risk genes in SZ.

Table 1.5. Evidence for Error-related-negativity as an endophenotype

Measure	Study	Sample	Co-segregates with illness	State-independence	Identified in 1st degree relatives; heritability	Associated with risk genes in SZ (gene)
Error-related negativity	Kopp & Rist (1999)	SZ=29 C=18	+			
	Mathalon et al. (2002)	SZ=18 C=18	+			
	Kim et al. (2006)	SZ=15 C=15	+			
	Kim et al. (2006)	SZ=15 C=15	+			
	Bates et al. (2004)	SZ=9 C=9		+		
	Anokhin et al. (2008)	MZ=99 DZ=175			+	

++ distinguishes a familial study from a twin study (+)
C=controls; MZ=monozygotic; DZ=dizygotic

1.3.6. Mismatch-Negativity as an endophenotype

1.3.6.1. *What does Mismatch Negativity (MMN) measure?* The MMN is an automatic response to the detection of differences between stimuli in an auditory environment and usually peaks around 100-240 msecs after the presentation of the deviant stimulus. It may differ in frequency, duration or intensity (Naatanen, 1995). Its topography generally lies over fronto-central areas (Umbricht & Krljes, 2005).

1.3.6.2. *What is the evidence that the MMN is state-independent and co-segregates with illness?* Several studies show impaired MMN in SZ (Baldeweg, Klugman, Gruzelier, Hirsch, 2004; Catts et al. 1995; Magno et al., 2008; Shelley et al. 1991; Umbricht et al. 2003). As to whether the MMN is trait, rather than state dependent, the evidence, thus far is mixed. Salisbury et al. (2002)

compared those with chronic SZ with those experiencing their first episode and with controls, and found that although the MMN was reduced by 47% in the chronic group, it was not reduced in those experiencing their first episode. There are similar findings from Shinozaki et al. (2002) who found that the MMN was reduced for the most-part during the acute phase of the illness, after which it was restored. This suggests that the MMN may be a better indicator of disease progression than a hallmark of the disease itself. However, one recent study Bodatsch et al., (2010) investigated MMN in controls, at-risk individuals and cases experiencing their first episode. They found that cases who went on to develop psychosis had significantly reduced MMN compared to those who did not. Those who never went on to develop psychosis, had MMNs which were comparable to healthy controls.

1.3.6.3. *What is the evidence of heritability of the MMN?* Hall et al. (2006) used 40 pairs of MZ and 30 pairs of DZ twins to establish the heritability of the MMN and estimated it to be 63% for peak amplitude and 68% for mean amplitude. However, the evidence that it is deficient in unaffected relatives is somewhat mixed. For example, Bramon et al. (2005) compared patients, unaffected first degree relatives and unrelated controls, and found that although those with SZ had smaller MMNs than controls, 1st degree relatives and controls did not differ. Similarly (Michie, Innes-Brown, Todd & Jablensky, 2002) found that patients with SZ and relatives had a similar MMN performance. This is the only study in support of heritability however. Elsewhere, there has been no finding of a difference between patients and controls (Jessen et al. 2001). Also, Schreiber, Stolz-Born, Kornhuber &

Born (1992) finding of a difference in amplitudes between those at high risk of developing SZ did not reach significance. Brockhaus-Dumke et al. (2005) found a non-significant reduction in MMN in prodromal participants, their amplitudes being intermediate between controls and patients with SZ. The MMN's failure to consistently meet the heritability criteria of an endophenotype and its apparent alteration across disease state, indicates that it might be better served as a marker of illness progression and cognitive dysfunction, with its magnitude correlating with other cognitive hallmarks of SZ (Baldeweg, Klugman, Gruzelier & Hirsch, 2004).

1.3.6.4. *What is the evidence of molecular genetic association with the MMN?* Baker et al. (2005) chose this paradigm to measure its association with a population with deletions of 22q11 (velo-cardio-facial syndrome). This is a group of individuals are greater risk of developing SZ (Baker & Skuse, 2005; Basset et al. 1998; Murphy, 2002; Papolos et al. 1996). COMT108/158Met allele on the remaining chromosome was associated with frontal MMN reductions.

The MMN, despite co-segregating with illness is not state-independent, and it does not consistently co-segregate with relatives. Curiously, it was used in the association study with COMT (Baker et al. 2005). However, meta-analysis challenges the claim that there is even an association between the COMT val allele and SZ in the first place (Munafo, Bowes, Clark & Flint, 2005) and it appears that, as a candidate gene in SZ it not have that much weight behind it (Glatt, Faraona & Tsuang, 2003). COMT expression, in terms of conveying risk for SZ may be

dependent on the *context* of its expression and may therefore be more involved in pre-frontal cortical functioning and cognition rather than in increasing illness-risk *per se* (Tunbridge, Harriss& Weinberger, 2006).

Table 1.6. Evidence for mismatch negativity as an endophenotype

Measure	Study	Sample	Co-segregates with illness	State-independence	Identified in 1st degree relatives; heritability	Associated with risk genes in SZ (gene)
	Catts et al. (1995)	SZ=33 C=33	+			
	Magno et al. (2008)	ChSZ=45 1stDegreeRel=25 1stepisodeSZ=12 C=27	+		--	
Mismatch negativity	Hall et al. (2009)	MZdiscortantBPD=10 MZconcordantBDP=6 MZcontrols=43 DZcontrols=33 BipolarDisorderfamilies=31 C=39MZ&DZ=94 BipolarDisorderFamilies=31 C=39	-		-- +	
	Shelley et al. (1991)	?	+			
	Umbricht et al. (2003)	SZ/SZAff=26 C=25	+			
	Baldeweg et al. (2003)	SZ=28 C=20	+			
	Salisbury et al. (2002)	ChronicSZ=16 1stepisodeSZ=21 OlderControl=13 YoungerControl=27		+		
	Hall et al. (2006)	MZconcordantSZ=16 MZdiscordantSZ=9 C=78			+	
	Michie et al. (2004)	SZ=22 1stdegreeRel=17 C=21			++	
	Brockhaus-Dumke (2004)	Prodromal=43 neuroleptic-freeSZ=31 C=33		-		
	Bramon et al. (2003)	SZ=25 1stDegreeRel=37 C=20	+		--	
	Jessen et al. (2001)	SZ=11 1stDegreeR=15 C=16			--	
	Schreiber et al. (1992)	SZ=21 C=21			--	
	Shinozaki et al. (2002)	SZ=13 C=13		-		
	Baker et al. (2005)	22a11deletion=25 C=25				+ (COMT)

++ distinguishes a familial study from a twin study (+)
C=controls; MZ=monozygotic; DZ=dizygotic; SZAff=schizoaffective; ?=unknown

1.3. Pre-pulse Inhibition as an endophenotype

1.3.7.1. *What does the PPI measure?* Pre-pulse inhibition involved the presentation of two stimuli in close succession. In this aspect, it is not unlike the P50. The PPI examines the inhibition of the startle reflex. During the PPI experiment, a startle-eliciting stimulus (e.g., a loud burst of noise) is presented. This stimulus is sometimes presented in close succession. When the non-startling "pre-pulse" precedes the startling "pulse" by an interval ranging from approximately 30-300msecs, the startle reflex is markedly inhibited compared to when the startle response is presented alone. On average, the startle reflex amplitude is inhibited by 50% or more, and in some instances, is completely suppressed. The startle-eliciting pulse is usually a brief burst of loud noise (95-105dB). The non-startling prepulse is usually a brief mild innocuous tone. It is thought that the PPI may reflect an automatic sensory gating mechanism, initiated by the prepulse that protects initial processing of the prepulse from the distractive effects of other sensory events, such as startle stimuli.

1.3.7.2. *What is the evidence that PPI is state-independent and co-segregates with illness?* The literature on PPI in SZ reports sensory filtering deficits in cases with SZ (Braff et al., 1978; Dawson et al., 1993; Duncan et al., 2003a; Grillon et al., 1992; Kumari et al., 2000; Kunugi et al., 2007; Leumann et al., 2002; Ludewig et al., 2002; Mackeprang et al., 2002; Oranje et al., 2002b; Parwani et al., 2000).

There is some evidence that atypical anti-psychotics can alleviate the PPI deficits in SZ (Aggernaes et al., 2010; Kumari et al., 2002;

2007a; Oranje et al., 2002b; Swerdlow et al., 2006a; Wynn et al., 2007), often bringing it to a level where it is no longer different from healthy controls. It has been suggested however that these studies only included chronic cases of SZ, perhaps lending it difficult to distinguish between the progress of the disease and potential medication effects (Aggernaes et al., 2010). In other studies, where anti-psychotic naïve or first-episode SZ cases were used, the beneficial effects of anti-psychotics in attenuating the deficit are less evident (Hatcher, Reavill & Jones, 2007; Mackerpang et al., 2002; Molina et al., 2010; Ludewig et al., 2003; Quednow et al., 2008). If anything, it seems that anti-psychotics which may improve PPI inhibition may have affinity for low D2 blockade in being able to alleviate PPI deficits e.g., older anti-psychotics such as haloperidol (Mackeprang et al., 2002).

In a study investigating the stability of PPI deficits in SZ over time, McDowd, Filion, Harris & Braff (1993) compared young normal controls, older adult normal controls and cases with SZ late in life. The older cases showed evidence of greater inhibitory dysfunction when compared with normal older adults. This suggests that these older cases were deficient due to the combined effects of ageing and their experience of psychosis as the older control participants were also less successful inhibitors than younger controls.

1.3.7.3. *What is the evidence of heritability of the PPI?* Several studies have looked at the heritability of the PP1 at various time intervals. Hasenkamp et al., (2010) conducted a study examining heritability of the PPI using SZ cases, first-degree relatives and healthy controls. They did not detect differences between

controls and either SZ cases or their family members for PPI startle magnitude or habituation but found that heritability was around 31%. Other studies estimate heritability to be between 32-38% amongst relatives (Aukes et al., 2008; Greenwood et al., 2007) and between 38-58% amongst mono- and di-zygotic twins (Anokhin et al., 2003).

As for deficits in the PPI amongst both SZ cases and their relatives, the evidence is mixed. Two studies have found reduced PPI in both SZ cases and non-SZ relatives compared to healthy controls (Cadenhead et al., 2000; Kumari et al., 2005) whilst another has found no such similarity of impairment (Wynn et al., 2004). It seems that such familial impairments are dependent rather on the specifics of the subject sample and the paradigm used for investigation.

1.3.7.4. *What is the evidence of molecular genetic association with the PPI?*

To date, there are seven studies finding association between PPI and candidate genes in SZ.

i) Hong et al., (2008) looked at two SNPs located on the neuregulin-1 (NRG1) gene, rs3924999 and rs10503929 and their association with the PPI in 244 SZ cases and 186 healthy controls. They found that the first SNP, rs3924999 was associated with the PPI, being lowest in subjects who were homozygous for the minor allele (A/A carriers), intermediate in A/G carriers, and highest in homozygous major allele G/G carriers. This SNP contributed to 7.9% of the variance. Roussos, Giakoumaki, Adamaki & Bitsios (2011) also looked at

polymorphisms on the NRG1 gene, amongst which was rs3914999 in 445 healthy young males. This SNP, when combined with two others, rs10503929 and rs2439272 was followed by PPI reductions.

ii) Quednow et al., (2008) investigated three serotonin-2A receptor polymorphisms and their association with the PPI in 68 SZ cases. Of these variants, cases carrying the TI02CTT and the A-14389 A/A allele showed significantly higher PPI levels and a faster early habituation compared to all other variants.

iii) Roussos, Giakoumaki & Bitsios (2008) looked at the dopamine D3 receptor gene and the PPI in 101 healthy males. They found that Gly/Gly individuals had the lowest PPI and the greatest onset latency facilitation. Ser/Ser individuals had the highest PPI and the lowest onset latency facilitiation, whilst Ser/Gly individuals were intermediate.

iv) The same group (Roussos et al., 2008) went on to examine possible genetic determinants of PPI and the COMT Val158Met polymorphism in 93 healthy males. Val/Val individuals had the lowest PPI, Met/Met the highest and Val/Met were intermediate. These findings suggested that the PPI was being regulated by the dopaminergic neurotransmitters in the pre-frontal-cortex where its level is dependent on the COM7Val158Met gene polymorphism.

v) Quednow et al., (2009) also looked at the COMTMet158Met genotype in 107 healthy males and found similar elevated PPI levels. This finding of an association with COMT Val158 Met

polymorphisms and the magnitude of the PPI was not found however in a previous study by Montag et al., (2008).

The PPI is an ERP which co-segregates robustly with illness, but whether its effects can or cannot be attenuated with anti-psychotic medications is slightly unclear. Likewise, evidence of heritability for the PPI remains at a lowly 32-38% compared to the much higher average scores for the sounder ERP, the P300 which is in the range of 60-76%. There are also rather mixed reports as to whether relatives are more impaired than healthy controls (Cadenhead et al., 2000; Kumari et al., 2005; Wynn et al., 2004). Despite this level of ambiguity surrounding basics elements of an endophenotype i.e., state-independence and heritability, studies have nonetheless persisted in examining association between this ERP and candidate genes in SZ such as NRG1, COMT, the Serotronin-2A receptor gene and the dopamine-D3 receptor gene with evidence that polymorphisms on these genes influence PPI inhibition.

Table 1.7. Evidence for the PPI as an endophenotype

Measure	Study	Sample	Co-segregates with illness	State-independence	Identified in 1st degree relatives; heritability	Associated with risk genes in SZ (gene)
PPI	Aggernaes et al., (2010)	Anti-psychotic naïve=34 1st episode=16 C=34	+	-		
	Braff et al. (1978)	SZ=12 C=20	+			
	Duncan et al. (2003a)	SZ=16	+			
	Kumari et al. (2000)	SZ=29	+	-		
	Mackeprang et al. (2002)	SZ=20 C=20	+			
	Oranje et al. (2002b)	SZ=44 C=35	+	-		
	Swerdlow et al. (2006a)	C=20		-		
	Wynne et al. (2007)	SZ=51		-		
	Quednow et al. (2008)	SZ=54 C=28		+		
	Molina et al. (2010)	SZ=21 C=16	+	+		
	Hatcher, Reavill & Jones (2007)	Sprague Dawley Rats=6		-		
	Hasenkamp et al. (2010)	SZ=34 1st degree relatives=43 C=100			++	
	Anokhin et al., (2003)	MZ=40 DZ=31			+	
	Greenwood et al. (2007)	Families=183			++	
	Cadenhead et al. (2000)	SZ=23 C=25 Relatives=34			++	
	Kumari et al. (2005)	C=19 Siblings=19			++	
	Wynn et al. (2004)	SZ=76 Siblings=36 C=41			-	
	Hasenkamp et al. (2010)	SZ=40 Siblings=58 C=100			++	
	Aukes et al. (2008)	Families=78			++	
	Hong et al. (2008)	SZ=244 C=186				+ (NRG1)
	Quednow et al. (2008)	SZ=68				+ (Serotonin-2A receptor)
	Roussos et al. (2008)	C=101				+ (Dopamine D3 receptor)
	Roussos et al. (2008)	C=93				+ (COMT)
	Quednow et al. (2009)	C=107				+ (COMT)
	Montag et al. (2007)	C=96				- (COMT)

++ distinguishes a familial study from a twin study (+)
C=controls

1.4. Best candidate ERP endophenotypes

The weight of the evidence would suggest that ERPs, as endophenotypes in SZ are not of equal merit, based on the criteria set of for endophenotypes. If the criteria required to meet the definition of an endophenotype is to be stringently employed in the first instance, it is debatable whether inclusion of ERPs which do not meet these requirements is worthwhile in association studies of risk genes in SZ at all. Clearly the evidence would suggest that the P300, P50, N1 and the P1 meet the criteria but that the MMN, ERN and PPI fall short. In addition to meeting several criteria for endophenotypes, P300, P50, P1 and N1 show several specific examples of association with risk genes in SZ (Blackwood & Muir 2004; Bramon et al., 2008; Donohoe et al., 2008; Ehlis et al., 2007; Freedman et al., 1997; Martin et al., 2007; Reif et al., 2006).

1.5. Discussion of the endophenotype approach

There are a number of genes which have been associated with SZ whose mechanisms of risk might be better understood at the endophenotypic stage, assuming that disruption to susceptibility genes and their combination and interaction with one another contributes to difficulties with the neurobiological and neurotransmitter systems which they code for. These systems are potentially involved in regulating neurodevelopment, synaptogenesis and, at a later stage, cognition and behaviour. As to mapping neurotransmitter and other biological systems to the gene, it may very well depend on what neural mechanisms the various risk genes are involved in. For example, many of the aforementioned studies involving association between electrophysiological measures and genetic markers will be related to genes which will be involved in an abundance of brain functions, relying on many neurotransmitters such as glutamate, GABA, aspartic acid, glycine, vasopressin, dopamine, serotonin, acetylcholine *inter alia*.

Risk genes for SZ appear to be involved in a myriad of specialized brain functions involving specialized brain structures. Many of the association studies already discussed are genes involved in glutamatergic neurotransmission, but this is just one such example. Glutamate activity is associated with psychopathology in SZ (Goff & Coyle, 2001). Neurodevelopmental theories of SZ are increasingly focusing on NMDA antagonism in the consequent disruption of normal neuronal development, migration and differentiation (Lipska & Weinberger, 2000). NMDA receptors regulate pruning of cortical connections during adolescence, making them a critical component of developmental

processes whose malfunction may lead to SZ (Goldberg et al. 2006). Reciprocal connections between corticocortical, corticolimbic and corticothalamic projections are predominantly glutamatergic (Owen, Williams & O' Donovan, 2004). This applies also to connections between corticolimbic regions such as the hippocampus and the amygdala and these are areas which are extensively researched in SZ as centres of neuropathology (Harrison, 2004). There are glutamate reductions in regulated pyramidal neurons in the hippocampal region and the frontal cortex generally (Lewis et al. 2003; Straub et al. 2002; Weinberger, 1999). Though doubts have been cast about the endophenotype's superior merits in SZ genetics when compared with the illness alone, there is at least acknowledgement of their potential usefulness in the determination of underlying brain processes and the identification of biological trait markers in SZ (Munafo & Flint, 2007). Such an approach may also more favourably address issues surrounding the likely biological heterogeneity of cognitive problems in complex psychiatric illnesses.

Bearden & Freimer (2006) advocate the comparison of candidate endophenotypic models across other complex disorders to assess their successfulness and value. For example, in asthma research there are good examples of the useful employment of quantitative rather than categorical traits in understanding the trajectory of the disease and identification of treatment targets. Hereby, serum immunoglobum E levels (IgE), which has a heritability of 40-50% (Palmer, Burton, James, Musk & Cookson, 2000) are found to be elevated in asthmatics. Anderson et al. (2002) went on to find an association between the total serum

ImE concentration and the microsatellite 13q14. This was subsequently localised to its underlying trait locus on gene PHD finger protein 11 (PHF11) (Zhang et al. 2003). Likewise, heart disease, which experiences many of the same difficulties inherent in SZ genetics: similar variability, late onset and many mild cases often flying below the radar (Almasy & Blangero, 2001), there are a plethora of useful diagnoses in heart disease, and identification of some of the risk factors has been quite bountiful in predicting risk and identifying illness trajectory e.g. familial co-morbidity, atherosclerosis, angina, anterioscelerosis, myocardial infarction. Similarly, the endophenotype approach to psychiatric illnesses such as SZ may be very useful for gene discovery and understanding pathophysiology and may subsequently be advantageous to intervention, by identifying therapeutic targets, or facilitating translating to a mouse model.

Reviews which have explored endophenotypes in SZ include those of Thaker (2008) and Bramon et al. (2004). Bramon et al. (2004) examined the P300 and the P50 exclusively, performing a meta-analysis of research to date, looking at the evidence of heterogeneity between studies and whether anti-psychotics and duration of illness influence these waveforms. Though this review was very informative and mentioned preliminary association studies completed at that time (Freedman et al. 1997; Gallinat et al. 2003) it did not expand on this. Thaker (2008) prepared a more complete survey of ERPs, covering smooth pursuit eye movement, P50, pre-pulse inhibition, P300 and mismatch negativity. This differs slightly from those included in the current research (ERN, N1, P1, P50, P300, PPI and MMN). Thaker (2008) reviewed much more the underlying mechanisms

and neuronal circuitry involved in the ERPs and how they correlate with psychotic symptoms and disorders e.g., bipolar disorder. The current chapter updates this account of ERPs meeting the criteria of an endophenotype and their association with molecular genetics, highlighting the impressive development in the use of ERPs as endophenotypes in genetic research, providing further validation of the overall utility of the approach.

It must be re-iterated that the evidence for any of these ERPs meeting the criteria for endophenotypes is far from satisfied if they are to be esteemed as robust and valid endophenotypes in SZ with all that entails. Clearly, some are better *fits* than others e.g., the MMN, ERN and PPI being less likely to represent good endophenotypes. Evidently some ERPs have received more attention than others, lending them to being a first port-of-call for researchers, particularly in molecular genetic association studies where more established endophenotypes with proven heritability are more desirable. Surprisingly however, it is fair to say that ERPs remains very much an under-utilised measure in molecular studies despite being described as a good candidate all of ten years ago (Freedman et al. 1999). It is unclear why this is the case- there may be several reasons. Firstly, it could be that this approach suffers because the candidate gene literature itself is so far from clear and remains as unproven as it is unreplicated e.g., Dysbindin and NRG1. Secondly, EEG, like many neuroscientific measures it is a costly and a time-consuming pursuit for research groups. The cost of measuring some of these ERPs, both in terms of man-power and equipment considerably hampers their meeting the huge sample sizes required for gene

studies (Walters & Owens, 2007). Thirdly, different groups use different paradigms and parameters, combined with a frequent lack of collaborative efforts between neuroscientists and geneticists aside entirely from the best method in identifying SZ gene markers. Nonetheless, these ERPs have many positive qualities which lend them to being very insightful measures. Undisputedly, they offer a direct measure of electrical activity with very high temporal resolution. In comparison to other neuroscientific methods e.g., fMRI, they are relatively inexpensive and quite convenient to record. In addition, animal models of these endophenotypes are often readily available and although large sample sizes may indeed be a necessity of gene studies, it is not unfeasible recruit such numbers (Luck et al., 2010).

The current review has outlined some of the risk genes in SZ which have already been associated with specific brain systems and functions through the use of electrophysiological paradigms. Where a known gene maps onto a particular brain system which regulates a specific function, there is the potential to understand an actual brain pathway which may be disrupted in SZ. One such example is the association between the alpha-7 nicotinic receptor gene on chromosome 15q14 and the P50 (Freedman et al. 1997). This gene is involved in nicotinic functioning (Gray et al,. 1996; Leonard et al. 1996; Vidal & Changeux, 1993). Association has also been found between Neuregulin-1 and the P300 (Bramon et al. 2008); Dysbindin and the P1 (Donohoe et al. 2008) and NOS-1 and the P300 (Reif et al. 2006; Reif et al. 2009). The coupling of the biology of the allele to the biology of the illness is a challenging goal and thus, electrophysiological

endophenotypes may be pivotal in identifying the effect of genetic variation on predictors of risk in SZ, bridging the gap, as it were, between molecular biology, behaviour and cognition.

Chapter 2

A switching-attention-paradigm as an executive functioning index in schizophrenia electrophysiology

Abstract

Impairments in executive functioning are seen as core deficits in SZ and may be a useful candidate endophenotype in this disorder. A reliable EEG-based endophenotypic marker of executive functioning deficits has yet to be established. Switching-attention paradigms are one way of assessing specific sub-components of executive functioning deficits, including context maintenance and response anticipation. This study investigated whether the Switching Attention task [SWAT], which is an EEG measure of task switching fufills the first basic criteria for a useful endophenotype: whether it reliably distinguishes between the performance of patients and healthy controls. 44 healthy controls and 29 SZ cases participated in this EEG study examining executive functioning deficits using the SWAT task. During the switching task, participants viewed letter-number pairs and alternated between competing rules to generate correct responses. 11 cases dropped out after practise because they were unable to understand the task. For those who could complete the task, cases were less accurate in their responses than controls. Measurement of the SZ group's evoked responses showed reduced activation of positivity in anticipation of the switch-trial between 326msecs and 2,000msecs compared to controls. However, the variance among the cases was such that these differences between groups failed to reach

significance. This appeared to result from an almost bimodal distribution in patient performance that suggested a divide between patients who performed reasonably and patient who struggled to achieve a minimum level of succes on the task, even after patients who could not perform the task at all were excluded. These results are compatible with impairment in SZ in endogeneous driven processes, such as anticipating a switch and recruiting anticipatory internalised responses. That this was seen in only half of the cases, in addition to a considerable drop-out rate, highlights the challenge in developing tasks whose difficulty parametrically varies sufficiently to enable testing of this very heterogenous patient group.

2.1. Introduction

2.1.1. Executive functioning

Executive functioning (EF) describes a collection of brain processes responsible for planning, cognitive flexibility, abstract thinking, rule acquisition, the initiation of appropriate actions, the inhibition of inappropriate actions and the selection of relevant sensory information (Stuss & Knight, 2002). EF is synonymous with pre-frontal-cortex (PFC) functioning, in the maintenance and manipulation of information, the linking of perception with action, attention to action, and cognitive control (Fuster, 1989; Koechlin & Summerfield, 2007; Miller & Cohen, 2001; Passingham, 1993; Petrides, 1996 & Shallice, 1988).

Recently, The Cognitive Neuroscience for Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) itemised what they considered to be the most important candidate mechanisms in executive functioning (EF) (Kerns et al., 2008):

- *Goal maintenance*: processing task critical information, rules, goals and intentions (Cohen & Servan-Schreiber, 1992; Cohen, Braver & O' Reilly, 1996); higher mechanisms ensuring maintaining "context" over time and delays (Cohen & Servan-Schreiber, 1992; Cohen et al., 1996). Top-down/higher processes also play a role in selective attention and inhibition of competing responses (Cohen et al., 1996).
- *Rule maintenance*: The role of the pre-frontal-cortex in rule reconfiguration and their representation has been the focus of a number of studies. The pre-frotnal-cortex (PFC) has been noted as being heavily involved in rule maintenance and the

reconfiguration of rules across each task (Duncan, 2001). The formulation of rules and their representation is believed to be another key component in EF (Kopp & Tabeling, 2006; Lie, Specht, Marshall & Fink, 2006; Monchi et al., 2001; Schmittmann et al., 2006; Kurtz & Waxler, 2006; Konishi et al., 2005). The PFC then updates representations of a rule. Dopamine receptor activation is believed to be involved in the rapid updating of rules or the maintenance of a particular rule (O' Reilly, 2006). Subcortical regions may also be involved in the selection and updating of rules (O' Reilly, 2006; Braver & Cohen, 2000), such as the basal ganglia. In addition to dopamine receptors, norepinephrine (Arnsten & Li, 2005) and NMDA receptors might be important in rule acquisition (Lapiz & Morilak, 2006; Stefani & Moghaddam, 2005; Castner & Williams, 2007).

- *Dynamic adjustments and control*: This refers to adjustments in cognition and cognitive flexibility in switching rapidly between different response sets and behavioural performance on the basis of ongoing performance monitoring (Botvinick et al., 2001). The system rapidly and appropriately increases executive control to meet performance demands (Cohen et al., 2000). For example, where there is high conflict in trials, there is an increasing use of controlled processing (Gratton, Coles & Donchin, 1992). The anterior-cingulate-cortex (ACC) is believed to be heavily involved in this kind of performance monitoring (Botvinick et al., 2001; Holroyd & Coles, 2002; Brown & Braver, 2005).

2.1.2. Executive functioning deficits in SZ

Although Executive functioning has been found to be consistently impaired in SZ (Chan et al., 2004; Mahurin et al., 1998), there are mixed and inconclusive findings in studies of EF difficulties in SZ. Amidst the impairment of EF in SZ, some heterogeneity has been reported (Chan et al., 2006a; Chan et al., 2006b; Greenwood et al., 2008). Positive symptoms have typically not been found to be correlated with poorer performance on EF (Eckman & Shean, 2000; Liddle 1987; Liddle & Morris, 1991), although two studies have found a positive correlation (Himelhoch et al., 1996; Zakzanis, 1998). More expectedly, measures of EF have been correlated with negative and cognitive impairment in SZ (Baxter & Liddle, 1998; Cuesta & Peralta, 1995; Himelhoch et al., 1996; Moritz et al., 2001). EF has been found to be both exclusively associated with cognitive symptoms in SZ (Eckman & Shean, 2000; Van der Does et al., 1993) and has also negative symptoms (Basso et al., 1998; Berman et al., 1997; Howanitz, Cicalese & Harvey, 2000; Marhurin, Velligan & Miller, 1998; Mattson, Berk & Lucas, 1997). Such inconclusivity in the EF literature on schizophrenia may stem from a tendency to look at EF globally, rather than in terms of its subcomponents (Donohoe & Robertson, 2003; Donohoe et al., 2006).

When sub-components have been more extensively researched in terms of executive subcomponents, EF deficits are found to be quite diverse in these areas, including planning, initiation, sustained attention, response-inhibition, set-shifting and updating working-memory (Chan et al., 2006a; Chan et al., 2006b). It has been suggested that inhibition and set-shifting

impairments are more associated with negative symptoms (Donohoe et al., 2006) and with cognitive symptoms (Liddle & Morris, 1991). Recently, Clark et al., (2010) performed a factor analysis that suggested two main components of EF in schizophrenia. The first reflected inhibition/set-shifting, and the other reflected mental flexibility. They found that the inhibition/set-shifting component was associated with both negative and cognitive symptoms and that the mental flexibility component was associated with only cognitive symptoms which included cognitive disorganisation, difficulties with abstract thought, stereotyped thought, poor attention and lack of insight as measured by the PANSS (Bell et al., 1994). Positive symptoms were found to be unrelated to impairments in either component.

There are various ways in which executive functioning deficits have been measured in SZ. Among these measures are neuropsychological tests e.g., the Wisconsin Card Sorting Task, the Intra-Extra Dimensional Shift of the Cambridge Cognition Test Battery (CANTAB), the Trail Making Test, The Stroop Interference Test and the Porteus Mazes test, to name but a few. Another way of looking at the brain's electrical response during the execution of executive functioning processes is through the use of event-related-potentials.

2.1.3. EEG Paradigms measuring executive functioning in SZ

As previously outlined in chapter 1, endophenotypes in the EEG literature have included both sensory and cognitive phenotypes. Phenotypes which index sensory activity at electrophysiological levels of analysis are automatic, and relate to sensory-level

perception. One example of a sensory phenotype is the P1, an automatic sensory response elicited by visual stimuli. Another example is mis-match negativity, an automatic response to the detection of differences in auditory stimulation. One example of a cognitive phenotype is the P300, which measures attention and memory. Another example include the P50 which measures inhibitory response mechanisms and the N1, a measure of discrimination processing and error-related-negativity which reflects a reaction to elicitation of an erroneous response. In SZ, there are deficits across a wide range of cognitive abilities, from the most basic levels of perception (P1, mis-match negativity) to the more cognitively mediated (P300, P50, N1 error-related-negativity). These latter event-related-potentials are robust indexes of cognitive processing. Executive functioning measures fall into the category of cognitive mediated mechanisms.

One task which is designed to explore executive functioning in this regard is the switching-attention paradigm (Meiran, 1996; Monsell, Yeung & Azuma, 2000; Rogers & Monsell, 1995; Rubinstein, Meyer & Evans, 2001; Rushworth, Passingham & Nobre, 2005; Wylie & Allport, 2000). During this paradigm, participants must shift between performing two or more tasks on the basis of cues (Monsell, 2003; Sohn & Anderson, 2001). Performance is usually dictated by the number of errors on switch as opposed to non-switch trials or reaction time costs on switch trials relative to non-switch trials. In addition to measuring switch aspects of executive-functioning, these paradigms carefully index endogenous processes in EF such as mental flexibility and context maintenance.

Table 2.1 details the major findings in the switching-attention literature in SZ to date. Of major note is that switch-costs are actually found to be *equal* between SZ cases and controls (Jamadar, Michie & Karanayidis, 2010; Kieffaber et al., 2006; Kieffaber, O' Donnel, Shekhar & Hetrick, 2007; Meiran, Levine, Meiran & Henik, 2000; Wylie, Clark, Butler & Javitt, 2008). Switch costs indicate the difference between switch and non-switch trials. When switching to a competing or novel trial responses are slower than on task-repetition trials. SZ are consistently not slower or less accurate when switching between these different trials. By contrast, where cases of SZ seem to exhibit costs is in areas of congruency, maintenance and mixing. Congruency costs occur when cases perform worse when stimuli are incongruent as opposed to congruent. Mixing costs occur when performance is worse in a dual versus single task condition. Maintenance costs refer to "holding over" rules and maintaining the task across a series of trials.

These more specific deficits in cases have been interpreted as reflecting poor memory for *task context*, rather than a specific task-switching deficit (Smith et al., 1998). Research has concentrated therefore in the most part on establishing which aspects of switching-attention best reflect real deficits in SZ in its potential as an electrophysiological endophenotype. Cases do not exhibit any greater switching costs but they do show reduced differentiation between switch and repeat ERPs in the anticipatory interval and after stimulus onset. This suggests that cases may be treating switch and repeat trials similarly (Karayanidis et al., 2006) and may be impaired in their use of internally-driven task cues (Williams et al., 2000).

These data support the distinction between attentional (sensory/perceptual) and intentional (response-delegation) processes. It seems that the former component in set-shifting may in fact be preserved in SZ (Kieffaber et al., 2006; Kieffaber et al., 2007). Maintaining task context and anticipating response delegations may most reliably distinguish between cases and controls.

Table 2.1. Summary of studies investigating switching-attention in SZ. SZ exhibit switch costs equal to those of controls but do demonstrate incongruence costs, maintenance deficits and mixing costs.

Study *[+ = indicates a deficit in the SZ group compared to the healthy controls]* *[* ERP data included in the study]*	*N*	*Comparable switch costs with controls*	*Incongruence costs*	*Maintenance deficits*	*Mixing costs*
Kieffaber, O' Donnell, Shekhar & Hetrick	20SZ 20HC	+	+	+	
Kieffaber et al. (2006)	33SZ 30HC	+	+	+	
Jamadar, Michie & Karayanidis (2010) *	12SZ 12HC	+			
Wylie, Clark, Butler & Javitt (2008)	16SZ 17HC	+	+		+

A switching-attention task is used in the current experiment with a view to validating it as an endophenotype. In order to be a useful endophenotype, it is vitally important to establish that differences in context maintenance and response anticipation reliably distinguish between cases and controls. Selective attention, context maintenance, cognitive flexibility/response anticipation are all components of EF identified by CNTRICS as being impaired in SZ. As previously outlined in chapter x, in establishing whether individual components meet the criteria for

endophenotype they must match the criteria set out by Gottesman & Gould (2003) and:

- demonstrate association with illness in the population
- be heritable
- be state-independent
- within families, the endophenotype and the illness must co-segregate
- in unaffected family members, there must be a higher rate than in the general population.

Variations in tasks measuring switching-attention in SZ remain at the preliminary stage of demonstrating that they are associated with this illness in the population. There has been only one study to date exploring heritability of the components within a switching task paradigm (Ceaser et al., 2008). In that study, performance on the intra-extra dimensional shift of the CANTAB task was compared between cases, their relatives and controls. Siblings were not found to be especially impaired relative to cases, suggesting that any impairment could not be explained by running in families. This is the only study known to us which attempts to explore the set-shifting aspect of EF as a potential endophenotype in SZ.

Given that switch costs, based on previous findings are expected to be identical between cases and controls our hypothesis takes a different line. We hypothesise that the difference should lie in the maintenance of task context and anticipatory-response delegations in the build up to the switch of task. This experiment would be predicted to reliably distinguish between cases and

controls. We have additional experimental developments diverging from previous research in this area. Unlike the work of Karayanidis (2006) who grouped all nested trials together, we have two nested trials in addition to a pre-switch trial to more accurately isolate this latter trial to explore any anticipatory activities across groups.

2.2. Materials and Methods

2.2.1. Participants

Seventy-three participants in total participated in the SWAT task, consisting of 29 patient participants and 44 healthy participants. All participants gave written informed consent to enter the study (see Appendix A). All EEG testing took place in Trinity College Dublin's Institute of Neuroscience. In line with School of Medicine ethics no payment was offered for participation in the study, but participants were reimbursed for expenses incurred in attending for testing.

2.2.2. Patient recruitment

For recruiting cases, approval was obtained from the ethical committees of St. James's and St. Patrick's Hospitals in Dublin. Cases were recruited who were already participating in a SZ genetic sample (the Regional Genomics Psychosis Ireland project) and who were attending community psychiatric services. The case sample was of Irish origin. All cases had to meet DSM-IV (American Psychiatric Association, 1994) criteria for schizophrenia, schizoaffective disorder or bipolar disorder

with a history of a psychotic episode as established by the structured clinical interview for the DSM-IV. For cases, inclusion criteria consisted of the following: (1) aged 18-60, (2) had no history of substance abuse in the preceding six months (3), had no secondary co-morbid Axis I or II psychiatric diagnoses in addition to schizophrenia/schizaffective disorder/bipolar disorder, (4) had no history of head injury or loss of consciousness, (5) and no history of epilepsy or seizures.

2.2.3. Recruitment of healthy participants

The healthy participants were recruited on the basis of responses to local media advertisement. Based on details provided to a check-list based clinical and medical history screening review healthy participants had to have(1) no history of psychosis, (2) no history of neurological disease (stroke, epilepsy), (3) no history of a head injury or loss of consciousness, (4) no history of substance or alcohol dependence, and (5) no first degree relative (parent or sibling) with a diagnosis of an Axis-I Disorder (DSM-IV) (6) had to be of Irish ancestry i.e., four grand-parents born in Ireland. All participants were aged between 18-65 years. Gender differences were apparent between groups.

2.2.4. Demographic information

Demographic information collected from participants including: gender; date-of-birth; medication; level of education (primary; completed junior cert; completed leaving cert; certificate; diploma; degree; post-graduate or higher). Contact details and

handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971) (see Appendix B). The inventory is a measurement scale which assesses a person's right or left hand dominance in daily life. The handedness i.e., right hand dominant, left hand dominant, ambidextrous is calculated using the formula: (Right – Left)/(Right + Left). 97.7% of controls were right-hand-dominant and 100% of cases were right-hand-dominant as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). All participants reported normal or corrected-to-normal vision. (see Table 2.2. for demographic information across groups).

2.2.5. Clinical Assessment of patients

DSM-IV diagnosis was confirmed by a psychiatrist trained to use the Structured Clinical Interview for DSM (SCID: American Psychiatric Association, 1997). The SCID is a semi-structured interview for making the major DSM-IV Axis IV diagnosis. It assesses current psychiatric patients and their lifetime psychiatric diagnosis. The SCID was not administered to patients who were considered to be cognitively impaired, to experience learning difficulties or who were deemed to be too medically or psychiatrically ill to participate in an interview or take part in the remainder of the study. Administration of the SCID averaged 90 minutes and was comprised of different modules which are relevant to particular disorders, including positive and negative symptoms. Positive symptoms were measured using the Scale for the Assessment of Positive Symptoms (SAPS) and negative symptoms were measured using the Scale for the Assessment of Negative Symptoms (SANS). The SAPS is designed to assess

positive symptoms in SZ. These symptoms include hallucinations, delusions, bizarre behaviour and positive formal thought disorder (Andreasen, 1984). Each of the major positive symptoms is rated on a clinical-rated Likert scale (0=none; 1=questionable; 2=mild; 3=moderate; 4=marked; 5=severe) and each has an overall global rating which considers the severity of the symptoms observed. The SANS is designed to assess negative symptoms in SZ. These sub-scales include affective flattening or blunting, alogia, avolition or apathy, anhedonia or asociality and attention. Both the SAPS and the SANS have comparable levels of inter-rater reliability and test-re-test reliability for each system measuring symptomatology (Norman, Malla, Cortese & Diaz, 1996; Schulberg et al. 1990) and factor-analysis suggests that the components are independent from one another (Andreasen, 2007). Details of medication were also taken during this time.

2.2.6. Clinical screening of healthy participants

It was important to screen healthy participants for the absence of psychiatric disorders. Initial screening for this was first conducted via phone. After participants had then travelled to Trinity's Institute of Neuroscience, more detailed medical and psychiatric histories were taken in relation to both themselves and their first degree relatives. Healthy participants were excluded from the study if they reported having a first degree relative with a history of psychosis.

Table 2.2. Sociodemographic characteristics of cases and controls for the SWAT task, including gender, medication details, years of education, age and symptomatology.

a. Demographic & medication variables (cases)	*N*	*Mn(SD)*	*%*
Male	12		66.6
Receiving atypical neuroleptics	18		100
Receiving anti-cholinergics	2		11.11
Age (years)		43.22 (12.46)	
Years in education		14 (14.06)	
Symptom severity			
SAPS		1.33 (.79)	
SANS		1.48 (.53)	
b. Demographic variables (controls)	***N***	***Mn(SD)***	***%***
Male	14		31.8
Age (years)		38.61 (12.6)	
Years in education		16.48 (1.95)	

2.2.7. EEG Stimuli and Procedure

The stimuli used for this experiment consisted of letter-number pairs. The letters were drawn from a set containing four vowels (A, E, I, U) and four consonants (G, K, M, R). The numbers were drawn from a set containing four even numbers (2, 4, 6, 8) and four odd numbers (3, 5, 7, 9). On every trial, one letter and one number were randomly chosen with the constraint that neither the letter nor the number were the same as on the previous trial. One of these characters was presented 1° to the left of central fixation, the other was presented 1° to the right of central fixation. The stimuli were coloured: for four consecutive trials, they were red and for the next four trials they switched to being green, for the next four they were red, and so on. Each letter-number-pair appeared for 2 seconds with a variable inter-

stimulus-interval (ISI) of 120msecs during which there was a blank black screen.

Participants were seated in a comfortable chair in a dimly lit room, 110cm from the computer screen. The paradigm was divided into a series of 2-minute blocks to allow resting periods. Each block required participants to alternate between two tasks, switching from one to the other on every fourth trial (see Figure 2.1. and Appendix C.4.). When the stimuli were coloured red, participants were instructed to make a go/noGo response after categorising the letter according to whether it was a vowel or a consonant; that is, they were told to respond, by button press, for vowels, and not to respond for consonants. After the stimuli switched to being green coloured, they were similarly instructed to categorise the number according to whether it was even or odd ("go" for even numbers). The categorisation of stimulus colour to task was counterbalanced across participants. That is, for half of participants, the categorisation was as described above. For the other half, responses would be to green vowels and red even numbers. In all cases, participants were asked to respond by pressing a button on a mouse pad with their right thumb. All possible combinations of letters and digits were sampled with equal probability.

2.2.8. Electrophysiological Data Acquisition

Continuous electroencephalographic EEG data were recorded to computer with the Biosemi Acquisition programme: ActiView /www.biosemi.com/. EEG was recorded using 128 scalp electrodes. Horizontal and vertical electro-oculograms were also

recorded by means of electrodes placed at the left and right external canthi and an electrode below the left eye. Data were recorded continuously at a digitization rate of 512Hz with an open pass-band. The Biosemi amplification system replaces the "ground" electrodes with two separate electrodes: common mode sense (CMS) active electrode and driven right leg (DRL) passive electrode (for more on the function of the CMS and DRL electrodes, see (www.biosemi.com/faq/cms&drl.htm). Stimuli were presented with "Presentation" (version 14.2 Neurobehavioural Systems). For the baseline correction, a baseline between -100 and 0 msecs was set. For analysis and display purposes, data were subsequently filtered with a 0-phase-shift 40Hz low-pass filter (48dB/octave) after acquisition. No high pass filter was used.

2.2.9. ERP Analyses

ERP analyses were performed using BESA Software Version 5.2. Any EEG channels which were noisy or which were not connected properly during recording were identified and switched off for further analysis. The surrogate model (Berg & Scherg, 1991) was then used for further artifact correction. Artifact correction in the current study was based on a model (Berg & Scherg, 1994; Lins, Picton, Berg & Schergm 1993) of artifact topography (the averaged artifact) and a set of brain topographies (multiple dipoles). The result was an estimation of artifact activation based on the linear combination of brain and artifact activities. Corrected-epoched data were also inspected for other artifacts using the BESA artifact rejection interface (Berg & Scherg, 1994). Grand averages were generated for each

participant for each identified component. Approximately 62.50 +/19.59 sweeps per individual were averaged for controls and 59.17+/-22.97 for the cases group with an epoch of 1 to 2,000 msecs. The average number of bad channels for the control group was 12.59 and 14.78 for the cases group (out of 128 channels). Each component was defined as the area under the curve (versus the 0μV baseline) generated by the switch, nested and pre-switch trials.

Based on the literature, we identified and selected electrode sites best representing the topography of the components in our data. The analysis strategy was guided by previous research which exhaustively probed componentry of the SWAT task (Wylie et al., 2003a). Wylie's study demonstrated there to be numerous components which were responsive to changes across switching tasks, thus allowing us to refine our selection of components. As a result of the studies by Wylie (Wylie et al., 2008; Wylie & Allport, 2000) and that of DeSanctis et al., (2009), it was decided that sites over the frontal scalp region and scalp sites over the occipital scalp region, denoted by their late positivity (326msecs and after) would be selected for analysis. These will hereafter be named the "P326", the "Late Anterior Positivity" and "Late Posterior Positivity", corresponding with the time courses 326-1160msecs, 1200-2000msecs and 1185-2000msecs respectively. Although a more complete evaluation of experimental effects was performed, it was decided to focus more particularly on components which would best reveal meaningful comparisons between our case and control groups with respect to the SWAT task. Selection of three main ERPs had the additional benefit of avoiding issues of multiple testing.

The lateral occipital electrode sites selected were P5, P3, P07 and P03 for the left hemiscalp, and P4, P6, P04 and P08 for the right hemiscalp. The frontal sites selected were AF3, F3 and F1 for the left hemiscalp and AF4, F2 and F4 for the right hemiscalp. These sites were used for statistical testing. For the eight posterior electrodes and the six anterior electrodes, the area under the curve (waveform) was calculated during the identified epochs. These area measuers were then used as the dependent variable. For analyses, the electrodes across each hemiscalp were collapsed across each other e.g., P5, P3, P07 and P03 were averaged together and P4, P6, P04 and P08 were averaged together, including hemisphere (right –vs left) as a factor. The electrodes selected were at homologous location on each side of the scalp for this purpose.

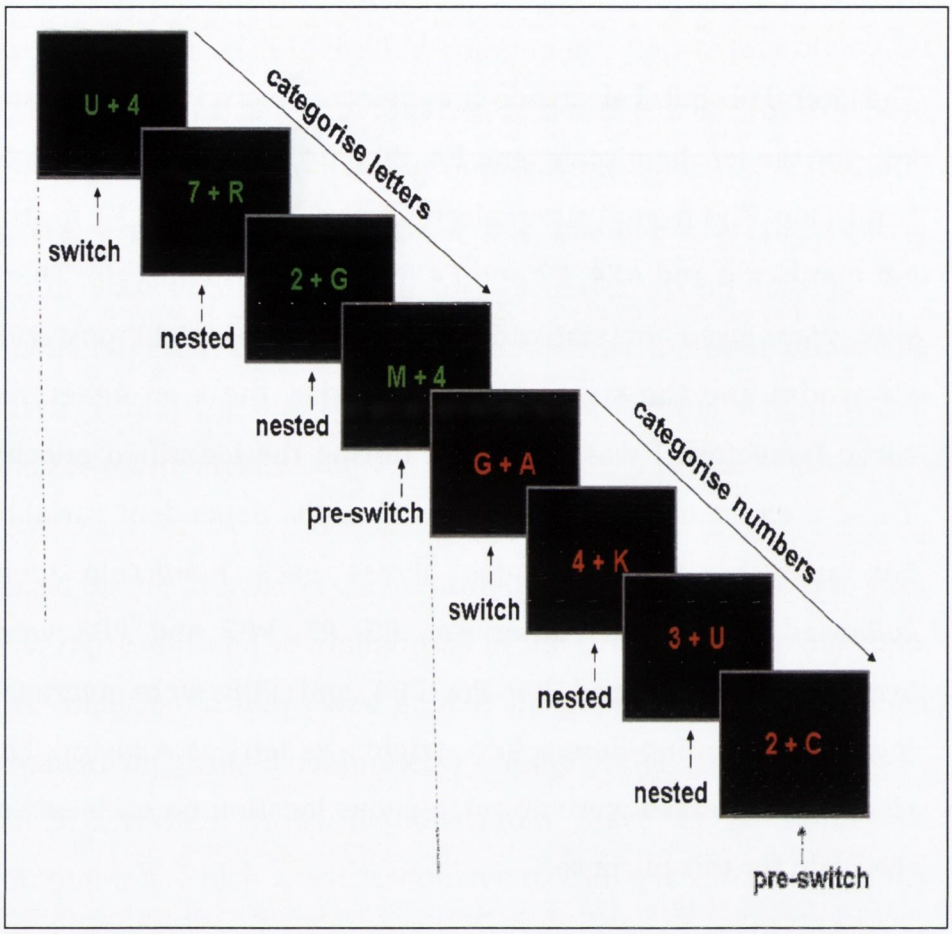

Figure 2.1. Task switching paradigm. Eight successive trials are shown. Participants were instructed to perform one task when the stimuli were one colour & to perform the other task when the stimuli were the other colour.

2.3. Results

2.3.1. Behaviour

Performance data from the SWAT task is summarised for each group in Figure 2.2. Of the 29 cases who attempted to participate in this task, 11 cases' participation was terminated before the completion of the minimum required number of blocks. In all, these 11 cases terminated their performance because they could not understand the instructions. This was despite careful re-wording of the task instructions and several runs of practise

blocks. Of those individuals who did complete the task, their performance in terms of reaction-time and percentage-correct is outlined in Figure 2.2. Response times for each trial were entered into a trial x diagnosis mixed model ANOVA. Accuracy data across trials were submitted to an equivalent ANOVA to that used for the reaction time data. Overall, mean reaction times were longer in cases. A *3x2* repeated measures ANOVA with factors of trial (switch –vs nested –vs pre-switch) and group (controls – vs cases) was performed. Although cases had longer reaction times than controls, there were no significant differences between groups [$F(1,58)=1.57$, $p>.059$].

2.3.1.1. Switch

Controls (472.33 +/- 129.68) had shorter reaction times than cases (497.66 +/-168.18) on switch trials.

2.3.1.2. Pre-switch

Controls (398.71 +/- 103.18) had shorter reaction times than cases (462.46 +/- 175.75) on pre-switch trials.

2.3.1.3. Nested

Controls (393.56 +/- 102.40) also had shorter reaction times than cases (461.89 +/- 221.96) on nested trials. There were significant differences between groups on proportion of correct responses, as a measured by percentage-correct [$F(1,58)=36.97$, $p=.00$]. Post-hoc analysis revealed cases to be significantly less accurate across all three trial types than controls [switch: ($t(60)=6.57$); nested: ($t(60)=6.12$) and pre-switch: ($t(60)=6.21$) [$p<.00$].

2.3.1.4. Switch

Controls (96.56 +/-13.02) were more correct than cases (76.36 +/- 20.07) on switch trials.

2.3.1.5. Pre-switch

Controls (96.88 +/-3.70) were more correct than cases (76.36 +/- 20.07) on pre-switch trials.

2.3.1.6. Nested

Controls (96.85 +/- 3.01) were more correct than cases (75.55 +/- 22.52 on nested trials.

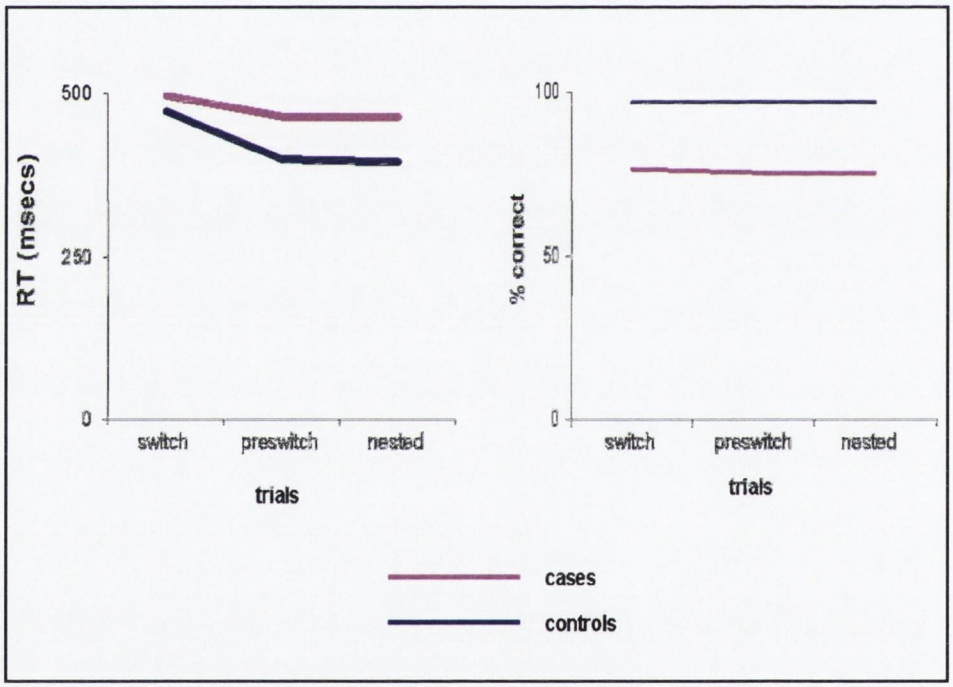

Figure 2.2. Behavioural results. Reaction time (RT) left panel, and proportion correct (% correct) right panel. The data are shown separated by task (switch, nested, pre-switch) and group (cases, controls) for clarity.

2.3.2. Electrophysiology

A series of repeated-measures analysis-of-variance was conducted to look at the ERPs associated with switch and repeated trials. This included a within-subjects factor of trial (switch –v- preswitch –v- nested) and a between-subjects factor of group (controls –v- case). Age and gender was co-varied for. The first examined P326 positivity, and there was no main effect of diagnosis between nested, switch and pre-switch [$F(1,58)=2.99, p>.05$]. The second ANOVA examined late-anterior-positivity and there was no main effect of diagnosis between nested, switch & pre-switch [$F(1,58)=.27, p>.05$]. The third ANOVA examined late-posterior-positivity, there was no main effect of diagnosis between nested, switch & pre-switch [$F(1,58)=.57, p>.05$].

The output from the ANOVA revealed that the standard error of the mean differed between controls and cases (see Table 2.3.). The grand average waveforms (see Figure 2.3.) demonstrate quite clearly that controls are more active on pre-switch and switch versus nested trials in a way that is different from cases. As seen in Figure 2.3. the grand-average waveforms of the cases indicate that their activity levels are pretty much identical during these three trial types, whereas controls are quite active in the build up the next switch trial. This is further illustrated in Figure 2.4. and Figure 2.5. voltage maps, indicating this difference across the range of the components, from 326msecs up to 2 seconds. In light of this, despite a post-hoc investigation not being part of our original hypotheses, it was decided to select control participants only and look at the difference between

switch, pre-switch and nested trials where grand average measures clearly differentiated their activity from cases in what looked like activation moving from the anticipation of a switch of task to the switch itself. As expected from these post-hoc tests, there were significant differences between pre-switch and nested trials for both the late anterior positivity and late posterior positivity components (p=.002 and .043 respectively). Conversely, in cases, there were no significant differences between nested and pre-switch trials [p>.05]. There were also significant differences between pre-switch and nested trials for the P326 and late-frontal-positivity (p=.02 and .003 respectively). There were no differences between switch and nested trials for late-posterior-positivity or between switch and nested trials for the P326. There were also no differences between switch and pre-switch trials for any of the three components.

Table 2.3. Standard error of the mean tables across components demonstrating larger variance in the case than control group.

		P326	Posterior Late Positivity	Anterior Late Positivity
Cases	*Nested*	1051	232.85	522.09
	Pre-switch	938.1	246.18	326.49
Controls	*Nested*	309.5	105.5	150.43
	Pre-switch	341.7	114.87	201.76

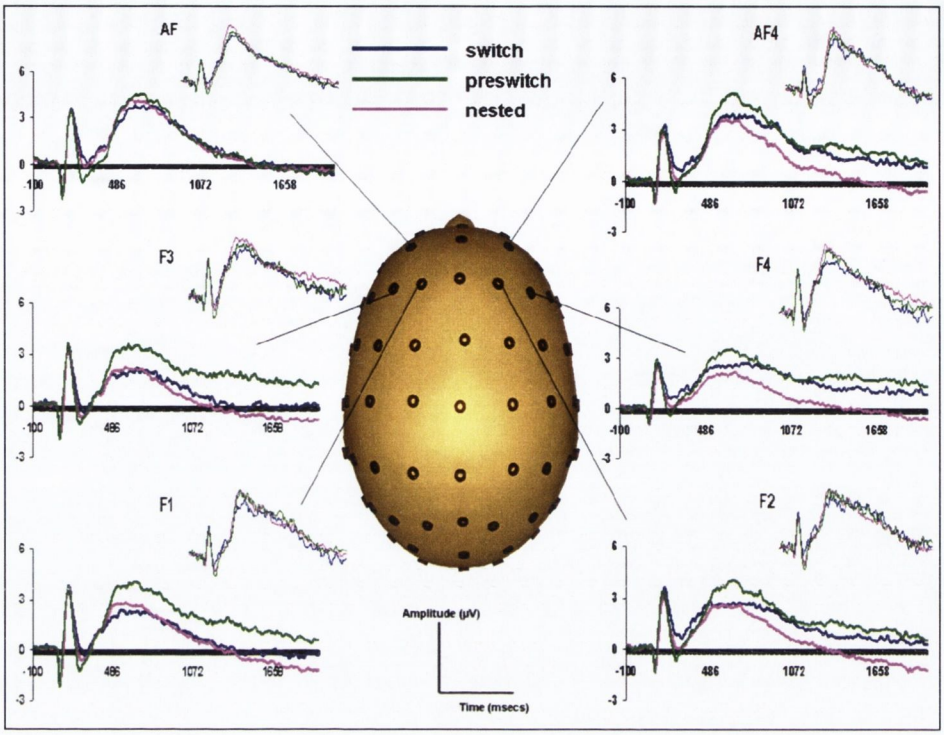

Figure 2.3. Overview of ERPs at bi-lateral anterior scalp sites. The smaller, accompanying waveforms depict the grand averages for switch, nested and pre-switch trials in the cases.

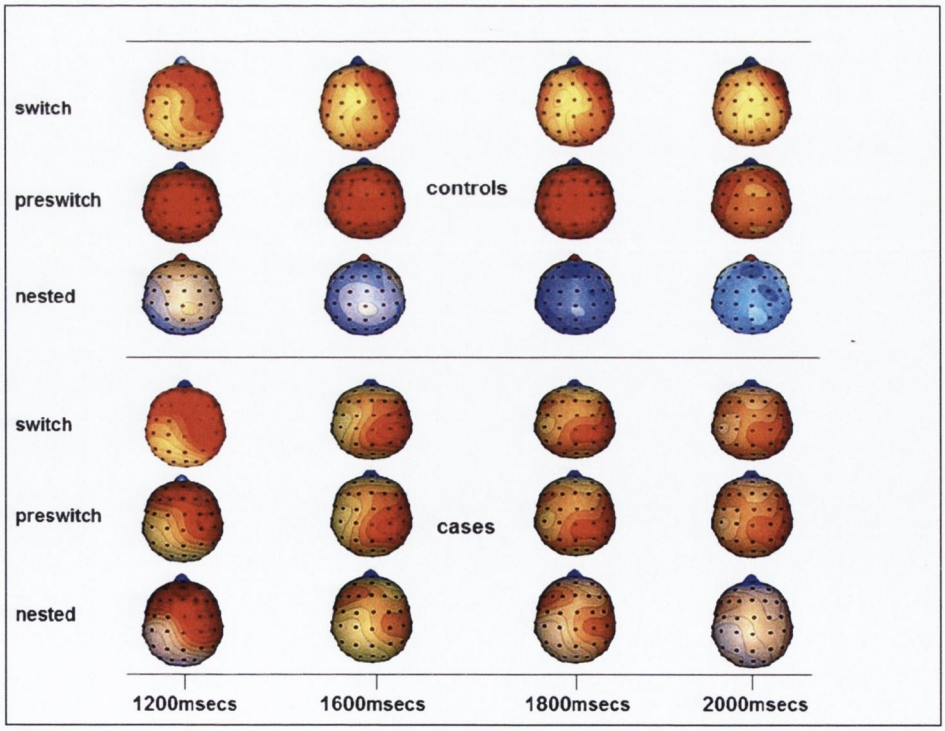

Figure 2.4. Scalp voltage maps for controls & cases for late-anterior-positivity at 1200, 1600, 1800, 2000msecs for pre-switch and nested trials.

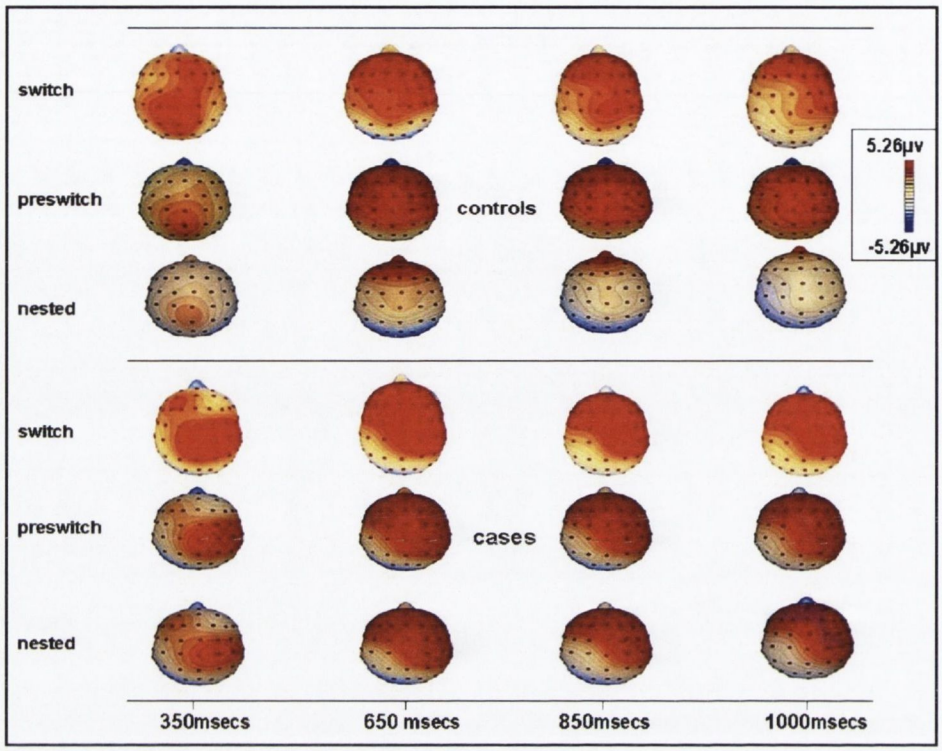

Figure 2.5. Scalp voltage maps for a. controls and b. cases for P326 at 350, 650, 850 & 1000msecs for pre-switch and nested trials.

Finally, to understand the apparent variability among cases, this group was also examined in isolation. Cases were subsequently split around the median amplitude scores into top-amplitude and bottom-amplitude groups, forming two separate groups. Topographic maps (see Figure 2.6.) illustrated that half of the cases had a markedly superior performance to the other half of the cases who were able to complete the SWAT task across the time range. Moreover, these cases demonstrated amplitude of responses significantly greater than controls [$F(1,53)=12.55$, $p=.001$]. Further post-hoc tests revealed significant differences between "best" and "worst" cases at late-posterior-positivity [$F(1,9)=17.54$, $p<.05$], P326 [$F(1,9)=5.89$, $p<.05$] and the late-anterior-positivity [$F(1,9)=7.40$, $p<.05$] in cases. It also seemed that some of this variability may have been accounted for by

differences in gender (males –versus females) in the cases group. As illustrated in Figure 2.7. females demonstrated a greater signal than males, particularly around the P326 component time-line. However, this difference did not survive statistical analysis, and the sample was possibly too underpowered to detect real gender differences [$F(1, 18)=.96$, $p>.05$].

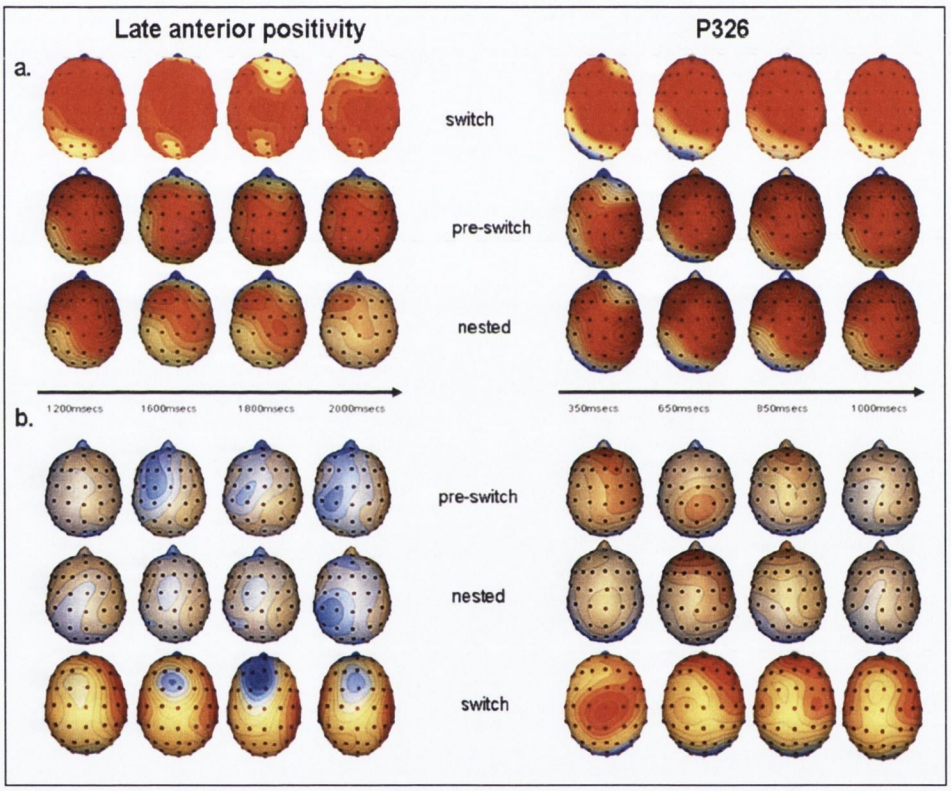

Figure 2.6. Scalp voltage maps for (a) cases with the largest amplitude (N=9) versus (b) cases with the smallest amplitude (N=9) for the late positivity ERP and the P326 ERP across the time range of the components.

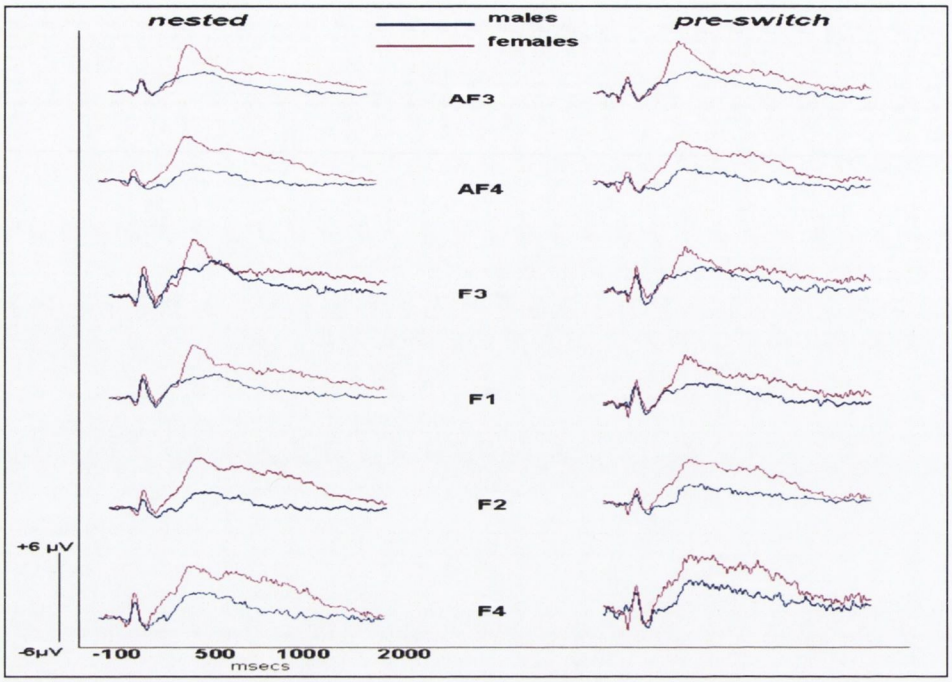

Figure 2.7. Overview of ERPs for the trial types nested and pre-switch for cases where differences are apparent between male and female participants.

In summary, cases were significantly less accurate than controls, making more errors overall on all trials compared to controls on this task. The main ERPs identified and explored were the P326, late-posterior-positivity and late-anterior-positivity. For these components, there were no significant differences between groups across trials when diagnosis was used as a factor, explained by the variance in cortical response in cases, as reflected by the standard error of the mean. Taking healthy-controls on their own, there were significant differences found for late-anterior-positivity and for the P326 components. Conversely, cases were divided into those who were "best performers" i.e., their data most closely mirrored that of controls and "worst performers." When cases were divided like this, there were significant differences between these "high" and "low" performing cases at both anterior and posterior late positivity components and the P326 component.

2.4. Discussion

This study was designed to investigate the usefulness of an executive functioning paradigm as an ERP endophenotype, and its potential to illuminate underlying neurobiological differences directing such mechanisms in a SZ population. Detailed analysis of the pattern of the ERP effects and differences in topographic scalp maps was undertaken to distinguish the pattern of brain activity in control and case groups.

Firstly, there was evidence that differentiated between trial types (i.e., switch –v- nested –v- preswitch) trials. This was evident at 650msecs in fronto-parietal regions in controls, but this effect was absent in cases. In cases, the large amplitude P326 activation had approximately the same temporal activation, but had considerably diminished amplitude. Activity in the controls was amplified and showed a stronger degree of differentiation between nested, pre-switch and switch trial types. Activity for nested trials was more attenuated in controls compared to activity on pre-switch and switch trials. There was a robust late sustained positivity seen in the control group that persisted throughout the entire two-second epoch. This sustained activity was highly attenuated in cases over the last 1600-2000msecs of the epoch. The sustained frontal involvement in controls continued to be robust over the full two-second interval. In controls for the pre-switch there was an increase in amplification at 650msecs, remaining amplified at 1000msecs, becoming more posterior as it approached 1200, 1600 and up to 1800msecs. At end of the pre-switch, and moving into the switch trial, this positivity became attenuated. In the change over to the switch,

there was less amplification compared to the pre-switch and activity remained more posterior. By 1200msecs, amplification decreased so that by about 1600msecs, there was minimal spreading. This indicates that most activity in controls took place between 650msecs in the pre-switch and 1,200msecs in the switch. In cases, activity across switch, nested and pre-switch trials looked broadly similar. Like controls, cases' amplification began to decline after about 1,600msecs and at 1,200msecs, it seemed that the strongest signal was on the switch, whereas this would have been in the pre-switch in controls.

In cases, hardly any differences between nested and pre-switch trials were observed until about 1600msecs. Crucially, when the cases were split into high-performance and low-performance groups, entirely different amplification patterns across these case-subgroups were evident, with the low-performance groups showing considerable attenuation in amplitude in both nested and pre-switch trials across the entire epoch.

Secondly, the differences between controls, high performing cases and low performing cases point to a different generator configuration underlying processes in this time-frame. These groups recruited a different network of brain areas in solving the preparation for an upcoming switch. In controls there is evidence of both anticipatory activity in preparation for the arrival of the stimulus on switch trials and switch-related effects during the subsequent processing period. Topographical mapping in controls revealed foci of distribution over the fronto-parietal and temporal cortex during the late sustained activity. In contrast, in cases, there was a considerably less broad maximum spreading

over fronto-parietal scalp regions and the activity was more posterior.

Thirdly, the main difference between cases and controls is that controls seemed to "anticipate" the switch to the alternate task around P326msecs as evidenced during the pre-switch trial i.e., the trial immediately preceding the switch to the alternative rule-set. This anticipatory mechanism was sustained to the end of the 2,000msecs epoch. Controls engaged this anticipatory response on the trial immediately preceding the switch and this mechanism was not seen on repeated "nested" trials. It seems that controls increased the gain of neurons responsive to the impending switch, such that output from these neurons was more likely to reach later stages of processing, consequently biasing the signal to promote task-appropriate responding (Miller & Cohen, 2001). The amplitude of the waveform for the pre-switch trial decreased to levels comparable to the switch-trials after the response decision had been made on the pre-switch trials. This is similar to what was found in a healthy control population by Wylie et al., (2003) who reported this same decrease in response in moving from the pre-switch to switch trials. They also account for the more posterior activations across the pre-switch trials as being indicative of a "top down re-weighting" of sensory processing in the stimulus analysis. In the current study this same posterior activation occurs.

Fourthly, cases simply did not engage in any obvious preparatory processes, suggesting that they were awaiting the external cue to engage in the task. Indeed, scalp voltage maps and grand average

waveforms indicate that cases were treating pre-switch and nested trials similarly. Controls clearly delineated between nested and pre-switch trials in a way that cases did not. This undoubtedly contributed to their highly accurate performance on this task (in the region of 95-100%). Controls obviously found this task very easy to understand and execute and were engaging their attention before the external stimulus indicated they should respond i.e., before the switch trial. Controls reached the stage where they were excellent predictors of the switch, having established a direct association between cues, response-mapping rules and motor responses quite early on.

The number of processes involved in this type of task is worth noting. Firstly, there is verbal coding of the task rules e.g., pressing to red vowels and green even numbers. Secondly, there is the storage of the way the task proceeds i.e., that there is a switch after every four stimuli and the sequence is "switch" "nested" "pre-switch" and so on. Thirdly, there is the anticipation of the next trial. Cases seemed to be struggling on this task because they could not manage the rules of the task and therefore they could not cope with competition when the trials changed around when the rules switched over. If they were not keeping up with the task, then it was nearly impossible for them to anticipate the change in rules and to consequently benefit from any preparatory interval before the change in task. This inability to maintain the rules in mind and stay on task may have been due to attentional difficulties, memory difficulties or semantic processing difficulties, which are all part of a broad range of cognitive difficulties associated with this illness. Such difficulties are in accordance with impairments across the board

in SZ involving processes such as learning sequences (Dominey & Georgieff, 1997), rule management (Laws, 1999), attention deficits (Bernard, Lancon & Bougerol, 1997), processing of context (Servan-Schreiber, Cohen & Steingard, 1996), forgetting task context (Cohen et al., 1999) semantic processing (Kuperberg, McGuire & David, 1998), failure to re-configure rules (Duncan, 2001) and a failure to benefit from preparatory intervals (Nuechterlein & Dawson, 1984).

Such difficulties have been well documented in the literature. Posada, Franck, Georgieff & Jeannerod (2001) found that cases with SZ learned a sequence almost normally during a spatial-working-memory task, but their anticipatory ability was reduced in comparison to normal participants across a variety of conditions in what they describe as a working-memory deficit (Posada et al., 2001). Their cases demonstrated major difficulties when switching from sensory-guided to memory-guided types of behaviour. They interpreted their findings as being indicative of a deficit in consciously controlling memory management in sensori-motor processing, consistent with original concepts of working-memory processing (Baddeley, 1998). Where this system failed, and there was poor synchronisation between memory and subsequent motor commands, anticipatory responses became disorganised. Cases were unable to deploy a task-appropriate attentional set using the contextual information provided. This was supported by the findings that reaction times were longer in general and their error rates were higher. Cases did activate similar regions and to the same degree in the three different trial types, and activated similar regions in nested trials as controls did in pre-switch trials. This suggests that cases

found the nested trials, where rule-repetition took place probably as difficult as task-switching. There may be a number of reasons for this. They may have been trying to overcome task interference during these repeat trials; they may have had to make more effort to avoid post-stimulus cross-task interference and to withstand this interference; they may have increased their activity on these nested trials in order to perform adequately on this task. Such compensatory activities have been previously reported on nested trials and have been interpreted as compensatory mechanisms to overcome difficulties in anticipating preparation and in compensating for the knock-on effects of task competition (Jamadar et al., 2010).

Any preparatory configurations in the control group may be consistent with evidence of a retrieval of a verbal task or goal representation held in working-memory (Goschke, 2003) which activates a frontal-parietal network during the anticipation of an upcoming task. There is evidence from the imaging literature that preparatory activity activates the poster-parietal, dorsal pre-motor cortex and fronto-parietal network (Linder, Iyer, Kagan & Andersen, 2010). If controls are "self-informing" about the upcoming switch in task this could be due to perceptual encoding (Logan & Bundesen, 2003), memory encoding (Altmann, 2002; Altmann, 2004) or to memory retrieval (Mayr & Kliegl, 2003). Controls' context maintenance and "self informing" may also have stemmed from their use of verbal self-instruction during the pre-switch trial. It has been found for example that during the preparatory interval on task-set activities, there is activation in dorsal Broca's area near the inferior-frontal-junction, in the left intra-parietal cortex and along the right

anterior frontal sulcus. Interestingly, similar brain activations have been repeatedly demonstrated to underlie the articulatory rehearsal component of verbal working-memory (Gruber, 2001; Gruber & von Cramon, 2001; Gruber & von Cramon, 2003; Chen & Desmond, 2005). Furthermore, where participants have been directed to articulate task-irrelevant words during a task-preparation interval, their performance on such tasks has been considerably impaired presumably due to the interference with these very verbal self-instructions (Goschke, 2000; Emerson & Miyake, 2003; Miyake et al., 2004; Saeki & Saito, 2004).

To return to the current study, on face value, as a phenotypic measure, it would appear that there were striking difficulties. The first criteria of an endophenotype is that it must reliably distinguish between cases and controls and reliably demonstrate association with an illness. In this study, one-third of cases could not even do the task. This was also a problem encountered by Karayanidis et al., (2006) who also had a 30% drop-out rate amongst cases in a switching-attention EEG paradigm. Similarly, Ceaser et al., (2008) found that roughly one-half of their cases were unable to complete the intra-extra-dimensional shift CANTAB task in an endophenotype study which included first-degree relatives. For this reason, and because they found their paradigm was of limited heritability, they concluded that the intra-extra dimensional shift task had limited use as an endophenotype. This drop-out rate has not been in evidence in cases who undertake the Wisconsin Card Sorting Task (WCST). The WCST was one of the first neuropsychological tests of set-shifting ability. It measures flexibility of decision-making in the face of changing schedules of reinforcement. During the course of

this test, participants are shown a series of cards with different designs. They are told that these cards are to be matched by colour, design or quantity. During the course of the test, the matching rules are changed and the time taken for the participant to learn the new rules and mistakes made during this learning are quantified. Performance on this task has been found to be impaired in SZ (Bernman et al., 1986; Bornstein et al., 1990; Goldberg et al., 1993; Weinberger et al., 1986). The same drop-out rate does not seem to apply when cases approach the WCST. For example, 282 out of 282 cases completed the WCST in a study by Polgar et al., (2010) and this competency has been found elsewhere (Breton et al., 2010; Wilmsmeir et al., 2010). Evidently, the substantial drop-out rate reported in both the current study and two other studies poses difficulties. If cases cannot reliably perform these tasks then they are surely inadequate at capturing executive-functioning deficits in this population at the electrophysiological level- the psychometric properties of this task are leading to floor effects. Although there are differences in activations in preparatory processes on tasks like these, which are very interesting, these tasks do not offer the best prospects at reliably delineating cases from controls.

There is a number of limitations in this study. The cases used in this study scheduled an appointment by phone and then travelled to a large university to complete the research study. Therefore, this sample is not the most representative of chronic SZ. Homogeneity of the sociodemographic and clinical characteristics of a case sample are desirable and advantageous. This study is inconclusive about how an unwell, disorganised case sample would behave who may not be adherent to

medication, may lead a somewhat chaotic lifestyle, and who may experience negative symptoms. It would be interesting to follow up this kind of research with a case sample with chronic SZ as well as unmedicated cases to obtain a more extensive picture of the nature of these impairments.

In the current study the cases who did manage to complete the task displayed such a variance in cortical activity that this paradigm falls short of reliably distinguishing between cases and controls in a manner comparable with the other paradigms (e.g. P300). In the current study, the variance is simply too large to refer to "cases" as a whole group which has already been considerably reduced due to drop-out rates. What results is a bimodal distribution into those who respond even greater than controls, and those who appear to barely respond to the task. The fronto-parietal distribution of response which was even stronger than that of controls in the "high performing" cases is consistent with previous evidence which found that cases employed compensatory mechanisms across all the trial types to perform more like controls (Jamadar, Michie & Karayanidis, 2010). There are no cases who perform somewhere in the middle-ground between these two modes. In summary, the fact that patients either could not do the task, or performed at a level comparable to controls, means that it did not adequately distinguish between the two groups, a paramount criteria for its use as an endophenotype.

2.5. Conclusion

The SWAT task fails to produce a reliable distribution of scores and does not possess good biometric or psychometric properly analysable on a quantitative scale rendering it unlikely to demonstrate acceptable levels of test-retest reliability in the future – core requirments for serviceable endophenotypes. In this light, the SWAT task may be better served in exploring the underlying aspects of executive functioning in terms of characterising the course of cognitive impairment in the difference types of psychoses or in identifying which cases are spared major context and cognitive deficits and why (Barch & Keefe, 2010).

Chapter 3

An investigation of the NOS1 variant rs6490121 and its association with the P1 visual evoked neural response in healthy controls

Abstract

The Nitric oxide synthasase–1 gene (*NOS1*) has been implicated in mental disorders including schizophrenia, and also with variation in cognition. The *NOS1* variant rs6490121 identified in a genome wide association study of schizophrenia has recently been associated with variation in general intelligence and working memory in both patients and healthy participants. Whether this variant is also associated with variation in early sensory processing remains unclear. Differences in the P1 visual evoked potential were investigated in 52 healthy controls in the current study using high-density EEG. Given both *NOS1*'s association with cognition and recent evidence that cognitive performance and P1 response are correlated, it was investigated whether *NOS1*'s effect on P1 response was independent of its effects on cognition using CANTAB's spatial working memory (SWM) task. It was found that carriers of the previously identified risk 'G' allele showed significantly lower P1 responses than non-carriers. It was also found that while P1 response and SWM performance were correlated- *NOS1* continued to explain a significant proportion of variation in P1 response even when its effects on cognition were accounted for. The schizophrenia implicated *NOS1* variant rs6490121 influences visual sensory processing as measured by the P1 response, either as part of the

gene's pleiotropic effects on multiple aspects of brain function, or because of a primary influence on sensory processing that mediates the effects already seen in higher cognitive processes.

3.1. Introduction

Nitric Oxide (NO) is a highly reactive messenger molecule, which diffuses freely across membranes stimulating guanylyl cyclase and modifying protein structure with multiple roles in immune, cardiac and neurological function. NO stimulates synthesis of cyclic guanosine monophosphase (cGMP), which activates intracellular protein kinases and strongly influences glutamate neurotransmission via N-Methyl-d-Aspartate (NMDA) receptor interaction (Akyol, Zoroglu, Armutcu, Sahin & Gurel, 2004; Brenman & Bredt, 1997). NO is also involved in uptake, release and storage of other CNS neurotransmitters including acetylcholine, dopamine, noradrenaline, and gamma-Aminobutyric-acid (GABA) (Boehning & Snyder, 2003; Pepicelli, Raiteri & Fedele, 2004). Abnormal distribution of nitrinergic neurons in frontal and temporal lobes in schizophrenia (SZ) (Akbarian et al., 1996), increased NO metabolites in the serum of patients with SZ (Das et al., 1995; Taneli, Pirlldar, Akdeniz, Uyanik & Arl, 2994; Yilmaz et al., 2007), and postmortem increased *NOS1* messenger RNA in prefrontal cortex of patients (Baba, Suzuki, Arai & Emson, 2004) collectively suggest a functional role for NO in abnormal signalling. NO is produced by different nitric oxidase synthetase (NOS) enzymes including neuronal NOS and transported to different cellular compartments by adaptor proteins to minimize non-specific interactions. Neuronal nitric oxide synthase (nNOS) accounts for 90% of nitric oxide (NO) in the central nervous system, production of which is dynamically controlled both during development and in response to brain injury (Calabrese et al., 2007; Cherian, Hlatky, Robertson, 2004; Iadecola, 1997).

The Nitric oxide synthasase-1 gene (*NOS1*; OMIM 163731), encoding nNOS and mapping to 12q24, shows some evidence of association with risk for psychiatric disorders. In schizophrenia, *NOS1* falls within a region showing modest evidence of linkage to schizophrenia (Abkevich et al., 2003; Bailer et al., 2000; Bailer et al., 2002; DeLisi et al.,. 2002). Four of five published *NOS1* candidate gene association studies in schizophrenia suggest evidence of association (DeLisi et al., 2002; Fallin et al., 2005; Reif et al., 2006; Shinkai, Ohmori, Hori & Nakumura, 2002; Tang et al., 2008), the exception being Liou et al. (2003). Molecular pathway analysis of structural variants implicated in SZ by Walsh et al., (2008) identified a significant excess of disrupted genes involving the NO signaling pathway. In their SZ genome-wide association study (GWAS), O'Donovan et al. (2008) identified a single-nucleotide polymorphism (SNP) at the *NOS1* locus (rs6490121) as being 1 of 12 SNPs with strong initial statistical evidence for association (p=9.82x10^{-6}). The same allele at this SNP was significantly associated in a replication sample of 1664 cases and 3541 controls of European ancestry but not in a sample of mixed European and Asian ancestry and not in subsequent schizophrenia GWAS. Three further replication studies have been reported for rs6490121, one reporting a positive association in an Asian sample (Cui et al., 2010) and two reporting negative associations in European and Asian samples respectively (Riley et al., 2009; Okumura et al., 2009).

Although the role of *NOS1* in schizophrenia susceptibility is uncertain, more consistent evidence of association with variation in cognitive function in both animal and human studies has been

reported. In mouse models, *NOS1* knockouts have repeatedly been associated with variance in cognition (Kirchner et al., 2004; Weitzdoerfer et al., 2004). Notably, phencyclidine hydrochloride–induced cognitive and behavioural deficits that model SZ symptoms (including pre-pulse inhibition, habituation of acoustic startle, latent inhibition, spatial learning, spatial reference memory, and working memory) can all be prevented by interfering with the production of NO (Johansson, Jackson & Svensson, 1997; Johansson et al., 1998; Klamer, Engel & Svensson, 2001; Klamer, Engel & Svensson, 2004; Klamer, Palsson, Revesz, Engel & Svensson, 2004; Klamer, Engel & Svensson, 2005; Palsson et al., 2007; Wass et al., 2006). In patients with SZ, Reif et al. (2006) reported that 2 of 4 genetic markers tested at the *NOS1* locus were associated with variance in performance on measures of prefrontal function (the Continuous Performance Task, P300 peak amplitude, and response latency). We recently found that the risk 'G' allele at the *NOS1* SNP rs6490121 identified by O'Donovan and colleagues, is associated with significantly poorer performance in measures of both verbal intelligence and working memory in both patients with schizophrenia and healthy controls. This finding was replicated in independent samples of German patients and controls (Donohoe et al., 2009). Based on this evidence, it was concluded that *NOS1*'s association with SZ may reflect this gene's broader role in cognition (Donohoe, 2009: 1052).

A critical question for cognitive neuroscience regards how individual genes contribute to variation in cognitive function. Among several possibilities which include impact on grey matter volume, white matter structure, white matter integrity, one

hypothesis relevant to SZ is that genetic variants impact on cognitive ability via an influence on sensory level processing. In schizophrenia, observed deficits in sensory level processing (Butler et al., 2007; Foxe, Doniger & Javitt, 2001) are predicted to lower signal-to-noise ratio and increase the cognitive demands and errors made during cognitive task performance (Butler et al., 2007). It has been suggested that deficits in encoding both auditory and visual information, as measured by sensory evoked potentials such as the P50, N1, P1 and the MMN may contribute to a variety of higher-level difficulties in SZ, including phonetic processing and facial recognition (Dias, Butler, Hoptman & Javitt, 2011; Javitt, 2009). Supporting this theory there is already evidence that at least one SZ candidate gene (DTNBP1) is associated both deficits in higher cognitive functions -lower spatial working memory performance, and deficits in early visual processing as measured by the P1 (Donohoe et al., 2007; Donohoe et al., 2008). Whether this represents the 'bottom up' effects of DTNBP1 on cognition, or multiple pleiotropic effects on sensory and cognitive processing (Donohoe et al., 2009) remains unclear.

In the present study we examined whether the *NOS1* SNP rs6490121, previously associated with variation in intelligence and working memory, was also associated with variation in early sensory processing as measured by the P1 component of the visual evoked potential (VEP). Specifically, we tested the hypothesis that the risk 'G' allele at rs6490121 would be associated with decreased amplitude of the P1. We further sought to investigate whether this response in turn predicted variation in cognitive ability, based on the SWM task employed in

our previous neuropsychological study of *NOS1.* Empirical evidence that the amplitude of the visual P1 response can partially predict SWM response has recently been reported (Haenschel et al., 2007) whereby a stronger P1 amplitude increase predicted better working-memory performance in healthy controls. Finally, we sought to determine if the P1 response mediated the relationship between *NOS1* and SWM (a 'bottom up' effect) or, alternatively, if the effects of *NOS1* on SWM had a 'top down' effect on the P1 such that the relationship between *NOS1* and either the P1 or SWM disappeared after the effects of the other had been accounted for.

3.2. Materials and Methods

3.2.1. Participants

54 participants took part in this study recruited *as per* section 2.2.2. and clinically screened *as per* section 2.2.6. All participants had been included in our original neuropsychological study of *NOS1* (Donohoe et al., 2008) and represented those who, when re-contacted, were consenting and available to participate in an EEG assessment (see Table 3.1. for demographic information across groups).

Table 3.1. Demographic information on participants including age, years of education and gender

	AA (n=23)	AG/GG (n=29)	sig
Age (years)	40 +/- 11.62	37.61 +/- 12.75	t=.40
Years education	16 +/- 2.08	16.28 +/- 2.18	t=.64
Gender (% male)	40.90%	78.60%	r=.006

3.2.2. Presentation

Participants were seated in a comfortable chair in a dimly lit room, 110cm from the computer screen. Stimuli were presented with "Presentation" (version 14.2 Neurobehavioural Systems). For the P1 paradigm, which was divided into a series of 3-minute blocks to allow resting periods, participants were presented with isolated-check images containing an 8 X 8 matrix of checks (7.3° wide by 7.3° tall at 64% contrast, 100 per block), and line drawings of two kinds of animals (5.2° wide by 3.6° tall; 40 per block) on a white background (Yeap et al., 2006). The 64% contrast condition was chosen to stimulate both the magnocellular and parvocellular systems (see figure 3.1.). Each image appeared for 60ms with a variable inter-stimulus-interval (ISI) between 740 and 1540ms (randomly in steps of 200ms) during which there was a blank white screen. The purpose of the target animal stimuli was to encourage participants to attend to the screen. Each block required participants to press the key-pad when they identified a target animal they were shown at the

start of each block. Participants were directed to only respond to the target animal and refrain from responding to the non-target animal. Target and non-target animals were presented randomly intermixed with the isolated-check stimuli, with both target and non-target animals appearing with equal probability. Each block contained a different animal pair (see Appendix C.3) with each animal-pairing being somewhat similar to ensure the task was sufficiently challenging and to promote alertness. On average participants completed 9.62 blocks (SD 0.86).

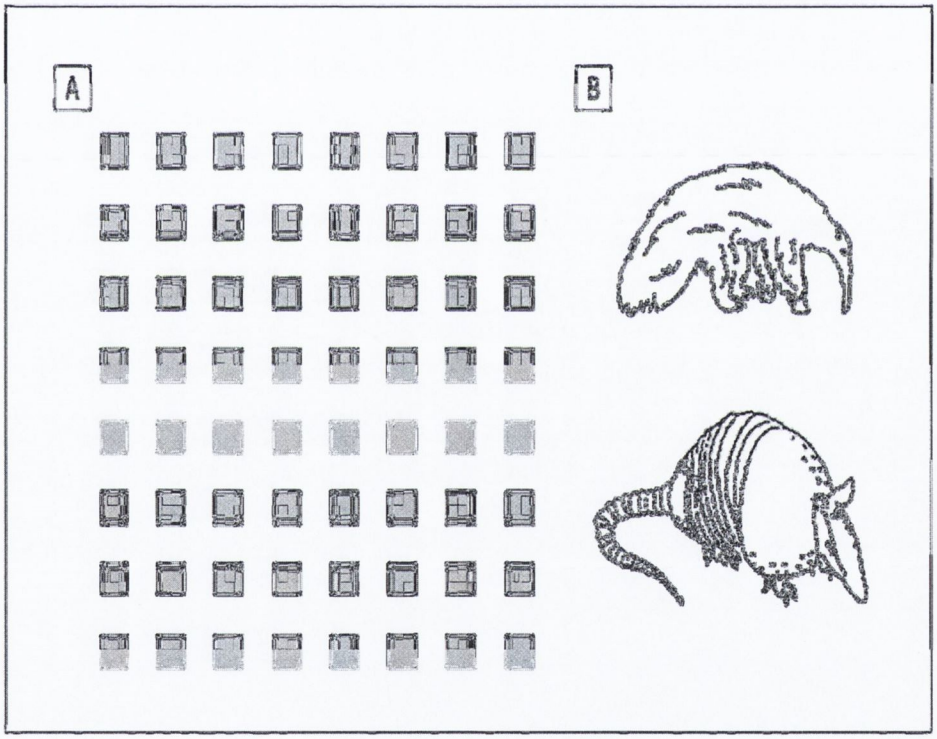

Figure 3.1. The centrally presented visual stimuli used in each task. ERP waveforms were derived from the A isolated check non-target stimulus whereas target discrimination was performed on the basis of B infrequently presented animal line-drawings.

3.2.3. Electrophysiological Data Acquisition

Continuous electroencephalographic (EEG) data were recorded *as per* section 2.2.8.

3.2.4. Spatial working memory assessment

All participants completed the SWM test from the Cambridge automated test battery (CANTAB Eclipse version, Cambridge Cognition, 2004) The touch screen computer task involves searching for 'hidden' tokens in boxes whose number increases from trial to trial. Participants are instructed to remember which box they visit as a token is never hidden in the same box twice. An error is committed when a participant returns to a box location from which a token has already been recovered [see Figure 3.2. for a stimulus example]. The dependent variable was the total numbers of errors made. Participants also completed subtests from the Wechsler Adult Intelligence Test (WAIS, 3rd edition) and the Wechsler Memory Scale (WMS, 3rd edition) to ensure that all participants' scored at or above the average range for IQ. In this instance, general cognitive functioning (IQ) was measured using selected subtests- vocabulary; similarities; block-design; matrix-reasoning from the Wechsler Adult Intelligence Scale, yielding full-scale verbal and performance IQ (see Donohoe et al., 2009).

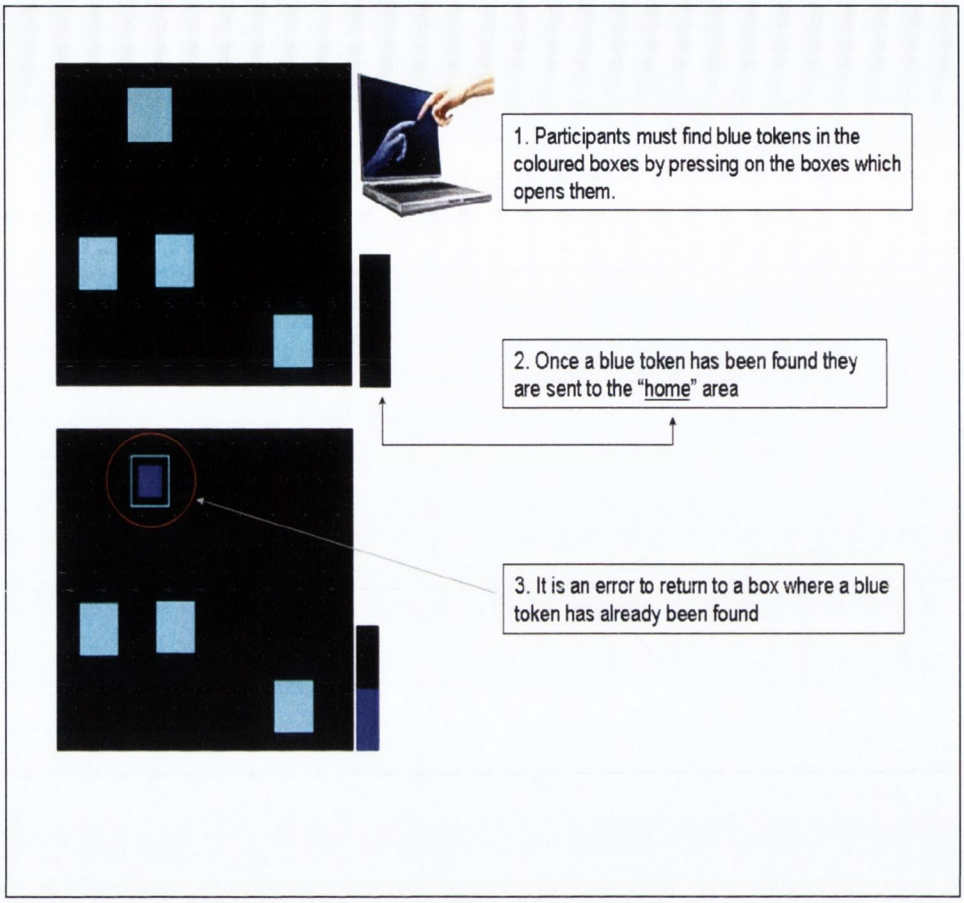

Figure 3.2. Example of stimuli for the spatial-working-memory (SWM) task; Cambridge Cognition (2008)

3.2.5. Genetic Analysis

The SNP rs6490121 was genotyped using a Taqman® SNP Genotyping Assay on a 7900HT Sequence Detection System (Applied Biosystems). The call rate for the Taqman genotyping was 100% and samples were in Hardy-Weinberg equilibrium ($p>0.05$). Along with these samples, a number of HapMap CEU DNA samples (www.hapmap.org) were genotyped for rs6490121 for quality control purposes and were all found to be concordant with available online HapMap data for this SNP. Only five participants were identified as GG genotype carriers (9.25% of sample). For statistical analyses, therefore, participants were

grouped as GG carriers and AG genotype carriers (n=29) versus AA genotype carriers (n=23). Mean scores and standard deviations are also reported for each genotype group separately to provide evidence of allele dosage effects.

3.2.6. ERP Analyses

ERP analyses were performed *as per* section 2.2.9. Grand averages were generated for each participant from the isolated-check stimuli only. Approximately 654 +/-241 sweeps per individual were averaged for the AA group and 669+/-262 for the GG+AG group with an epoch of -200 to 1,000 msecs. The average number of bad channels for the AA group was 8.41 and 11.15 for the GG+AG group. The P1 was defined as the area under the curve (versus the 0μV baseline) generated by the 64% contrast isolated-checkerboard stimuli within the post-stimulus window of 70-110 msecs spanning the P1 component. For the baseline correction, a baseline between -200 and 0 msecs was set. A set of six symmetrical pairs of scalp sites were chosen over occipital scalp sites from which P1 amplitudes were extracted (Left hemisphere: P1/P3/P03; Right hemisphere: P4/P6/P04). These sites were chosen based on topographical analysis of the grand-average group data which revealed lateral-occipital topographies consistent with those previously reported in the literature (e.g. Foxe and Simpson, 2002), for left and right hemispheres respectively.

For statistical analyses, P1 measures were submitted to analysis-of-covariance (ANCOVA) using SPSS Software (SPSS Inc., Chicago, Illinois Version 16.0) with the *NOS1* genotypes (AA versus

GG/AG) as the between subject factor and P1 response (both averaged across all six target electrodes and for left lateral occipital and right lateral occipital regions taken separately) as the within-subjects factor, with age and gender entered as covariates of no interest in the analysis. To further investigate possible relationships between P1 and SWM in relation to *NOS1*, multiple regression analysis was performed, first to examine whether the P1 response predicted SWM performance, and second to examine whether any relationship observed between *NOS1* and P1 performance was independent of variance in the P1 due to variance in SWM.

3.3. Results

As this study was based on an opportunistic sample of consenting individuals who were still available following our original neuropsychological study, *NOS1* genotype groups were not matched in advance for age, years in education or gender. No differences in age, education, or handedness were observed (Age: AA=24.8 [SD=12.45], AG/GG=29.1 [SD=12.45], t=0.69; p=0.49; years in education: AA=16.0 [SD=2.1], AG/GG=16.3 [SD=2.2]; t=0.46; p=0.64; handedness: AA: 21/22 right handed; AG/GG: 28/30 right handed; χ^2=0.15; p=0.69]. Differences in gender were observed (AA: 10/24 male, AG/GG: 21/29 male; χ^2=7.41; p=0.006). Consequently, gender was used as a covariate in all subsequent analysis of ERP components; age was also included as a covariate of no interest in the analyses.

To ensure comparability between GG/AG 'risk' and the AA 'non-risk' genotype groups in attending to the visual P1 eliciting

stimulus (checkerboard) the reaction time and accuracy were examined with which both groups identified the animal line drawings dispersed between the checkerboard stimuli. The mean reaction-time for the AA group was 432.92 (+/- 37.85) and for the GG/AG group was 430.54 (+/-42.17). The mean rate of correct responses for the AA group was 192.16 (+/- 7.89) and for the GG/AG group was 192.24 (+/- 12.95). The mean rate of incorrect responses to non-targets was 12.53 (+/- 6.66) for the AA group and 8.52 (+/- 4.24) for the GG/AG group. Between group differences on each of these metrics of performance were all non-significant (all *p*-values >0.05). Collectively these data suggested that participants in both groups were equally engaged in the task, and given the high hit-rates, clearly focused their attention centrally towards the screen throughout each block presentation.

3.3.1. Differences in P1 VEP according to *NOS1* genotype

Figure 3.3. shows the bilateral occipital distribution of the P1 in *NOS1* risk 'GG+AG' and non-risk 'AA' genotype groups. The map of the difference topography between these genotype groups, captured at maximal amplitude at 90ms, illustrates the reduction in P1 amplitude in the 'GG/AG' group relative to the 'non-risk' AA group. Figure 3.4. illustrates the individual P1 morphology for electrode sites included in the statistical analysis. At each site the 'risk' GG/AG genotype group shows a reduced P1 response compared to the 'non-risk' AA genotype group. Over the right lateral occipital region, where the P1 amplitude difference was maximal, the mean P1 amplitude was 147.25 +/-75.25 for the AA genotype group and 86.84 +/- 52.42 for the GG+AG group. Figure

3.5. presents a scatterplot of P1 amplitudes measured at electrode sites included in the analyses (10/20 equivalents of: P1/P3/P03 & P4/P6/P04).

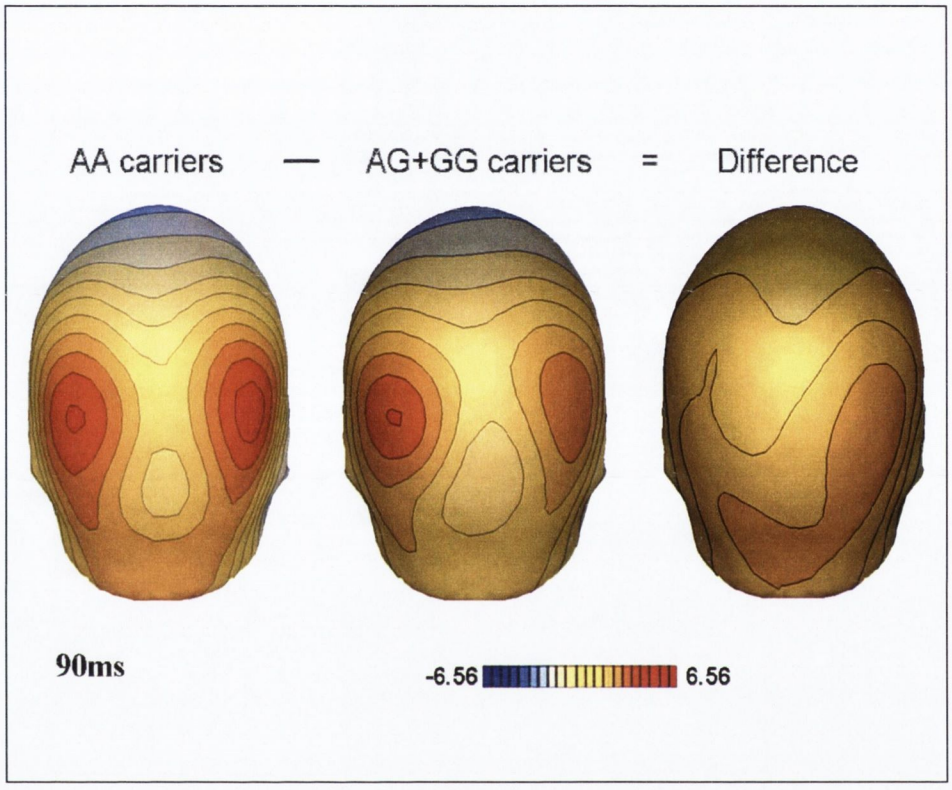

Figure 3.3. Mapping of the difference topography associated with NOS1 genotype. The grand averaged waveforms of each group were subtracted from one another to enable the difference effect to be illustrated.

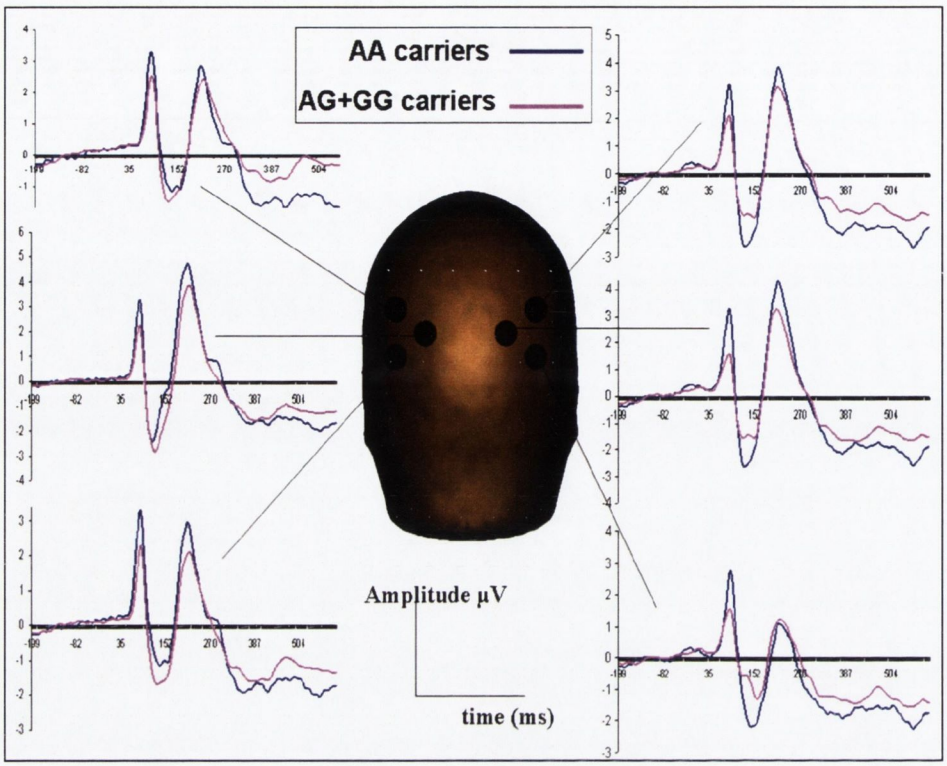

Figure 3.4. This illustrates the individual P1 morphology for electrode sites included in the statistical analysis.

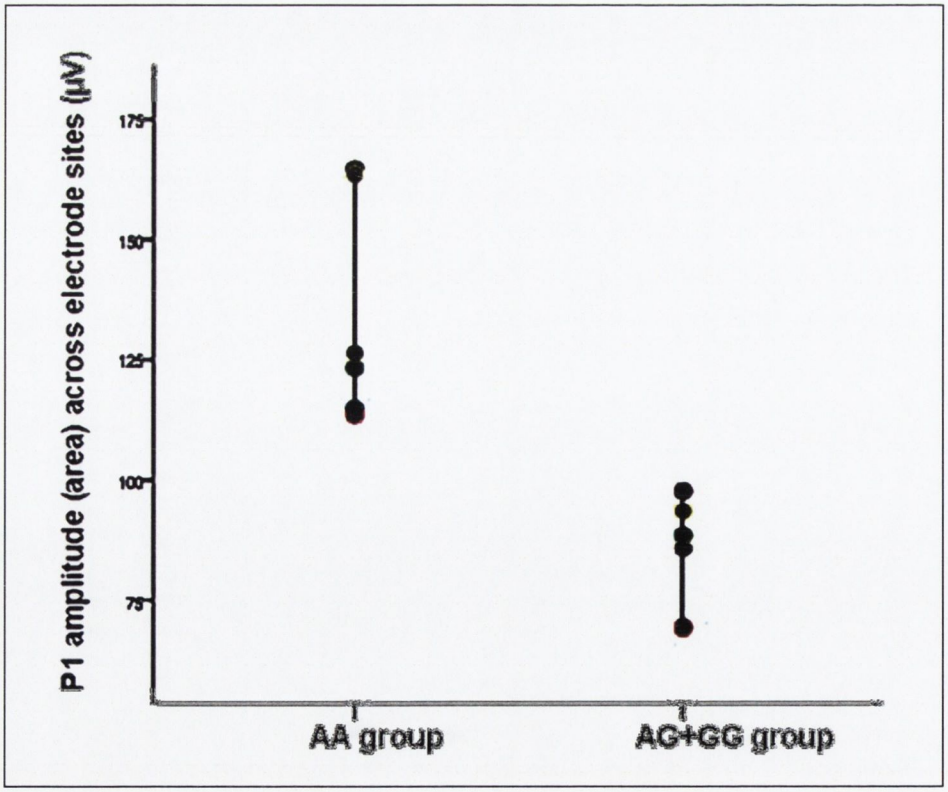

Figure 3.5. Scatterplot of P1 amplitudes (area under the curve) across electrodes used in statistical analysis.

Reflecting these differences, a significant main effect of genotype group was observed, showing reduced P1 (measured as area under the curve) in the 'risk' GG+AG genotypes group compared to the 'non-risk' AA genotypes group ($F(2,52)=13.85$; $p=.001$). Differences associated with *NOS1* were found to be more robust over the right than the left hemiscalp [right: $F(3,52)=16.73$, $p=.00016$]; [left: $F(3,52)=3.14$, $p=.083$]. As mentioned the low frequency of GG carriers (n=5) prevented a statistical analysis of GGvAGvAA groups separately. However, inspection of means and standard deviations across these groups suggested a gene dosage effect such that GG genotype individuals showed a less robust P1 evoked response than the AG group, who in turn showed a less robust P1 evoked response than the AA group for both hemiscalps (see Table 3.2.).

Table 3.2. Differences in P1 response according to genotype group (measured as area under the curve)

	GG (n=5)	AG (n=25)	AA (n=22)
P1 left hemisphere	65.77 (55.46)	97.70 (60.98)	118.64 (59.56)
P1 right hemisphere	78.53 (51.24)	88.47 (52.45)	150.04 (76.02)
P1 both hemispheres combined	72.15 (50.44)	91.58 (44.96)	134.34 (52.33)

Group differences were also calculated for the N1 (97-185msecs) and P2 (160-300msecs). No significant differences were observed for either right or left hemisphere electrodes for these ERPs. Latency measures were also examined. The mean latency

for AA carriers was 85.59 +/- 12.32 and was 93.31 +/- 12.92 for AG+GG carriers. These differences were not found to be significant [$F(1,50)=3.30$, $p=.07$].

3.3.2. P1 VEP, NOS1 genotype and SWM performance

Given previous evidence of association between P1 and SWM performance, and evidence of association between *NOS1* and SWM in our previous study, it was investigated whether P1 performance predicted SWM performance in the present study using regression analyses. For this analysis SWM task performance was entered as the dependent variable. Age and gender were entered on the first step of the equation as covariates of no interest and P1 performance (electrode sites for left and right hemiscalps averaged together) was entered on the second step as the independent variable of interest. After the effects of age and gender were accounted for, P1 response explained a further 12.9% of variance in SWM performance (F change $(1,40)=7.74$, $p=.009$).

3.3.3. NOS1 effects on sensory and cognitive processing: top down versus bottom up influences

It was next determined, using a multiple regression analysis, whether *NOS1*'s observed influence on the P1 response might be accounted for by the previously observed influence of *NOS1* on SWM performance. To do this the P1 response was entered as the dependent variable, SWM performance as the independent variable in the first step of the analysis, followed by *NOS1* as the independent variable in the second step. P1 response was again

measured in terms of the area under the curve, based on the electrode site in which differences between *NOS1* risk carriers and non-carriers were maximal (i.e. right occipital electrodes P4/P6/P04). It was reasoned that if the effects of *NOS1* on the P1 response were being mediated by SWM, *NOS1*'s effects on the P1 response would become non-significant once the variance attributable to SWM was accounted for. Instead, it was found that even after accounting for the effects of SWM performance on the P1 response (which accounted for 26% of the variance in P1 response), *NOS1* independently explained a further 9% of variation in P1 response. (R^2 = .35; F (1,40)=5.04, p=.03). This suggested that at least some of the effects of *NOS1* on P1 performance are independent of *NOS1*'s previously reported influence on SWM. It was also intended to examine whether *NOS1*'s influence on SWM performance was mediated by P1 response. Unfortunately, we were prevented from doing so due to insufficient power to detect association between *NOS1* and SWM performance in the restricted EEG sample (n=54 versus the overall neuropsychological sample of n=160) and so this analysis could not be undertaken.

3.3.4. NOS1 effects on the P300

Following these analyses, it was also decided to explore the association between this NOS1 variant and the P300 elicited during the performance of an auditory oddball task [as outlined in Appendix C.1.]. The P300 ERP is denoted by its association with structures involved in the intergreity of memory, attentional and stimulus processing mechanisms. For statistical analyses, peak amplitude and area-under-the-curve P300 measures were submitted to analysis-of-covariance (ANCOVA)

using SPSS Software (SPSS Inc., Chicago, Illinois Version 16.0) with the *NOS1* genotypes (AA versus GG/AG) as the between subject factor and P300 response (across the midline electrode sites Cz and CPz) as the within-subjects factor. As illustrated in table 3.3, there were no differences between genotype groups based on age, gender or years of education so they were not included as co-variates in analysis. There were no significant differences between genotype groups for P300 measures taken at CPz for area-under-the-curve [$F(1,76)=.004$, $p=.948$], peak amplitude [$F(1,76)=.109$, $p=.742$]; and at Cz for area-under-the-curve [$F(1,76)=.092$, $p=.76$] or peak amplitude [$F(1,76)=.97$, $p=.328$]. This is further illustrated in Figure 3.6 which illustrates grand average waveforms per genotype group.

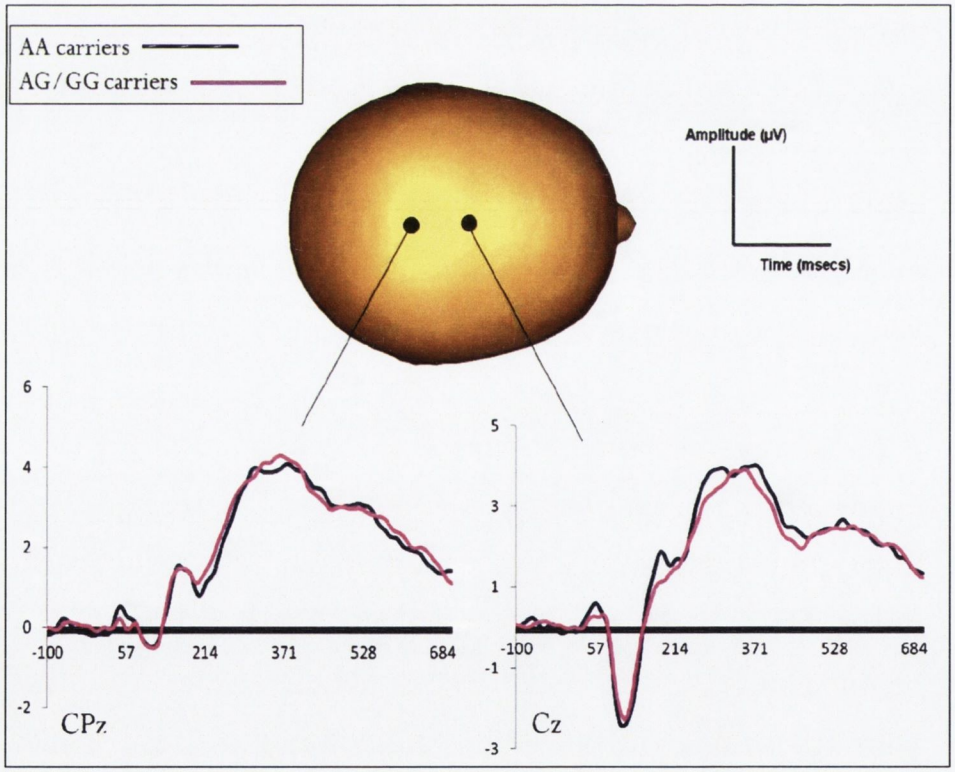

Figure 3.6. This illustrates the individual P300 morphology for electrode sites included in statistical analysis. At each site, the "risk" AG/GG genotypes show a similar P300 response to the "non-risk" AA genotype groups.

Table 3.3. Demographic information on healthy controls as per genotype group for the P300 including age, years of education and gender.

	AA (N=32)	AG/GG (N=44)	Sig.
Age	40.02 (11.05)	36.87 (12.75)	t=.376 N.S.
Years of Education	15.24 (2.86)	15.91 (2.58)	t=.669 N.S.
% Male	45.70%	54.50%	X^2=1.437 N.S.

3.4. Discussion

It has previously been reported that the risk 'G' allele at the SZ GWAS identified *NOS1* variant rs6490121 was associated with poorer performance in SWM and verbal IQ in independent samples of both SZ patients and healthy controls. Following up these findings, the present study investigated whether the same *NOS1* variant was also associated with poorer performance in sensory level processing as measured by the P1 visual evoked potential in a sample of healthy participants. Consistent with our hypothesis, we observed that the associated risk allele at rs6490121 was associated with a significantly reduced P1 response bilaterally. No differences in N1 or P2 response associated with *NOS1* were observed.

As an endophenotypic measure, the P1 has the major advantage of being relatively easy to measure quickly and accurately. The large differences between healthy controls and both patients and their first-degree relatives suggest this component is heritable (Donohoe et al., 2008; Donohoe et al., 2007; Haenschel et al., 2009; Yeap et al., 2006). As a largely automatic response, it is not as susceptible to the same motivational factors or fluctuations in clinical state other cognitive components which often index

cognition more generally. However, this is not to say that the P1 is not cognitively penetrable. Although early stages of perceptual processing (from as early as 50 -100 msec post-stimulus) serve an important role in "spotlighting" of relevant information for later processing, these early processing stages (from 70 msec onward) appear to be reciprocally modulated by higher processing areas (Martinez et al., 1999).

It is interesting to speculate about the twin effects of *NOS1* on (in our larger sample Donohoe et al., 2009) SWM, and (in the present study), the P1 response. These associations may reflect the reciprocal relationship between early sensory and higher cognitive function, particularly for visual information. On one hand, deficits in "capturing" visual information are likely to increase difficulties in efficiently maintaining and updating that information "online" during SWM tasks. Conversely, an inability to maintain context during later stages of processing leads to difficulties focusing on relevant information during earlier stages of visual processing. A relationship between the P1 response and SWM performance has been empirically demonstrated previously (Haenschel et al., 2007) and, in the present study, this evidence was replicated: the P1 response significantly predicted SWM task performance in our participants.

In the current study it was possible partly to test whether the genetic effects on either of these stages of processing (early visual sensory versus SWM) were being mediated by the other. Although insufficient power prevented the determination of whether *NOS1*'s effects on SWM were mediated by P1 performance, it was possible to reject the hypothesis that *NOS1*'s

effect on the P1 was being mediated in a 'top-down' fashion by *NOS1*'s influence on SWM performance. In a multiple regression analysis, while SWM significantly predicted variance in the P1 response, *NOS1* continued to explain a significant amount of variance in the P1 response even after the variance associated with SWM was accounted for. This data was interpreted as suggesting that *NOS1* has a direct influence on visual sensory processing as measured by the P1 response, either because of pleiotropic effects of this gene on multiple aspects of brain function, or because of a primary influence on sensory processing that mediates the effects already seen in higher cognitive processes. This evidence supports the increasingly popular theory that some deficits in cognitive processing may result at least in part from sensory level processing deficits (Dias et al., 2011; Javitt, 2009; Sehatpour et al., 2010) which are most likely affecting magnocellular input which is believed to be the visual stream most disrupted in SZ and concerns fast-conducting neurons which then feed onto more ventral streams and so on in visual perception (Butler et al., 2007; Coleman et al., 2009; Kiss, Fábián, Benedek & Keri, 2010; Sehatpour et al., 2010). Specifically, Dias et al., (2011) recently found that deficits in sensory processing, as measured by the C1, P1 and N1 contributed significantly to behavioural outcome on an AX-continuous performance task used to evaluate the neural basis of working-memory and executive processing. However, these findings require testing in a larger sample to confirm the effect of the P1 response as mediating the influence of *NOS1* on cognition.

A limitation of these findings concerned the observed gender and sex differences between genotype groups. Although these

differences were co-varied for in the analysis and did not appear to influence the significance of our results, replication of these findings in more gender and sex matched genotype groups will enable a better assessment of the contribution of these variables. In the current study, the GG groups were grouped together as the frequency of the GG genotype group was too low. Future replication studies could also include a sample where AG and GG groups are better individually represented.

3.4.1. *NOS1*: Molecular mechanism and functional implications

The implicated SNP (rs6490121) has no obvious functional effect and may reflect a proxy association with one or more other causal genetic variants in SZ. Based on HapMap CEU data, rs6490121 is not in high linkage disequilibrium (LD; $r2>0.80$) with any other common SNP at this locus. *NOS1* is characterized by complex transcriptional regulation. It was previously investigated whether the cognitive effects of this *NOS1* variant could be explained by the dinucleotide variable-number tandem repeat located in the core promoter region of exon 1f, the short arm of which is associated with electrophysiological measures of attentional control (Reif et al., 2009) and which is in partial LD with this SNP (D'=0.70, $r^2=0.26$; ref 37). However, there was no evidence that this variant explained variation in cognition in our samples.

Since its original identification as a common genetic variant associated with SZ risk by (O' Donovan et al., 2008) none of the subsequent genome wide association studies of SZ have

identified *NOS1* rs6490121 as achieving genome wide level significance (ISC, 2009; Stefansson et al., 2008; Walsh et al., 2008). It has previously been suggested that *NOS1* may be a modifier gene that influences cognitive ability without having a direct influence on disease risk. The present data suggest an even broader role for *NOS1* in information processing, impacting early sensory as well as later cognitive function. This broad influence on information processing is consistent with the known biology of *NOS1*, including negative feedback on *N*-methyl-D-aspartate (NMDA) receptor function and inhibition of synaptic reuptake of dopamine. This position at the crossroads of two mutually regulating messenger systems, and its ubiquitous expression throughout the brain, together make a discrete influence on only one level of information processing unlikely. A wider role for genetic variants influencing NMDA at the levels of both SWM and P1 response has already been reported in the case of Dysbindin-1 (DTNBP1; Donohoe et al., 2008; Donohoe et al., 2007).

3.5. Conclusion

As originally conceived, the use of cognitive and EEG measures as 'intermediate' or 'endo'-phenotypes was proposed as a strategy for reducing the genetic complexity of broader clinical phenotypes that would allow greater power for identifying genes of small effects (Gottesman & Gould, 2003). Since then, several EEG studies have focused on confirming the effects of variants already associated with increased disease risk on individual brain systems for the purposes of characterizing the effects on these variants on individual aspects of brain function. Such an approach may be helpful in elucidating gene-disease pathways

(Walters & Owen, 2007) and, eventually, therapeutic targets. However, there is currently little evidence that the genetic architecture of cognition is much less complex than that of disease phenotypes. Thus, cognitive neuroscience studies of psychiatric disease associated variants, in which information processing is disrupted, is likely to have an equally valuable role in elucidating the molecular biology of information processing in the general population. Evidence of *NOS1*'s role in early visual processing presented here is therefore likely to be relevant not just to schizophrenia pathophysiology, but to understanding the molecular basis of visual processing more generally.

Chapter 4

A neurophysiological investigation of the genome-wide associated SZ risk variant ZNF804A rs1344706

Abstract

The zinc-finger protein gene (ZNF804A) has been implicated in schizophrenia susceptibility by a genome-wide association study, with support from replication. The current study aimed to investigate whether the risk allele rs1344706 is associated with variation in electrophysiological cortical response in cases and healthy controls as measured by EEG. We previously observed that the associated variant at ZNF804A delineated a case sub-group characterised by relatively spared cognitive ability. A comparison was performed of both cases and controls grouped according to their ZNF804A genotype (AA –v- AC/CC) and the event-related-potential endophenotypes, the P300 and the P1. These event-related-potentials are good candidate endophenotypes- they are easily measured, heritable, stable and reliably distinguish between cases and controls. Association was first tested between ZNF804A and the P1 and then the P300. It was observed for the P300 that in both cases and healthy controls, those carrying the ZNF804A risk genotype demonstrated greater cortical response (as measured by area-under-the-curve and peak amplitude) at the central electrode site CPz compared to the non homozygous risk-genotypes. Finding an association between relatively larger P300 responses and ZNF804A risk carrier status again suggests a relative advantage for carriers in cortical processes relevant to attention

and memory function. This study extends our previous findings not least because the larger P300 response was found in both cases as before but also in healthy controls. This study contributes to the growing body of evidence that ZNF804A may increase illness risk via its effect on brain structures associated with memory functioning and attention. Although it remains slightly unclear by which mechanisms ZNF804A may be increasing illness risk and whether they may be related to other risk-mediating effects, the current findings would certainly suggest that it is unlikely to be via a deleterious impact on the neural mechanisms underlying traditional cognitive deficits in SZ.

4.1. Introduction

A single-nucleotide-polymorphism (SNP) rs1344706 located within the zinc finger binding protein (ZNF804A) was the first genetic variant to achieve genome-wide-significance for psychosis (OR=1.1p=9.96x10^{-11}) (O' Donovan et al., 2008). Association with schizophrenia (SZ) has been replicated in a series of additional studies since then (Steffanson et al., 2009; Shi et al 2009; Riley et al 2009; Zhang et al., 2010; Steinberg et al., 2010). A meta-analysis by Williams et al. of 21,274 cases and 38,675 controls has confirmed this association with both schizophrenia (OR 1.10; P=2.5 x 10^{-11}) and schizophrenia and bipolar disorder combined (OR 1.11; P=4.1 x 10^{-13}). In addition to the common variants identified, evidence of excess copy number variants at the ZNF804A locus in psychiatric cases has also been reported (Steinberg et al 2010), although a study of rare variants within coding regions of ZNF804A failed to identify significant rare non-synonymous risk variants at the ZNF804A locus (Dwyer et al., 2010). Similarly, after de novo polymorphism discovery and detailed association analysis in the Williams et al. (2010) meta-analysis, rs1344706 remained the most strongly associated marker in the gene. Collectively, therefore, these data make the association between the ZNF804A SNP rs13447060 and schizophrenia one of the most compelling findings in SZ genetics to date (Donohoe et al., 2010).

rs1344706 is located in intron 2 of ZNF804A that maps to a short region of conserved mammalian sequence on chromosome 2q32.1. Consisting of 4 exons and transcribing a protein of 1210 amino acids, ZNF804A contains a C2H2-type domain associated with the zinc-finger protein family and is known to be brain

expressed. The function of this protein is unknown. Proteins with this zinc-finger domain were originally identified as DNA-binding molecules with a role in transcription but have diverse interactions with many molecules including RNA and proteins. Bioinformatic analysis of the conserved mammalian sequence around rs1344706 suggests the presence of transcription factor-binding sites. Riley et al. (2009) in their analysis suggested that the 2 alleles result in differential prediction of 2 brain-expressed transcription factors, Myt1L zinc-finger protein and the POU3F1/Oct-6 POU domain transcription factor, both of which are involved in oligodendrocyte differentiation and proliferation. The mouse homologue of *ZNF804A*, zfp804a, has recently emerged as a target for HOXC8 suggesting that the gene may also be involved in the regulation of early neurodevelopment (Chung et al, 2010).

The functional mechanism by which the risk allele contributes to etiology also remains to be determined. Williams and colleagues (2010) examined genotype and lymphoblastoid expression data from the GeneVar database and identified that rs1344706 was significantly associated with expression of *ZNF804A* mRNA, and the risk allele was associated with higher expression. They then measured the relative expression of each parental copy of *ZNF804A* in postmortem brain mRNA taken from 34 individuals heterozygous carriers of a proxy for the rs1344706 risk SNP (rs4667001, D'= 1). They determined that the risk allele was associated with a 1.13-fold (SD 0.08) increase in ZNF80A expression. Using human brain samples to test the *cis*-acting effects of ZNF804A on protein expression levels in multiple brain regions, based on a proxy SNP for rs4667001 (rs12476147), Buonocore et al. (2010) observed a general regional pattern of

allelic expression at the assayed SNP, along with tissue specific allelic expression between the brain regions assayed.

A critical dimension to understanding the biological mechanisms by which genetics variants such as ZNF804A may increase illness susceptibility has been to investigate the *in vivo* effects of these variants on brain structure and function using neuropsychological, structural and functional brain imaging, and EEG recordings. An important hypothesis for this endophenotypic approach is that at least some of the deleterious effects of the risk allele are mediated via effects on the core functional and neuro-anatomical characteristics of the disorder, including poorer memory and executive function, reduced grey matter volume, and reduced evoked potential during sensory and cognitive task performance.

The results of cognitive studies to date diverge from what would typically be expected from a SZ risk gene. Williams et al. (2010) reported that in patients, but not controls, carriers of the risk allele showed relatively preserved cognitive functioning in the areas of both episodic and working memory in large independent Irish and German samples. They further observed that when patients with lower general cognitive ability were removed from the analysis the association with SZ risk strengthened. This led them to conclude that ZNF804A may be associated with an illness phenotype in which cognitive deficits are relatively less impaired than phenotypes associated with other common risk variants.

This hypothesis is supported by two further studies. In the first, they focused on clinical symptom severity, finding that risk carriers were observed to present with higher symptom levels of mania (Cummings et al., 2010). Consistent with the evidence that ZNF804A is associated with both SZ and bipolar disorder, and a less cognitively impaired phenotype, the modest association with elevated mania symptoms may again reflect ZNF804A's association with a psychosis in which affective rather than cognitive symptoms are more prominent. In the second study (Donohoe et al., 2010), the risk allele was associated with relatively intact grey matter volumes compared to non-carriers, notably in brain regions associated with memory function (superior temporal gyrus, hippocampus), consistent with the earlier neuropsychological study. Again, these data were interpreted to suggest relative cortical intactness associated with the genotype rather than that the genotype bestowed a cortical advantage (as it was not seen in healthy controls), again consistent with the idea of a phenotype characterized by less impaired cognitive deficits.

As noted this data, and their interpretation, diverge from what would normally be expected in schizophrenia intermediate phenotype studies in that the ZNF804A genotype is associated with fewer cognitive symptoms, smaller loss of grey matter volume and increased affective symptoms. However, a number of other studies support the view that ZNF804A may mediate illness risk via an influence on affect rather than cognition. Esslinger et al (2009) reported that ZNF804A phenotype was not associated with variation on measures of cognition in healthy controls but was associated with an altered pattern of

connectivity between several regions including the dorsolateral pre-frontal cortex, hippocampus and amygdala. While the authors initially concluded that this may be relevant to the cortical control of cognitive abilities, a subsequent study from the same group suggested that the impact of this altered connectivity between areas such as frontal and temporo-parietal regions may instead be more indicative of difficulties processing of socially relevant cues. In this study by Walter et al. (2010) risk carriers performing a theory-of-mind task exhibited a significant risk allele dose effect on neural activity in the medial prefrontal cortex and left temporo-parietal cortex. Supporting the idea that ZNF804A genotype might be particularly relevant for processing social information was the evidence that parts of the human anologue of the mirror neuron system (the left inferior parietal cortex and left inferior frontal cortex) were also significantly affected.

While the distinction between the processing of cognitive information and the processing of social information is interesting as an explanation for some of the findings associated with ZNF804A, the data does not appear to support such a straight forward distinction. Firstly, Esslinger et al., (2010) noted an abnormal pattern of connectivity during both a measure of facial affect recognition and a measure of working memory in a sample of healthy controls. Secondly, two smaller studies reported evidence that risk allele carriers showed poorer performance on measures of visual memory and executive control, respectively (Hashimoto et al., 2010; Balog et al., 2010). Finally, Lencz et al. (2010) found that risk carriers showed reduced cortical thickness compared to non-carriers. Each of

these findings is obviously not beyond dispute. The connectivity analysis by Esslinger et al., (2010) failed to demonstrate effects on performance on either task so that the functional effects of the presumed 'dis-connectivity' observed is unclear, particularly as it was only observed in healthy controls and did not involve patients. Hashimoto et al. (2010) reported lower visual memory scores among risk carriers in a small sample of patients (n=113); however this association did not survive correction for multiple testing (no association was found in the healthy control sample). Balog et al., (2010) found association with slower reaction times in healthy controls (patients were not included in the study) on one aspect of the Attentional network Task (ANT) task – the 'executive' component - which indexes the ability to maintain set and respond attentively despite the conflicting stimuli being presented. This report has not been independently replicated and multiple testing was not corrected for. However, Lencz et al., (2010) also noted that risk carriers (again healthy participants) showed slower reaction times on an attentional measure – the Trails A task. A provisional conclusion from this data is that ZNF804A may be important to attentional control.

The purpose of the present study was to investigate the effects of the identified risk 'A' genotype at ZNF804A rs1344706 on electrophysiological indices of evoked response to visual and auditory stimuli previously identified as endophenotypes for schizophrenia, namely the auditory P300 and the visual P1. These ERPs have been widely used to investigate SZ risk variants to date (Bramon et al., 2008; Donohoe et al., 2008; O' Donoghue et al., 2011; Gallinat et al., 2003; Golimbet et al., 2006; Reif et al., 2009; Sinkus et al., 2009). The visual P1 provides and index of

sensory level visual processing while the P300 is considered a marker of attentional processing & stimulus evaluation. Based on our earlier studies the null hypothesis was tested that ZNF804A would have no influence on performance on either of these markers. The alternative hypothesis was that, as per the studies by Lencz et al al., (2010) and Balog et al., (2010) for attention, and Walter et al., (2010) for theory-of-mind, ZNF804A would be observed to have a deleterious effect on these measures. These hypotheses were tested in a sample of both patients with SZ and healthy controls.

4.2. Method

4.2.1. Participants

Participants were recruited *as per* section 2.2.1.

4.2.2. Patient recruitment

Patients were recruited *as per* section 2.2.2.

4.2.3. Recruitment of healthy participants

Healthy participants were recruited *as per* section 2.2.3.

4.2.4. Demographic information

Demographic information was collected *as per* section 2.2.4.

4.2.5. Clinical Assessment of patients

As per section 2.2.5.

4.2.6. Clinical screening of healthy participants

As per section 2.2.6. Demographic variables as per group (control –v- case) and as per genotype (AC/CC –v- AA) are included in Table 4.1.

4.2.5.1. P1 paradigm

150 participants completed the P1 paradigm. From this number, 20 data sets had to be removed due to excessive noise, lending their data sets to be unusable. Clean data was important in order to lend confidence and much stronger conclusions around any experimental effects found. In such instances, artifact correction was unable to compensate for participants who consistently blinked during collection of the EEG or who emitted continuously high-amplitude alpha activity. A further 18 participants had no genotype information available on rs1344706. In the end, clean data and genotype information was available for 112 participants on the P1 task.

4.2.5.2. P300 paradigm

134 participants completed the P300 paradigm. From this number, 11 data sets had to be removed due to noise with the same intentions as for the P1 in terms of maintaining a clean data set. A further 24 participants had no genotype information available for this SNP. In the end, clean data and genotype

information was available for 97 participants on the P300 paradigm.

Table 4.1. Demographics by group and ZNF804A genotype for (a.) the P1 and (b.) the P300 component respectively. Note that the statistical comparisons consider the difference between "A" allele homozygous individuals and a combined sample of one or two "C" copy carriers. [N.S. = non-significant].

a.

	Cases				Controls			
	AA (N=17)	AC (N=18)	CC (N=7)	Comparison	AA (N=39)	AC (N=31)	CC (N=9)	Comparison
Age (years: mean (s.d.))	48.65 (11.50)	41.33 (12.14)	47.15 (9.02)	p (.07)=N.S.	37.42 (11.57)	38.21 (13.21)	40.78 (12.69)	p (.69)=N.S.
Gender (# females)	6	6	1	X^2(.57)=N.S.	11	19	5	X^2(.27)=N.S.
Education (years: mean (s.d.))	13.12 (3.03)	13.47 (2.40)	13.86 (1.86	p (.71)=N.S.	16.81 (1.32)	15.97 (2.28)	16.11 (1.96)	p (.08)=N.S.
PANSSpositive	25.40 (6.27)	29.25 (8.31)	26.75 (7.18)	p (1.02)=N.S.				
PANSSnegative	17.60 (6.84)	26 (19.42)	26.00 (6.21)	p (1.42)=N.S.				
SAPS	.98 (.96)	1.79 (.43)	1.10 (1.31)	p (1.84)=N.S.				
SANS	1.03 (.75)	1.27 (.85)	1.45 (1.70)	p (.49)=N.S.				
chlorpromazine equivalent	456.78 (402.95)	706.60 (641.48)	285.83 (105.65)	p (.31)=N.S.				

b.

	Cases				Controls			
	AA (N=11)	AC (N=13)	CC (N=6)	Comparison	AA (N=31)	AC (N=29)	CC (N=7)	Comparison
Age (years: mean (s.d.))	41.00 (13.70)	47.83 (11.17)	40.15 (9.65)	p (.14)=N.S.	38.83 (11.05)	41.07 (13.29)	40.15 (9.65)	p (.69)=N.S.
Gender (# females)	5	6	0	X^2(.09)=N.S.	13	18	3	X^2(.02)=sig
Education (years: mean (s.d.))	13.50 (2.32)	12.23 (2.45)	13.29 (1.38)	p (.45)=N.S.	16.94 (1.34)	16.23 (2.32)	16.29 (1.70)	p (.14)=N.S.
PANSSpositive	25.28 (3.54)	28.75 (4.46)	26.75 (7.18)	p (-1.64)=N.S.				
PANSSnegative	19.14 (7.71)	19.62 (7.53)	26.00 (6.21)	p (-.12)=N.S.				
SAPS	1.31 (.66)	1.55 (.66)	1.10 (1.31)	p (-1.09)=N.S.				
SANS	1.28 (.75)	1.07 (.85)	1.45 (1.70)	p (.38)=N.S.				
chlorpromazine equivalent	753.33 (681.34)	570.75 (254.92)	296.00 (147.07)	p (-.67)=N.S.				

4.2.6. EEG stimuli and presentation

4.2.6.1. The P1 paradigm

As per section 3.2.2. On average participants completed 9.74 blocks (SD 1.70).

4.2.6.2. The P300 paradigm

Participants were seated in a comfortable chair in a dimly lit room. Stimuli were presented through bilateral intra-aural earphones (Sennheiser PXC 300 Noise Guard Advance). The P300 was evoked by using an auditory oddball paradigm with pseudo-randomised binaural presentation of frequent (non-target) beeps at 1000 Hz and a rare target stimuli (at 1,500 Hz), in an inter-stimulus-interval of 1560, with a tone loudness of 80 dB. 80% of the tones were "non targets" of 1000Hz and 20% were "targets" of 1,500Hz in a random sequence. Participants were instructed to listen to the tones whilst keeping their eyes open, and press a mouse key whenever they identified the target tones only which were 1,500 Hz tone (see Appendix C.1.).

4.2.7. Electrophysiological Data Acquisition

A number of cases had their data collected at the Cognitive Neurophysiological Laboratory, St. Vincent's Hospital, Fairview with a 64 10/20 channel system. Hereafter, the number of recording electrodes was increased to 128 following an upgrade in the recording equipment. Data collection was then moved from Fairview to Trinity's Institute of Neuroscience. Twenty-one

participants had their data recorded using the 64 channel system whilst the remainder had their data recorded using the 128 high-density system. Both systems acquired data through the ActiveTwo BioSemi electrode system digitised at 512Hz with an open passband from DC to 150Hz.

In the analyses that followed, only the data from electrodes that occupied the same site on the scalp in the 128-channel and the 64-channel caps were used. These electrode sites were determined by digitising the electrode locations from both caps and projecting these digitised montages onto an average head which consisted of 81 channels, derived from the BESA 81-channel configuration (www.BESA.de). BESA requires only twelve electrodes for this to be done. BESA uses a spherical-spline-interpolation in this method, interpolating to an internally pre-defined set of 81 standard electrodes. The interpolation not only interpolates to new virtual electrode locations, but it also changes the reference; the interpolated data is in a so called "reference-free" montage i.e., the reference for each channel is the signal averaged over the whole scalp.

Only sweeps related to the isolated-check stimuli were included in the analysis for the P1 paradigm. Only sweeps related to correct responses to the target tones were included in the analysis for the P300 paradigm.

4.2.8. Genetic Analysis

The SNP rs1344706 was genotyped using a Taqman® SNP Genotyping Assay on a 7900HT Sequence Detection System (Applied Biosystems). The call rate for the Taqman genotyping

was 100% and samples were in Hardy-Weinberg equilibrium ($p>0.05$). Along with these samples, a number of HapMap CEU DNA samples (www.hapmap.org) were genotyped for rs1344706 for quality control purposes and were all found to be concordant with available online HapMap data for this SNP.

4.2.8.1. The P1 paradigm

Fourteen individuals were identified as homozygous for the "C" allele of the ZNF804A polymorphism, forty-seven as homozygous for the "A" risk allele and forty-one heterozygous. The control group consisted of thirty "A" homozygous, nine homozygous "C" carriers and thirty-one heterozygous.

4.2.8.2. The P300 paradigm

Forty-four individuals were identified as homozygous for the "A" risk allele of the ZNF804A polymorphism, fourteen "C" homozygous and forty-three heterozygous. The control group consisted of thirty-four "A" homozygous, seven "C" homozygous and thirty homozygous.

4.2.9. ERP Analyses

ERP analyses were performed using BESA Software Version 5.2.

4.2.9.1. The P1 paradigm

Grand averages were generated for each participant from the isolated-check stimuli only. For controls, approximately 698.79

+/- 208.45 sweeps per individual were averaged for the AA group and 669.18+/- 236.34 for the AC/CC group with an epoch of -200 to 1,000 msecs. For cases, approximately 823.44 +/- 246.83 sweeps per individual were averaged for the AA group and 658.50+/- 318.96 for the AC/CC group with an epoch of -200 to 1,000 msecs. The average number of bad channels for the AA group in controls was 10.43 +/- 7.31 and 10.08 +/- 4.34 for the AC/CC group. The average number of bad channels for the AA group in cases was 13.06 +/- 4.90 and 12.83 +/-4.61 for the AC/CC group. The P1 was analysed *as per* section 3.2.6.

4.2.9.2. The P300 paradigm

The average number of channels excluded in this manner from analysis was 11.66 +/- 7.13 for controls and 12.81+/- 6.90 for cases. The surrogate model (Berg & Scherg, 1991) was then used for further artifact correction. Artifact correction was based on the same method as for the P1 paradigm. Grand averages were generated for each correct response to the target sound only. For controls, approximately 59.85 +/- 23.41 sweeps per individual were averaged for the ZNF804A AC+CC genotype group and 67.03+/- 24.72 for the AA group with an epoch of -100 to 1,000 msecs. For cases, approximately 40.20 +/- 25.38 sweeps per individual were averaged for the AC/CC group and 48.40+/- 27.28 for the AA group with an epoch of -100 to 1,000 msecs. The average number of bad channels for the AC/CC group in controls was 11.35 and 12.31 for the AA group. The average number of bad channels for the AC/CC group in cases was 13.60 and 13.60 for the AA group. The P300 was defined as the positive waveform generated by the target tones and peaking between

250-550 post-stimulus (versus the 0μV baseline). A set of four scalp sites was chosen over midline scalp sites from which P300 amplitudes were extracted (FCz, Cz, CPz). These sites were chosen based on topographical analysis of the grand-average group data which revealed a midline-parietal topography consistent with that previously reported in the literature. 9 out of the 11 participants whose data was considered too noisy to be included in the P300 paradigm analysis were cases. In these cases, the pre-stimulus baseline activity contributed to excessive pre-stimulus activity differences across experimental paradigms i.e., across genotype groups. Therefore, any differences in measured amplitudes between conditions might potentially reflect pre-stimulus differences rather than post-stimulus differences. Although, the pre-stimulus baseline is not perfectly neutral (as is rarely the case), having removed this selection of cases, the voltage slopes during the pre-stimulus interval were considerably improved.

The current study was designed to investigate the association between the SZ risk variant rs1344706 and the ERP components, the P1 and the P300. These components were elicited during the performance of a task which included visual presentation of checkerboards, designed to stimulate the visual cortex and the P1 and the performance of an auditory odd-ball task, where, during responses to an odd-ball sound, the P300 was elicited. In the current study, a measure of P1 amplitude was defined as the area under the curve and the peak amplitude (vs the 0-uV baseline) in the interval 70-110msecs, spanning the P1 component, chosen based on grand average waveforms. A measure of P300 amplitude was defined as the area under the

curve and the peak amplitude, and mean amplitude (vs the 0-uv baseline) in the interval 250-550msecs, spanning the P300 component. For the P300, it was decided to also measure the mean amplitude over the time window. This is because the mean amplitude captures almost all the component and is less sensitive to the noise of the P300 than peak amplitude measures. Additionally, mean amplitude measures have the benefit of a linear measure i.e., the mean voltage from multiple single trials which are then averaged together will be equal to the mean voltage measures from the averaged waveform. Mean amplitude measures also negates any latency variability (Luck, 2010).

These measures were then submitted to a repeated-measures multivariate analysis of variance (MANOVA), using SPSS software (SPSS Inc., Chicago, Illinois Version 16.0), with between-subjects factor of diagnosis group (controls –v- cases) and genotype group (AC/CC versus AA carriers) and a within-subjects factor of region: left versus right with respect to the P1 and midline-central with respect to the P300. All tests were 2-tailed with a preset alpha-level of $p<.05$.

4.3. Results

4.3.1. P1 paradigm

The mean reaction time to targets (the checkerboard stimulus), the mean number of correct responses and the mean number of incorrect responses is outlined in Table 4.2. The mean rates did not differ significantly between genotype groups for cases or controls [p>.05] on any of these measures. These rates indicate

that subjects were actively engaged in this task and must have been centrally fixated to accurately identify target stimuli. Figure 4.1. is a map of the difference topography associated with ZNF804A. Subtraction of the grand-averaged waveforms of the AA homozygous group from the AC/CC group enables the difference effect to be isolated and mapped. As can be seen, there are no differences between genotype groups for either cases or controls. Figure 4.2. shows event-related potential morphology across the scalp for both groups (cases are represented on to the top left hand corner of each control representation) illustrating responses from six representative electrodes spanning the occipital scalp region.

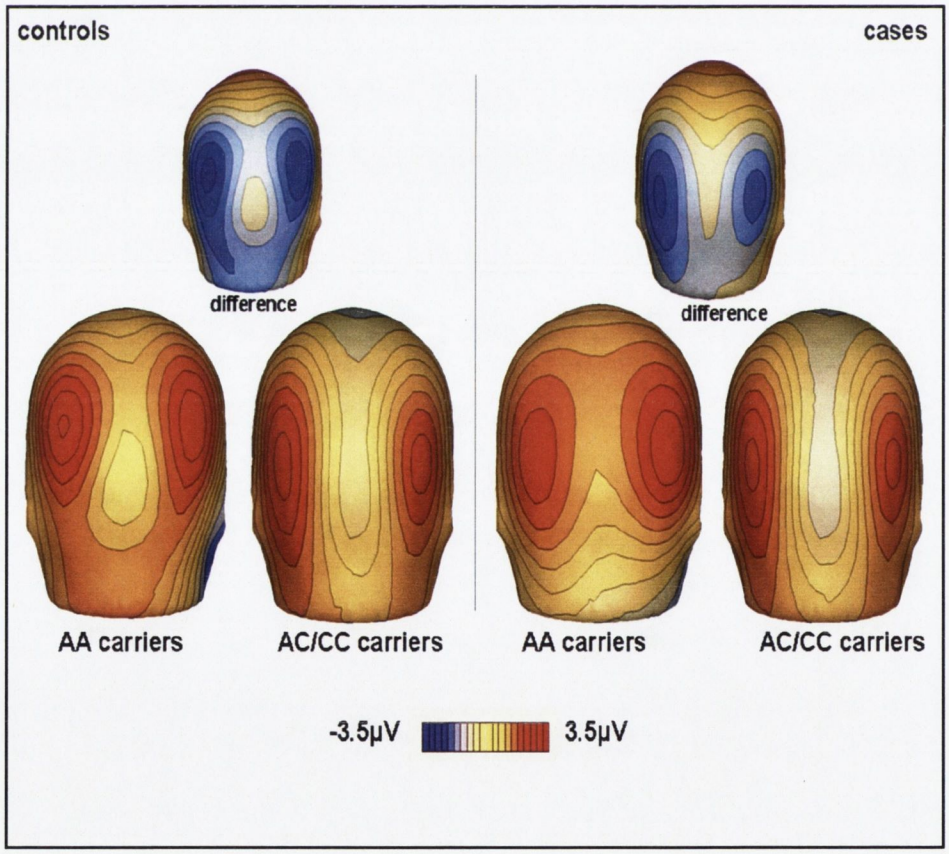

Figure 4.1. Mapping of the difference topography associated with ZNF804A. As can be seen, there are no differences between genotype groups for either cases or controls.

Table 4.2. Mean rates times (plus standard deviation) of correct responses, incorrect responses and reaction time.

	Cases			Controls		
	AC/CC	AA	comparison	AC/CC	AA	comparison
Mean Reaction Time (mean (s.d.))	447.31 (54.09)	462.56 (55.27)	t=.65 N.S.	433.50 (53.67)	444.07 (40.91)	t=.22 N.S.
Correct Responses (mean (s.d.))	180.88 (18.41)	172.36 (21.31)	t=.63 N.S.	193.31 (9.38)	188.86 (18.83)	t=.21 N.S.
Incorrect Responses (mean (s.d.))	34.94 (28.67)	32.60 (30.83)	t=.80 N.S.	12.08 (9.03)	14.43 (19.50)	t=.51 N.S.

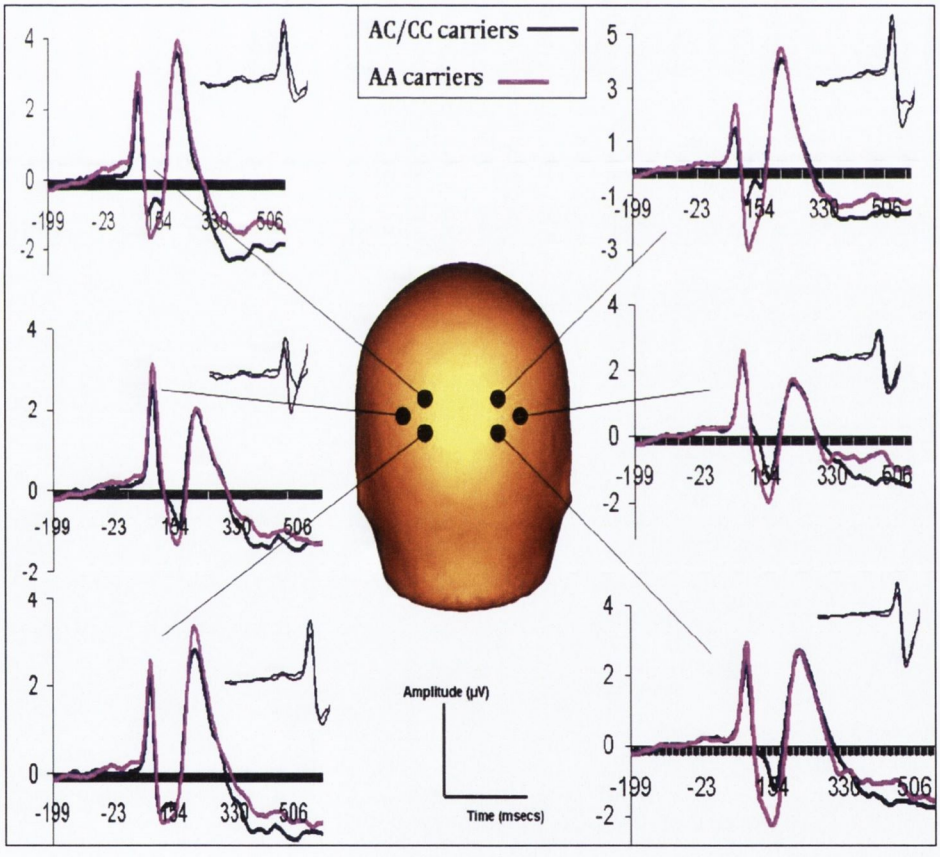

Figure 4.2. Event-related potential morphology across the scalp for both groups [cases are represented on to the top left hand corner of each control representation] illustrating responses from six representative electrodes spanning the occipital scalp region.

A multi-variate analysis of variance (2 classification groups x2 genotype groups x2 scalp regions) was used to compare P1 amplitudes between groups over the left and right lateral occipital visual areas. For the P1 (area under curve) there was no main effect of genotype observed for the left hemisphere [$F(1,113)=.20$, $p=.65$] or the right hemisphere [$F(1,113)=1.09$, $p=.29$]. There was also no interaction effect for the left hemisphere [$F(1,113)=.46$, $p=.49$] or the right hemisphere [$F(1,113)=.20$, $p=.65$]. There were also no significant main or interaction effects observed for the N1 or the P2 [$p>.05$].

4.3.2. P300 paradigm

Table 4.3. shows the behavioural responses for the P300 oddball task. There were no significant differences between genotype groups based on the number of targets, the number of correct responses and the number of errors made. Figure 4.3. shows contour maps of the different genotype groups across cases and controls. Figure 4.4. provides an overall illustration of morphology across the scalp for cases and controls across genotype groups from three representative electrodes in the midline, parieto-temporal region where the P300 was detected greatest.

Table 4.3. Mean rates times (plus standard deviation) of correct responses, incorrect responses and reaction time.

	Cases			Controls		
	AC/CC	AA	comparison	AC/CC	AA	comparison
Mean Number of Targets (mean (s.d.))	101.86(29.76)	108.12 (31.45)	t=-1.91 N.S.	101.86 (29.76)	94.90 (30.47)	t=-.98 N.S.
Correct Responses (mean (s.d.))	98.37 (29.47)	103.47 (29.86)	t=-1.25 N.S.	98.37 (29.47)	94.14 (30.62)	t=-.82 N.S.
Incorrect Responses /Errors (mean (s.d.))	0	0	N.S.	0	0	N.S.

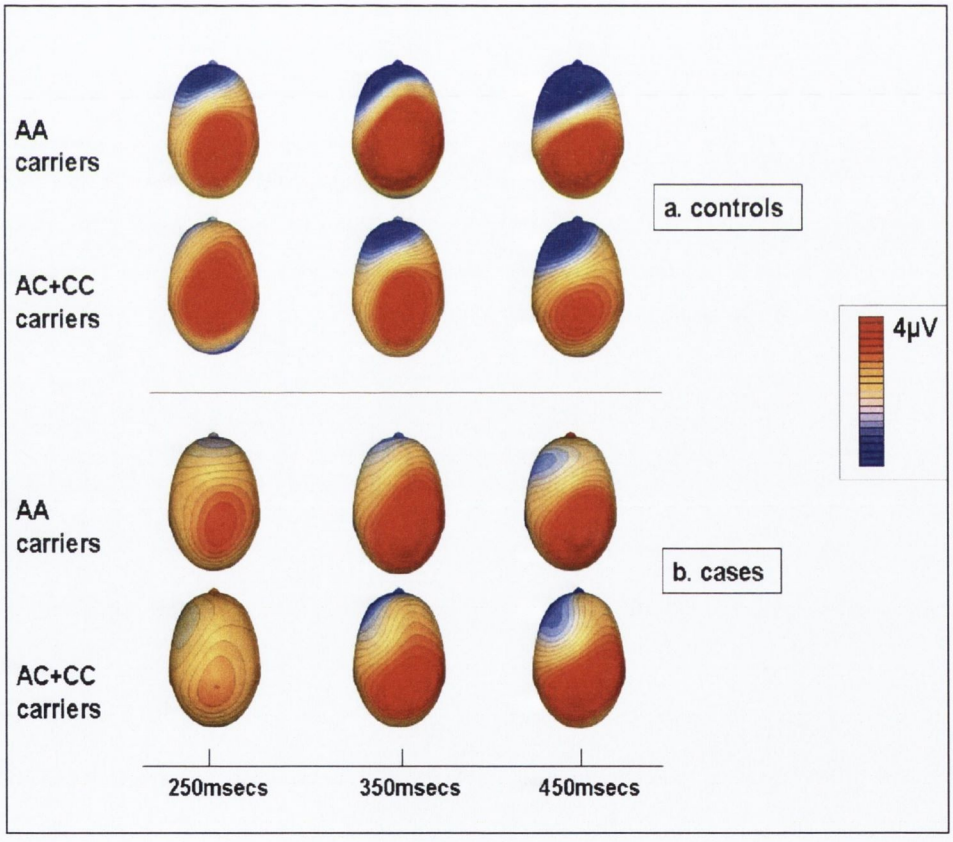

Figure 4.3. Mapping of the topography associated with ZNF804A as illustrated by contour maps taken at 250, 350 and 450 msecs representing the P300 component.

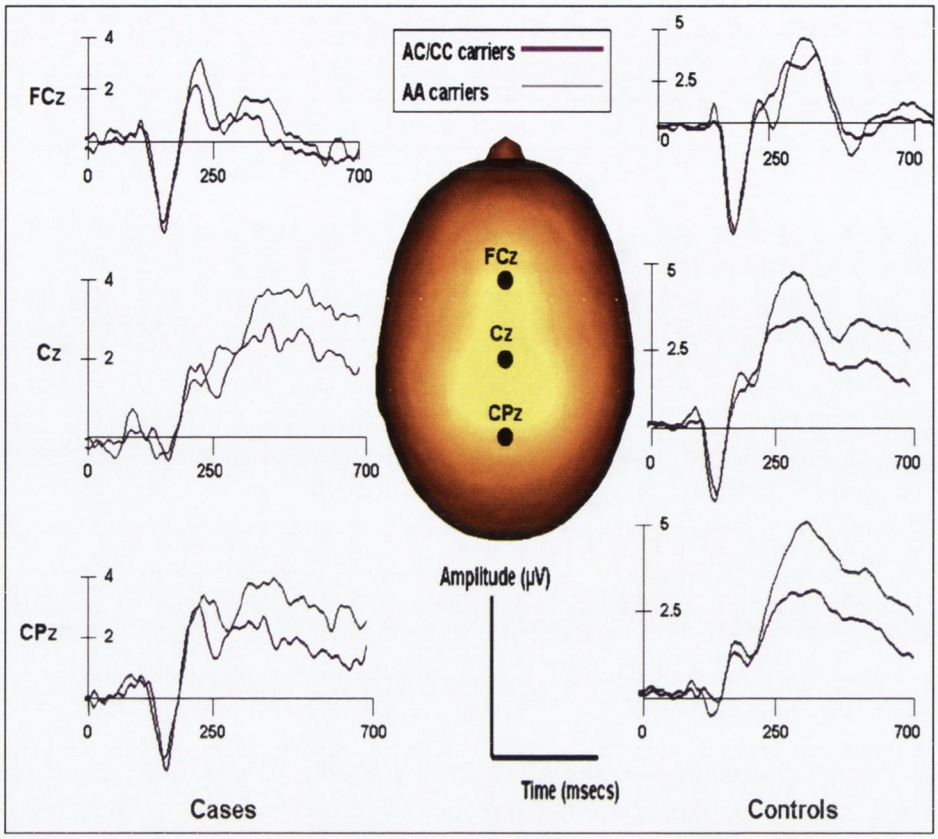

Figure 4.4. Event-related potential morphology across the scalp for both genotype groups [AC/CC carriers in purple; AA carriers in grey] illustrating responses from the three representative electrodes FCz, Cz and CPz spanning the temporo-parietal scalp region.

The electrode sites FCz, Cz and CPz were entered into a repeated measures analysis of variance (2 diagnosis groups x2 genotype groups x3 scalp sites). For electrode CPz there was a main effect of genotype found for area under the curve measures [$F(1,97)=7.55$, $p=.007$]. There was also a main effect of genotype for peak amplitude measures at CPz [$F(1,97)=5.26$, $p=.02$]. There was no interaction effect found at CPz for genotype and diagnoses groups. To capture the whole component, and overcome issues of latency variability and lack of linearity between single trial and grand average waveform measures, mean amplitude measures were also tested using multi-variate-analysis of variance. There was a main effect found for ZNF at electrode site

CPz [F(1,101)=7.44, p=.008]. In both cases and controls, homozygous risk-allele carriers had greater mean amplitudes than AC/CC carriers [Cases: AA carriers mean=3.22 +/- 2.48; AC/CC carriers mean=2.28 +/- 1.84]; [Controls: AA carriers mean=4.22 +/- 2.49; AC/CC carriers mean=2.61 +/-1.51].

Grand average morphologies seemed to indicate that the association with ZNF was being driven by differences between AC/CC carriers and AA carriers in the control group, with homozygous risk allele carriers demonstrating greater amplitudes than the AC/CC group. In controls alone, there were significant differences between genotype groups for peak amplitude measures [F(1,67)=5.11, p=.02], area under the curve measures [F(1,67)=8.23, p=.006] and mean amplitude measures [F(1,71)=11.06, p=.001] respectively. For cases alone, there were no significant differences found for peak amplitude [F(1,30)=1.68, p=.20], area under the curve measures [F(1,30)=1.34, p=.25] or mean amplitude measures [F(1,30)=1.37, p=.25] at CPz.

4.4. Discussion

ZNF804A is the first gene to achieve genome wide level significance for association with schizophrenia, an association that has now been replicated in several additional samples. The mechanism by which SZ risk is being increased by ZNF804A is unclear, although work by several groups suggests that this risk may be independent of an effect on neuropsychological measures of cognition. Previous work by our own group suggests that the identified risk "A" allele at ZNF804A might be associated with

relatively spared cognitive function, particularly for neuropsychological indices of episodic and working memory. The purpose of the present study was to investigate whether the identified risk 'A' allele at the disease-associated SNP rs1344706 was associated with variation in electrophysiological cortical responses to either visual sensory or auditory information using EEG in cases and controls. For the auditory P300 a main effect of genotype was found at the electrode site CPz for genotype for both area under the curve, peak amplitude and mean amplitude, again indicating that "AA" risk carriers had a greater cortical response compared to non-risk "AC/CC" carriers. No effects of ZNF804A was observed for any of the earlier visual P1, the N1 or the P2 responses.

A central tenet of the intermediate or endophenotype approach in SZ genetics research is that the mechanism by which SZ risk is increased by genetic variants is via a deleterious effect on brain structure or function. In this view, risk for clinical diagnosis is thought to be mediated in whole or in part via the effects on brain structures which subserve cognitive processes. Examples that support this view include Dysbindin, COMT, and NRG1 (Donohoe et al., 2007; Egan et al., 2001; Hall et al., 2006). By contrast, the results of the current study suggest that not only was ZNF804A not associated with a deleterious effect on the measures of cortical processing indexed (visual P1, N1, P2, auditory P3), homozygous risk allele carriers actually show a heightened P300 cortical response relative to non-carriers.

In so doing the current findings tie in with early findings from our lab that this risk allele is associated with relatively preserved

components of cognitive functioning in patients (Walters et al., 2010). In this earlier study, patients who were risk carriers had smaller deficits in performance during both auditory and visual working memory and episodic memory tasks in large independent samples of Irish and German patients [in the current study, there was less of a P300 response]. Although the P300 is not in itself a direct homologue of memory processes *per se*, the P300 has consistently been associated with memory engagement and memory processing following initial stages of stimulus evaluation and working-memory load has also been shown to affect the P300 component (Azizian & Polich, 2007; Donchin, 1981; Donchin & Coles, 1988; Kok, 2001; Oliveira et al., 2011; Wijers et al., 1989). Finding an association between relatively larger P300 responses and ZNF804A risk carrier status again suggests a relative advantage for carriers in cortical processes that may be relevant to the integrity of structures involved in memory and attentional processes. That the association found here may relate to such cortical processes is further supported by the previous report from our group, based on cases and controls not included in the present study, in which ZNF804A was associated with larger grey matter hippocampal volumes (Donohoe, 2010).

The present study also extends earlier findings by revealing that the association between ZNF804A and relatively stronger auditory P300 response was seen in both patients *and* in healthy controls. One explanation as towards understanding why an effect of ZNF804A was seen here in healthy controls in the present study but not in previous behavioural or structural imaging studies is that it has consistently been maintained that

imaging techniques have greater power to show association with risk variants (Meyer-Lindenberg & Weinberger, 2006; Kempf & Meyer-Lindenberg, 2006). For example, Flint & Munafo (2007) and Mier et al. (2010) found that the highest effect sizes were for functional imaging studies, ahead of neurocognitive-behavioural measures. Electrophysiological measures came in at a close second to imaging studies in revealing how variants are producing their effects. Finding association with healthy control subjects in the present study may suggest that the P300 represents an endophenotype more closely related to the ZNF804A risk genotype than phenotypes. In summary, the context of earlier behavioural evidence implicating ZNF804A and preserved memory function, the earlier structural MRI evidence associating the ZNF804A risk allele with preserved hippocampal volumes, the present study based on auditory evoked responses again supports ZNF804A's role in functions associated with memory engagement.

Collectively, the above findings are confusing: how might a by now replicated common variant associated with increased risk for SZ be associated with relatively unimparied memory function, given the prevalence of memory deficits seen in SZ? Earlier studies on ZNF804A (Walters, 2010, Donohoe et al., 2010) argued that these findings suggested that the ZNF804A risk allele was not associated with better cognitive function and larger grey matter hippocampal volumes but instead with preserved cognitive function and cortical volume *relative* to non-carriers. This argument rested on the fact that these associations were seen in patients only and not in healthy controls. The authors argued that for these patients, their ZNF804A-associated

pathway into SZ was relatively independent of the cognitively deleterious pathway into SZ associated with other risk factors. Further support for this interpretation came from the evidence that the association between ZNF804A and SZ risk increased when lower IQ patients were excluded. This hypothesis was supported by the fact that the psychosis risk associated with ZNF804A's is not specific to schizophrenia but includes bipolar disorder (Williams et al., 2010), in which traditional neuropsychological deficits are less significant (see Krabbendam, Arts, van Os & Aleman, 2005 for a review). It is also well established that schizophrenia as clinically defined is symptomatically heterogeneous and a substantial subset of patients (~20-40%) have a relatively good outcome (Breier, Schreiber, Dyer & Pickar, 1991). The effect of ZNF804A was possibly either an illness modifier, or a marker for this patient group. The findings of the present study, however, by showing a similar association with healthy controls, suggest the need to re-appraise this explanation. While it might have made sense to argue that ZNF804A risk carrying patients appeared relatively preserved by comparison with patients carrying other risk factors, there is no reason to believe that healthy controls are enriched for other (i.e. non-ZNF804A) cognitively deleterious risk factors so as to make the ZNF804A risk carriers look relatively better.

The alternative but counter-intuitive explanation of these findings is that the ZNF804A risk variant actually confers a small but statistically significant advantage to carriers either as part, or independently, of the mechanism by which SZ risk is being increased. In this context, it is interesting to note the reports of

Esslinger et al (2009) and Walter et al (2010) with regard to healthy controls. Esslinger et al. reported both hypo- and hyper-connectivity associated with the ZNF804A risk allele in their sample. Neither kind of dysconnectivity was associated with variation in behavioural performance during the working memory paradigm used in the study; neither were regional differences in activations associated with ZNF804A observed. They concluded that both forms of dysconnecivity was deleterious either because of impaired coupling bilaterally within dorsolateral pre-frontal cortex (in the case of hypo-connectivity) or a failure to de-activate aspects of the default mode network between dorsolateral pre-frontal temporal, and amydala regions (in the case of hyperconnecivity). Following on the evidence above of the association between ZNF804A and memory function, the present study suggests that the cortical effects of this altered connectivity is not associated with a deleterious impact on the associated cortical regions but may actually have a facilitative effect.

By comparison, Walter et al (2010) and Esslinger (2010) suggest that altered connectivity in other brain regions may have a deleterious effect not on cortical processes underlying memory function, but instead on aspects of social cognition. In a Theory of Mind study, which involves comparing the mental state decoding and reasoning response of ZNF804A risk carriers to non-risk carriers, the risk carriers were observed to show significant impairments relative to the non-carriers. In light of the evidence that (1) that ZNF804A's association with psychosis is not specific to schizophrenia but includes bipolar disorder (in which cognitive deficits are less apparent) and (2) that ZNF804A has

been associated with small increases in affective symptoms (Cummings, 2010), (3) the relatively strong P300 seen in carriers together with the problems with social cognition and affective processing seen elsewhere may reflect a double dissociation in ZNF804A's cortical impact. Such double dissociations are not uncommon in neurological and psychiatric disorders. By this means, variation at this marker would be functionally dissociated by two types of tests, indexing social functioning and memory functioning, each aspect of cognition being affected by variation in one portion without impacting the other.

Accordingly, ZNF804A could be impacting social and non-social cognitive processes differently. There is some evidence in the literature that social cognition may for example be subserved by a system of brain regions neuroanatomically distinct from those involved in cognitive processes (Frith & Frith, 2001; Gallagher & Frith, 2003) and by implication, may be engaging slightly different brain networks (Mitchell, Macrae & Banaji, 2004). Inevitably, further studies of both memory function and social cognition will be required to substantiate such a dissociation. Supporting such associations is challenging, with the potential for both false positive and false negative reports from smaller studies likely to add to these difficulties, evidence for which is likely to be challenged not least by smaller studies likely to report both false positives and false negatives (e.g. Hashimoto et al., etc).

4.4.1. Methodological considerations

The above-average IQ of the control sample might be a point of contention in this study and may even have affected the results. This bias towards above-average IQ controls stems from the opportunistic sampling method used in recruiting participants who were generally recruited via local advertising on a national volunteering website and on posters located around the city. The nature of the research may unwittingly have appealed to those from a higher IQ group who were eager to participate in this type of study. It would be of interest to repeat the current study in an independent control sample with an IQ in the average range to better represent the general population. However, it must be noted that the current control sample was not exactly chosen randomly. The participants in this study are a subset of participants who previously took part in our behavioural and imaging studies that were agreeable to return to participate in an EEG study (see Walters et al., 2010). Another issue might be that cases contributed to the minority of the sample. Although the overall genotype effect was found in an overall sample of 101 individuals, it would be interesting to follow up this research with a larger case sample to confirm that with greater power from this group, the effect of genotype would still prevail. Another issue is that of combining genotype groups. In the current study, the AC/CC groups were grouped together as the frequency of the CC genotype was too low individually to allow it to be representative of itself individually. Future replication studies could also include a sample where AC and CC groups are better individually represented.

4.4.2. ZNF804A functional studies

The SNP rs1344796 is located in an intron of ZNF804A, mapping to a region on 2q32.1. As previously stated, it is by far the most robust SNP associated with SZ to date. This SNP at rs1344706 has achieved genome-wide significance for psychosis in several independent studies (Riley et al 2009; Shi et al 2009; Steffanson et al., 2009; Steinberg et al., 2010; Zhang et al., 2010), representing a common variant of small effect. Although known to be brain expressed, little else is known about the biological function of ZNF804A. The fact that this gene contains a zinc finger suggests that it may be a transcription factor - recent bioinformatic analysis suggest exactly that (Riley et al., 2009). Functionality studies also suggest a role for it as in ZNF804A messenger-RNA expression, with the risk allele being associated with higher expression (Williams et al., 2010). Buonocore et al., (2010) found differences in allelic expression between brain regions including the temporal cortex, parietal cortex, amygdala, hippocampus, nucleus accumbens and caudate at another SNP, rs12476147 of ZNF804A, demonstrating the *cis*-effects on RNA expression of ZNF804A across the brain. Linkage disequilibrium mapping has also shown that rs1344706 is by far the most strongly associated marker in the gene (Williams et al., 2010).

4.5. Conclusion

The current study sought to elucidate the phenotypic effects of an identified risk allele on indices of cortical synaptic function, at a temporally accurate perceptual stage of cognition. In this study, carrying two copies of this risk allele at rs1344706 was

associated with variation in performance in the P300 ERP with risk carriers demonstrating a greater magnitude of response. The results of this study support the idea that this risk variant is relatively advantageous in cognitive information processes associated with memory and attention and supports the position that not all genetic risk factors may be having a deleterious impact on brain function. These kinds of findings help to understand the molecular and cortical responses as impacted by ZNF804A. Although this variant is of unknown function, this study improves our understanding of the molecular biology of SZ by demonstrating how this variant has a beneficial impact on cortical function, which lies on a cognitive pathway associated with attention and memory and which is indepenent of diagnosis. If this finding is replicated in the future with independent case/control samples, it may have important implications for the way we understand how cognition is structured generally and the pathways into SZ.

Chapter 5

A neurophysiological investigation of the genome-wide associated SZ risk variant NRGN rs12807809

Abstract

The NRGN gene has been implicated in schizophrenia susceptibility by recent genome-wide-association studies. The current study aimed to investigate whether the risk associated single-nucleotide-polymorphism at rs12807809 is also associated with variation in electrophysiological cortical response in cases and healthy controls. We previously failed to find any association between this variant and cognitive performance on a range of neuropsychological tests, despite evidence that NRGN is strongly linked to cognition. A comparison was performed of both cases and controls grouped according to their NRGN genotype (TT v CC/CT) and the event-related-potentials the P1 and the P300. Significant differences between TT and CC/CT carriers were observed in healthy controls and cases in both the P1 and the P300 event-related-potentials. This finding indicated that this polymorphism was influencing both automatic sensory and higher cognitively mediated levels of processing as measured by the P1 and P300 respectively. The current findings are consistent with the known biology of NRGN and its role in calcium-calmodulin binding and NMDA receptor functioning. Calcium-calmodulin is involved in synaptic plasticity and long-term-potentiation, believed to be part of the cellular mechanism by which memories are formed. Evidence also suggests that NMDA mediates the magnocellularly driven P1. It

seems likely that NRGN could be mediating its effects on SZ via its role in synaptic function, and is likely to be relevant not just to SZ pathophysiology but to normal cognitive variation as well.

5.1. Introduction

The single nucleotide polymorphism (SNP), rs12807809 is located 3,457 bases upstream from the neurogranin gene and identified as being associated with SZ. The original genome-wide-association study by Stefansson et al., (2009) included 2663 SZ cases and 13,498 controls from eight European locations within the SGENE consortium. They then combined findings from the top 1,500 markers with results for these same marks from both the International-Schizophrenia-Consortium (ISC) (2602 cases/2885 controls) and the European-American portion of the Molecular Genetics of SZ (MGS) (2687 cases/2656 controls) study. The top markers were followed up in 5013 cases and 15,559 controls from four sets of additional samples from Europe samples, leading to the identification of three novel SZ loci namely: Neurogranin, TCF4 and the human leukocyte antigen (HLA) region. The marker rs12807809 from the Neurogranin gene (NRGN) has a combined odds-ratio (OR) of 1.15 with no significant OR heterogeneity between the study groups (p=.74). Recently, a GWAS was performed using a large Chinese case-control study (2496 cases/ 5184 controls), which broadly replicated the association findings of Stefansson et al., (2009) for chromosome 6 (SNP rs6932590) and TCF4 but failed to confirm any association with SNP rs1280709 in the NRGN gene (Li et al., 2010).

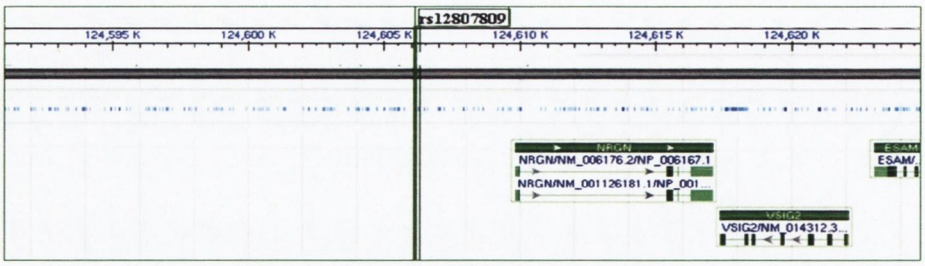

Figure 5.1. The SNP rs12807809, located 3,457 bases upstream from the NRGN gene has been associated with SZ.

The human neurogranin (NRGN) gene (see Figure 5.1.) is located on chromosome 11 in the region 11q23.3-q24.1. This gene spans twelve kilo-bases and contains four exons and three introns (de Arrieta, Jurado, Bernal & Coloma, 1997) and is a calmodulin binding protein (Devireddy & Green, 2003). Its first two exons include the nucleotide sequence that encodes the complete 78 amino-acid sequence of neurogranin (Mertsalov et al., 1997). NRGN is the main post-synaptic protein regulating the availability of calmodulin. Calmodulin is a calcium-binding protein expressed in all eukaryotic cells. A role for calcium/calmodulin-dependent-protein-kinase has been extensively researched in models of synaptic plasticity and studies of long-term-potentiation (Funauchi, Tsumoto, Nishigori, Yoshimura, Hidaka, 1992; Lledo, Hjelmstad, Mukherji, Soderling, Malenka & Nicoll, 1995; Malinow, Schulman & Tsien, 1988 & Silva, Stevens, Tonegawa & Wang, 1992).

Its association with long-term-potentiation (LTP) stems from its binding with calmodulin. During LTP, high-frequency stimulation to synaptic excitatory pathways causes a sustained increase in the efficacy of synaptic transmission. This model has come to dominate models of synaptic plasticity and memory formation (Bliss & Collingridge, 1993). During the induction of LTP,

depolarisation of the post-synaptic cell takes place. Magnesium (Mg^{2+}) becomes dissociated from its binding site within the NMDA receptor, allowing calcium (Ca^{2+}) to enter the spine. The local increase in Ca^{2+} within the spine allows calmodulin to be in its Ca^{2+} binding conformation and activates subsequent targets. A relatively large increase in Ca^{2+} concentration occurring over a short period of time activates Ca^{2+}/calmodulin-dependent-protein-kinase-II (CaMKII), leading to the induction of LTP by activating downstream effectors (Zhong, Cherry, Bies, Florence & Gerges, 2009). As neurogranin is one of the most abundant post-synaptic calmodulin-binding proteins (Alvarez-Bolado et al., 1996; Gerendasy et al., 1994a; Represa et al., 1990; Watson et al., 1994; Zhabotinsky et al., 2006), its targeting of calmodulin within the spine enhances the probability of inducing LTP (Gerendasy, 1999; Prichard et al., 1999; Zhabotinsky, Camp, Epstein & Lisman, 2006).

Induction of long-term-potentiation (LTP) is known to depend on Ca^{2+}/calmodulin-dependent protein kinase II (Zhabotinsky, Camp, Epstein & Lisman, 2006). Calmodulin and Calmodulin kinase II inhibitors suppress the induction of LTP (Lovinger et al., 1987; Malinow et al., 1988; Reymann et al., 1988; Malenka et al.,1989; Malinow et al., 1989). The functional role of calmodulin/NRGN in synaptic-plasticity has been suggested in both human and animal studies. Zhong et al., (2009) found that mutants of NRGN are incapable of calmodulin-binding and unable to enhance synaptic-transmission. Mutants of NRGN were found to be incapable of releasing calmodulin with the ensuing increase in Ca^{2+} concentration, and lacked the ability to potentiate synaptic transmission. They found that acute knock-

down of NRGN blocked LTP induction and that NRGN was regulating the availability of calmodulin within the dendritic spine. Alpha-calcium/calmodulin-dependent-protein-kinase-II deficient mice have also demonstrated diminished visual cortical plasticity (Gordon, Cioffi, Silva & Stryker, 1996; Huang, Huang, Jager, Reyman & Balschun, 2004). Likewise, Pak et al., (2000) found that deletion of the Ng gene (the equivalent of the NRGN gene in mice) caused impairment in spatial learning and alterations in hippocampal short and long term plasticity. As expected, these deficits were accompanied by a decreased basal level of the activated calcium/calmodulin dependent kinase II. In these mutant mice, the basal level of the activated CaMKII was reduced to about 60%. In another mouse study, short-term-memory formation was disrupted by alteration to alpha-CaMK-II (Wang et al., 2008).

Although LTP has traditionally been associated with the hippocampus in both rodent and human brains, a functional role of synaptic plasticity in other brain regions, such as the pre-frontal-cortex has also been implicated. This is an area of the brain which also receives projections to and from the thalamus, hippocampus, amygdala and sensory cortex. Not surprisingly, disruptions to the pre-frontal-cortex have also been associated with synaptic plasticity impairments, with the suggestion that the pathophysiology of SZ may be influenced by disruptions to this region (Goto, Yang & Otani, 2010). Two studies of note concerning SZ and NRGN find evidence of pre-frontal-cortex disruption. Broadbelt, Ramprasaud & Jones (2006) examined the expression of NRGN in the pre-frontal-cortex using tissue from seven cases with SZ and seven controls, finding a significant

reduction in its expression in layers III and V. This reduction was produced by the loss of protein produced by cells with alteration occurring at calcium-calmodulin dependent pathways. Ruano et al., (2008) studied the association between NRGN and SZ in 244 cases and 210 controls and found association with a SNP rs7113041.

Recently, the association between rs12807809 and cognitive deficits in SZ has been investigated in an Irish and German case/control sample (Donohoe et al., 2010). In the Irish sample, working memory, episodic memory and attentional control were measured. Working memory was measured using the Letter-Number-Sequencing task from the WAIS and Spatial-Working-Memory-Task from the Cambridge Test Automated Battery (CANTAB). Episodic memory was measured using the Logical Memory task of the WMS-III. This was measured both immediately (Logical Memory I) and after a delay (Logical Memory II). The other episodic memory task included the CANTAB Paired-Associated-Learning task. Attentional control was measured using the Continuous-Performance-Task and the Intra-Extra-Dimensional task from the CANTAB. For the German sample, working memory was measured using the WAIS digit span and the WMS spatial span. Episodic memory was measured using Logical Memory I (immediate) and Logical Memory II (delayed) and the WMS visual memory task. Attentional control was measured using the Continuous Performance Task and the Wisconsin Card Sorting Task. Both groups were also tested for their general cognitive ability (IQ) as measured by an abbreviated version of the Wechsler Adult Intelligence Scale (WAIS-III).

No association was found for any of the neuropsychological variables assessed in both the Irish or subsequently, the German sample. This is despite many of the samples included in this study having been included in the ISC replication of NRGN as a risk variant in the original study by Stefansson.

Rs12807809 is a genome-wide supported risk variant in SZ, located upstream of the NRGN gene which encodes post-synaptic protein-kinase (Stefansson et al., 2009; O'Donovan et al., 2008;) and is involved in long-term-potentiation, the molecular basis of learning and memory, through its interaction with calmodulin binding proteins. This marker itself is not in a protein-coding region and its functional effects on the NRGN have yet to be clarified. This marker may still have consequences for gene splicing and transcription factor binding upstream from a gene which is a strong candidate risk variant in SZ. The original GWAS identified "T" as the risk allele. The allele distribution at rs12807809 in all published association for C-allele in SZ cases is .16 and .18 in healthy controls. The allele distribution of the T-allele in SZ cases is .84 and is .82 in healthy controls. This means that homozygous non-risk "CC" carriers are difficult to come by in any opportunistic sample.

One argument made in the SZ genetics endophenotype literature is that imaging based endophenotype (e.g. fMRI, ERP based EEG) may represent more sensitive modalities for identifying the effects of risk variants on cortical function than behavioural measures (Meyer Lindenberg & Weinberger, 2006). On this basis, the present experiment seeks to establish the influence of this risk variant on cortical activaton as measured by EEG.

Specifically, the basic neuroanatomical modulars of visual perception and cognitive processing by which risk may be increased are being explored. NRGN has previously been associated with SZ and is therefore likely to contribute risk at least in part via a deleterious effect on cognition (Stefansson et al., 2009). NRGN has also previously been implicated in long term potentiation (LTP), an important cellular basis for memory function (Wang et al., 2008; Zhong et al., 2009). While we previously failed to find evidence of this at a behavioural level (Donohoe et al., 2010) we hypothesised that this risk variant influence on the cortical processes underlying higher cognitive functions such as memory might be more apparent using EEG measured ERPs. In particular, in light of the fact that P300 is thought to index memory related cortical activity, it was hypothesised that NRGN risk "T" carriers might show lower evoked potentials during performance on this paradigm. Finally, an exploratory hypothesis was included that NRGN may have a role in sensory processing as measured by the visual P1 because the magnocellular stream's contribution to the P1 ERP is mediated by NMDA receptors (Butler et al., 2005; Fox, Sato & Daw, 1990; Kwong, Nelson, Toth & Sur, 1992) and NRGN is associated with NMDA receptor processing through NDMA's links with calmodulin protein binding.

5.2. Method

5.2.1. Participants

As per section 2.2.1.

5.2.2. Patient recruitment

As per section 2.2.2.

5.2.3. Recruitment of healthy participants

As per section 2.2.3.

5.2.4. Demographic information

As per section 2.2.4.

5.2.5. Clinical Assessment of patients

As per section 2.2.5.

5.2.6. Clinical screening of healthy participants

As per section 2.2.6.

5.2.7.1. P1 paradigm

150 participants completed the P1 paradigm. From this number, 20 data sets had to be removed due to excessive noise, rendering their data sets unusable. Clean data was important in order to lend confidence and stronger conclusions around any experimental effects found. In such instances, artifact correction failed to compensate for participants who consistently blinked during collection of the EEG or who emitted continuously high-amplitude alpha activity. A further 17 participants had no

genotype information available on rs12807809. In the end, clean data and genotype information was available for 113 participants on the P1 task. Demographic details for participant groups for the P1 are included in Table 5.1.

5.2.7.2. P300 paradigm

134 participants completed the P300 paradigm. From this number, 13 data sets had to be removed due to noise with the same intentions as for the P1 in terms of maintaining a clean data set. A further 24 participants had no genotype information available for this SNP. In the end, clean data and genotype information was available for 97 participants on the P300 paradigm. Demographic details for participant groups for the P300 are outlined in Table 5.3.

Table 5.1. Demographics by group (controls –v- cases) and NRGN genotype (TT –v- CC+CT) for age, gender, years of education, symptomatology (PANSSpos, PANSSneg, SAPSP, SANSN) and medication for the P1 paradigm.

	Cases			Controls		
	TT	CC/CT	Comparison	TT	CC/CT	Comparison
	(n=31)	(n=10)		(n=48)	(n=24)	
Age (years mn (sd))	45.94 (12.02)	44.70(11.47)	t(.77)= N.S.	40.37(12.56)	34.12 (11.65)	t(.042)= sig
Gender (% female)	10 (67.7%)	5 (50%)	x2(.65)= N.S.	24 (47.9%)	12 (50%)	x2(.77)= N.S.
Education (years: mn (sd))	13.33 (2.53)	13.60 (1.89)	t(.76)= N.S.	16.48 (2.25)	16.00 (1.76)	t(.45)= N.S.
PANSSpos (mn (sd))	27.91 (7.89)	26.60 (4.15)	t(.66)= N.S.			
PANSSneg (mn (sd))	24.84 (15.66)	18.80 (9.85)	t(.35)= N.S.			
Chlorpromazine equivalent (mn (sd))	642.10 (586.96)	358.30 (145.58)	t(.30)= N.S.			

Table 5.2. Demographics by group (controls –v- cases) and NRGN genotype (TT –v- CC+CT) for age, gender, years of education, symptomatology (PANSSpos, PANSSneg, SAPSP, SANSN) and medication for the P300 paradigm.

	Cases			Controls		
	TT (n=20)	CC+CT (n=9)	Comparison TT (n=46)	CC+CT (n=22)	Comparison
Age (years mn (sd))	45.63 (9.59)	42.89 (10.15)	t=.50	39.78 (12.82)	33.95 (10.83)	t(.07)=N.S.
Gender (% female)	36.80%	44.40%	x^2(.33)=N.S.	47.80%	50%	x^2(.25)=N.S.
Education (years: mn (sd))	12.95 (2.01)	13.67 (2.00)	t(.38)=N.S.	16.41 (2.33)	16.23 (1.77)	t(.74)=N.S.
PANSSpos (mn (sd))	27.25 (5.57)	26.60 (4.15)	t(.79)=N.S.			
PANSSneg (mn (sd))	21.58 (5.97)	18.80 (9.85)	t(.58)=N.S.			
Chlorpromazine equivalent (mn (sd))	718.60 (519.50)	385.50 (152.66)	t(.26)=N.S.			

5.3. EEG Stimuli and Presentation

5.3.1. The P1 paradigm

As outlined in section 3.2.2.

5.3.2. The P300 paradigm

As outlined in section 4.2.6.2.

5.3.3. Electrophysiological Data Acquisition

High-density event-related potentials (ERPs) were acquired from 64 (21 participants for the P1 paradigm; 21 for the P300 paradigm) and 128 scalp electrodes (129 participants for the P1 paradigm and 102 participants for the P300 paradigm). For the 72 scalp electrode participants, that data was acquired through the ActiveTwo BioSemi electrode system digitised at 512Hz with an open passband from DC to 150Hz. The 128 scalp electrode

data was also recorded using the ActiveTwo BioSemi electrode system digitised at 512Hz with an identical passband. In the analyses that follow, only the data from electrodes that occupied the same site on the scalp in the 128-channel and the 64-channel caps were used as previously outlined in section 4.2.7.

5.3.4. Genetic Analysis

The SNP rs12807809 was genotyped using a Taqman® SNP Genotyping Assay on a 7900HT Sequence Detection System (Applied Biosystems). The call rate for the Taqman genotyping was 100% and samples were in Hardy-Weinberg equilibrium ($p>0.05$). Along with these samples, a number of HapMap CEU DNA samples (www.hapmap.org) were genotyped for rs12807809 for quality control purposes and were all found to be concordant with available online HapMap data for this SNP. Only one participant (a case) was identified as a CC genotype carrier. Evidently, the number of homozygous non-risk "C" allele individuals was very low in this sample. In the original GWAS study which identified the genome-wide significant marker (p=2.4 x 10-9) at 11q24.2 (Stefansson et al., 2009). It was stated that the risk allele in this instance was "T." Obviously, the current sample does not afford the opportunity to compare homozygous "C" carriers with homozygous "T" and heterozygous "CT" carriers. Therefore it made sense to group the "CT" and the "CC" carriers together. This was also a strategy previously employed during the association study between NRGN and cognitive functioning (Donohoe et al., 2010). Here, there was also a low frequency of homozygous C allele carriers for the neuropsychological analyses, so individuals were grouped as

homozygous T carriers versus homozygous and heterozygous C carriers (i.e., TT –v- CT/CC). This low frequency of C allele carriers is anticipated. In a European population, the allele frequency is distributed such that 71% will be TT homozygous, 21% will be CT heterozygous and .06% will be CC homozygous (www.ncbi.nlm.nih.gov/snp=rs128078090).

5.3.4.1. The P1 paradigm

For statistical analyses, therefore, participants were grouped as CC/CT carriers (controls: n=24; cases: n=10) and TT genotype carriers (controls: n=48; cases: n=31).

5.3.4.2. The P300 paradigm

Participants were grouped as CC/CT carriers (controls: n=22; cases: n=9) and TT genotype carriers (controls: n=46; cases: n=20).

5.4. ERP Analyses

5.4.1. The P1 paradigm

The average number of channels excluded from analysis was 10.49 +/- 5.96 for controls and 13.08 +/- 5.40 for cases. For controls, approximately 70.30 +/- 22.61 sweeps per individual were averaged for the TT group and 69.35+/- 23.17 for the CT group with an epoch of -200 to 1,000 msecs. For cases, approximately 69.50 +/- 20.58 sweeps per individual were averaged for the TT group and 65.00+/- 18.87 for the CT group

with an epoch of -200 to 1,000 msecs. The average number of bad channels for the TT group in controls was 9.94 and 11.39 for the CT group. The average number of bad channels for the TT group in cases was 12.33 and 15.50 for the CC/CT group. The P1 was analysed as outlined in section 3.2.6.

5.4.2. The P300 paradigm

The average number of channels excluded in this manner from analysis was 11.66 +/- 7.13 for controls and 13.52 +/- 7.69 for cases. The surrogate model (Berg & Scherg, 1991) was then used for further artifact correction. Artifact correction was based on the same method as for the P1 paradigm and is as outlined in sections 2.2.8 & 2.2.9. Grand averages were generated for each correct response to the target sound only. For controls, approximately 63.28 +/- 22.71 sweeps per individual were averaged for the TT group and 68.57+/- 22.34 for the CT group with an epoch of -100 to 1,000 msecs. For cases, approximately 46.22 +/- 28.06 sweeps per individual were averaged for the TT group and 38.22+/- 19.35 for the CT group with an epoch of -100 to 1,000 msecs. The average number of bad channels for the TT group in controls was 9.70 and 16.38 for the CT group. The average number of bad channels for the TT group in cases was 14.52 and 13.11 for the CT group. 9 out of the 13 participants whose data was considered too noisy to be included in the P300 paradigm analysis were cases. In these cases, the pre-stimulus baseline activity contributed to excessive pre-stimulus activity differences across experimental paradigms i.e., across genotype groups. Therefore, any differences in measured amplitudes between conditions might potentially reflect pre-stimulus

differences rather than post-stimulus differences. Although, the pre-stimulus baseline is not perfectly neutral (as is rarely the case), having removed this selection of cases, the voltage slopes during the pre-stimulus interval were improved to an acceptable level for later analyses.

5.5. Results

The current study was designed to investigate the association between the SZ risk variant rs12807809 and the P1 and the P300 ERP components. These components were elicited during the performance of a task which included visual presentation of checkerboards, designed to stimulate the visual cortex eliciting the P1 and the performance of an auditory odd-ball task, where, during responses to an odd-ball sound, the P300 was elicited. In the current study, a measure of P1 amplitude was defined as the area under the curve and the peak amplitude (vs the 0-uV baseline) in the interval 70-110msecs, spanning the P1 component, chosen based on grand average waveforms. A measure of P300 amplitude was defined as the area under the curve and the peak amplitude (vs the 0-uv baseline) in the interval 250-550msecs, spanning the P300 component. These measures were then submitted to a repeated-measures multivariate analysis of variance (MANOVA), using SPSS software (SPSS Inc., Chicago, Illinois Version 16.0), with a between-subjects factor of diagnosis group (controls –v- cases) and genotype group (CC/CT versus TT carriers) and a within-subjects factor of region: left versus right with respect to the P1 and midline-central with respect to the P300. All tests were 2-tailed with a preset alpha-level of $P<.05$.

5.5.1. P1 paradigm

Figure 5.2 provides an overall illustration of ERP morphology across the P1 bi-lateral-occipital scalp-regions for both groups where the P1 is demonstrated. Behaviourally, controls were more accurate and were quicker to respond to target stimuli. They had overall shorter reaction times and had a greater number of correct responses (see Figure 5.5.). There were significant differences between CC/CT and TT carriers for the cases on the number of correct responses. CC/CT carriers had significantly more correct responses than TT carriers. Table 5.5. outlines mean measures across genotype and diagnosis groups for area-under-the-curve and peak amplitude measures. Figure 5.3 shows mapping of the difference topography associated with genotype and diagnosis groupings. Gender and level-of-education were not significantly different between groups. As age was significantly different between diagnosis groups this was entered as a co-variate in analysis. There was no main effect of genotype nor was there an interaction effect found for the area under the curve. Similarly, there was no main effect of genotype nor was there an interaction effect for either the N1 or P2.

Table 5.3. Behavioural data for cases and controls as per genotype (CC/CT versus TT carriers). Mean reaction times, mean number of correct responses and mean number of incorrect responses are included.

	Cases			Controls		
	CC/CT (N=10)	TT (N=30)	comparison	CT/TT (N=21)	TT (N=48)	comparison
Mean Reaction Time (mean (s.d.))	441.67 (55.09)	452.91 (54.90)	t(.69)= N.S.	432.28 (29.34)	443.06 (57.94)	t(.31)=N.S.
Correct Responses (mean (s.d.))	191.60 (3.71)	175.24 (20.18)	t(.00)= sig	194.32 (8.76)	190.43 (15.84)	t(.19)=N.S.
Incorrect Responses (mean (s.d.))	34 (24.43)	34.65 (29.78)	t(.96)= N.S.	10.82 (7.25)	13.91 (16.17)	t(.28)=N.S.

Table 5.4. The mean area under the curve measure and mean peak amplitude measure for cases and controls as per genotype

	Cases		Controls	
	CC/CT (N=10) Mn(SD)	TT (N=31) Mn (SD)	CC/CT (N=24) Mn (SD)	TT (N=48) Mn (SD)
Area under the curve				
Left hemisphere	50.07 (35.57)	76.34 (40.76)	89.37(52.81)	104.26 (56.15)
Right hemisphere	96.83 (62.35)	90.24 (54.69)	87.78(52.82)	122.31 (62.05)
Peak amplitude				
Left hemisphere	1.54 (1.65)	1.44 (2.05)	2.01 (1.62)	3.28 (2.50)
Right hemisphere	1.85 (2.13)	1.07 (1.98)	1.90 (1.96)	3.12 (2.86)

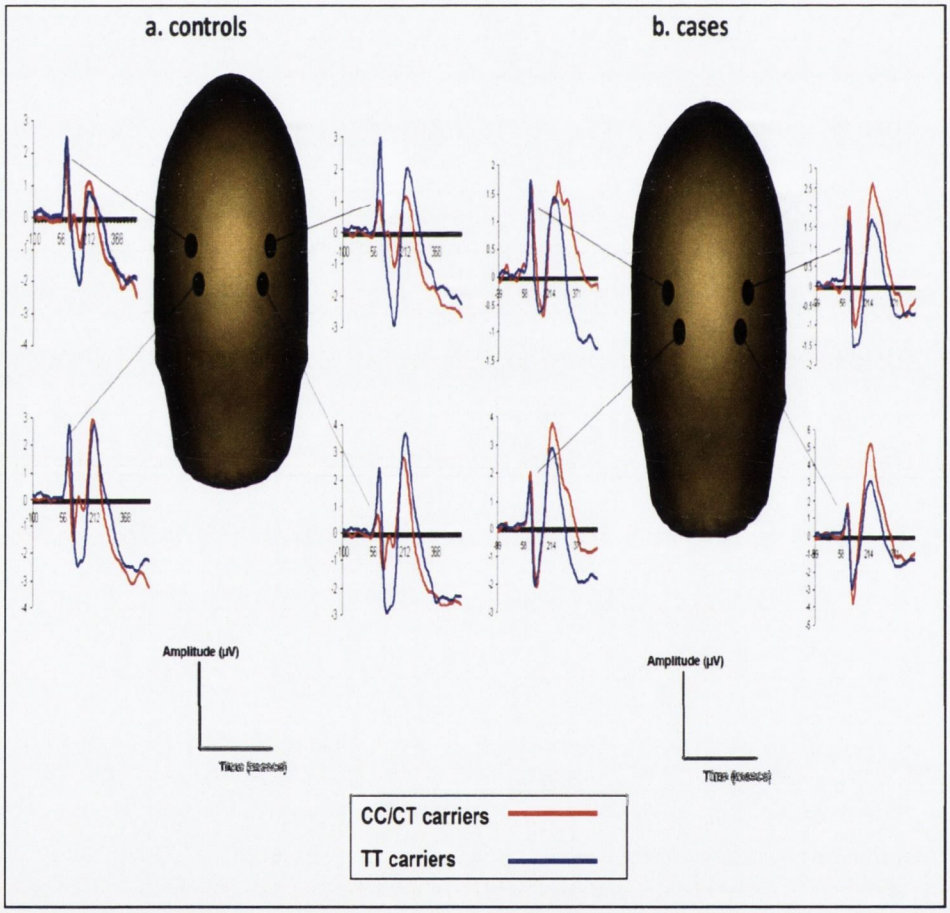

Figure 5.2. Event related potential morphology across the scalp for both groups illustrating responses from representative electrodes spanning the occipital scalp region where the P1 was observed bilaterally, illustrating responses for both diagnosis groups [controls (a.) and cases (b.)] and genotype groups [CT carriers in red and TT carriers in blue].

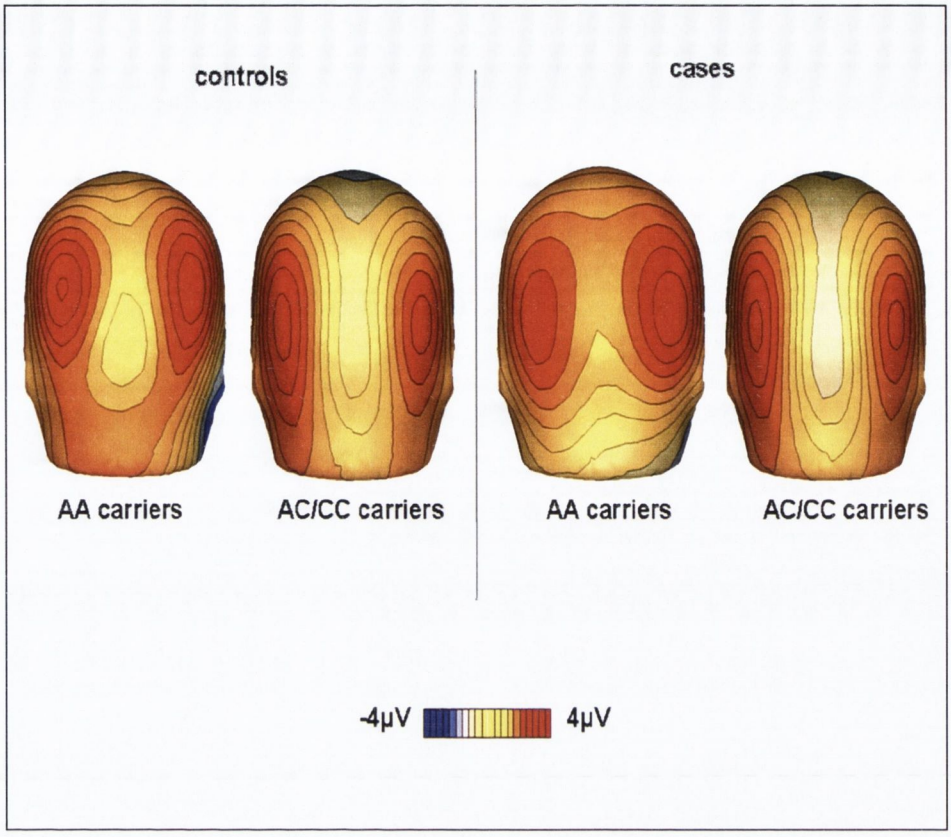

Figure 5.3. Mapping of the difference topography associated with NRGN. Subtraction of the grand-averaged waveforms from one another enables the difference effect to be isolated and mapped.

For the P1 component, there was no main effect of genotype or diagnosis, nor was there an interaction effect. The grand average waveforms did indicate however, that homozygous TT carriers in the control group demonstrated a greater P1 response at the right hemiscalp-region. While this trend was not anticipated and was not in-keeping with our hypothesis, we followed these findings with an *a posteriori* hypothesis that NRGN may have a specific role in controls. These post-hoc tests revealed there to be significant differences between CT and TT carriers in controls in the right hemisphere for peak amplitude measures [$F(1,73)=4.18$, $p=.04$] and also for area-under-the-curve [$F(1,73)=4.66$, $p=.03$]. There were also significant differences found between the genotype groups for the N1 component for

the right hemiscalp [F(1,73)=4.58, p=.03]. There were no differences for the left hemiscalp for the N1, and no differences at either hemiscalp for the P2 [p>.05]. Age was not significantly different between genotype groups amongst controls, therefore it wasn't entered as a co-variate in the post-hoc analysis. There were no significant differences between cases per genotype group [p>.05].

5.5.2.P300 paradigm

For statistical analyses, P300 measures were submitted to multi-variate analysis of variance (MANOVA) using SPSS Software (SPSS Inc., Chicago, Illinois Version 16.0) with the NRGN genotypes (CC/CT versus TT) and diagnosis (cases versus controls) between subject factors and the P300 response as the within-subjects factor. Gender and level-of-education were not significantly different between groups. As age was significantly different between groups, this was entered as a co-variate in analysis. Figure 5.4. provides an overall illustration of ERP morphology across the P300-scalp-region for both groups. It represents responses from the FCz, Cz and CPz electrodes where P300 differences were found to be largest across groups and genotype. Figure 5.5. provides an illustration of the topography of the P300 component per genotype group for cases and controls.

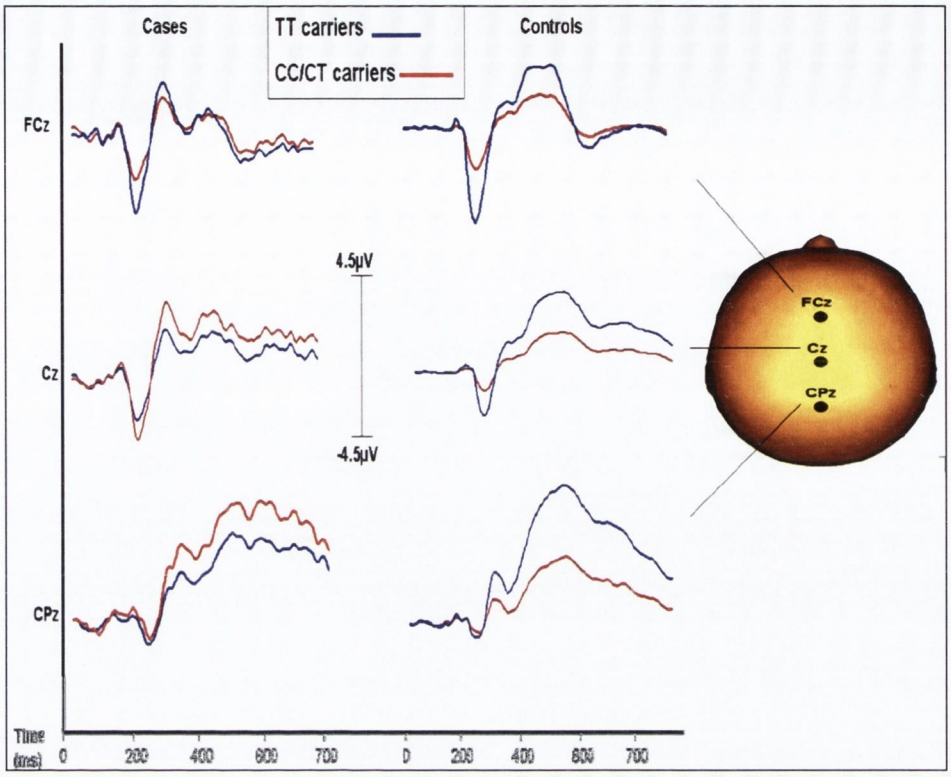

Figure 5.4. Grand average waveforms illustrating responses from the representative electrodes FCz, Fz and CPz spanning the temporo-parietal scalp region where the P300 was observed, illustrating responses for both diagnosis groups (controls and cases) and genotype groups (CT carriers in red and TT carriers in blue).

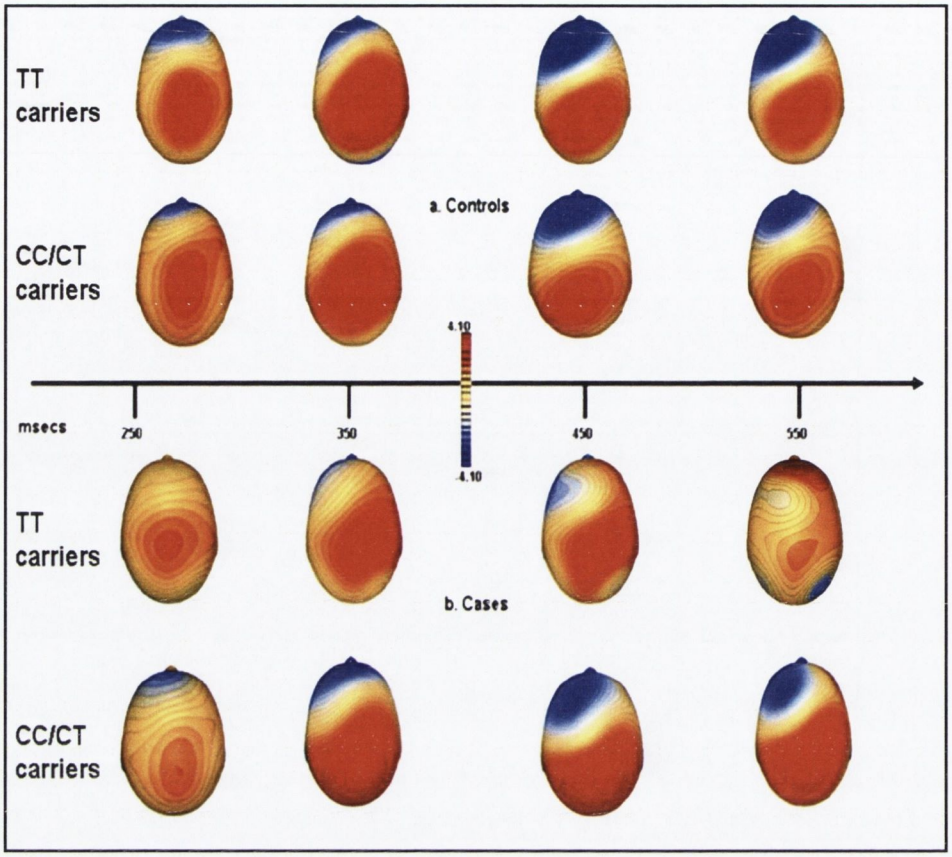

Figure 5.5. This provides an illustration of the topography of the P300 component per genotype group for cases and controls across the component as represented by contour maps taken at 250, 350, 450 and 550 msecs.

For the P300 component there was neither a main effect of genotype or diagnosis, nor was there an interaction effect. The grand average waveforms did seem to indicate however, that TT carriers in the control group demonstrated a greater P300 response than CT carriers. As with the P1, this trend was not anticipated. In a similar fashion however, it was decided to run the post-hoc analyses, examining each group in isolation at the electrode where group differences were found to be greatest: at electrode CPz. For controls only, there were significant differences between CT and TT carriers for the area under the curve measures [$F(1,68)=3.29$, $p=.04$] and similarly, there were significant differences found for peak amplitude measures

[F(1,68)=4.51, p=.01]. There were no differences found when cases were examined in isolation [p>.05].

5.6. Discussion

The current study extends previous reports of a relationship between NRGN and cognition by performing an association study looking at variance at rs12807809 and variation in the P1 and P300 event-related-potentials in a sample of cases and healthy controls from an Irish population. Impaired P1 and P300 generation have repeatedly been demonstrated in cases with SZ (Butler et al., 2001; Butler et al., 2005; Doniger et al., 2002; Foxe et al., 2001; Foxe et al., 2005; Schechter et al., 2005; Bharath, Gangadhar & Janakiramaiah, 2000; McCarley et al., 2002; McCarley et al., 1993; Renoult et al., 2007) with evidence in their first degree relatives supporting a genetic contribution to this deficit (Blackwood et al., 2001; Blackwood & Muir, 2004; Katsamis et al., 1997; O' Connor, 1994; Polich & Burns, 1987; Rogers & Deary, 1991; van Beijsterveldt et al., 1998b; Weisbrod et al., 1999; Wright et al., 2001).

The chromosomal region where the NRGN gene is located has been implicated in SZ by a large GWAS study (Stefansson et al., 2009). Variants in NRGN have been identified as associated with calcium-calmodulin dependent pathways, visual cortical plasticity and short-term memory formation in SZ (Broadbelt et al., 2006; Gordon et al., 1996; Huang et al., 2004; Pak et al., 2010; Ruano et al., 2008; Wang et al., 2008). Donohoe et al., (2010) previously reported that there were no significant interactions

between rs12807809 for any of a range of neuropsychological variables.

In the current study, no significant interactions between the NRNG genotype and diagnosis in our primary EEG analysis were observed. While it was not part of the primary hypothesis to look at controls separately, the data indicated that there were differences between TT and CC/CT carriers in the control group. In a post-hoc analysis significant differences were found between TT and CC/CT carriers. For controls, homozygous TT carriers showed greater P1 responses at right hemiscalp locations. A significantly greater N1 response for the right hemiscalp in these same controls was also observed. The same pattern prevailed for the P300. Homozygous TT carrying controls demonstrated greater strength of response than CC/CT carriers with greater P300 amplitudes at a central electrode site. These results may suggest a role for NRGN in cortical synaptic activity, impacting automatic information sensory processing (as indexed by the P1) as well as stimulus evaluation processes (as indexed by the P300). This influence on these sensory and cognitive activity levels would be consistent with the known biology of NRGN, including its role in calmodulin binding and NMDA receptor functioning. However, whether the observed effect here is robust would need to be clarified by a follow-on study using a second, independent data set.

As for the cases, there may be several reasons why there were no differences between genotype groups. Cases predictably were impaired compared to controls on their cortical activity as measured by the P1 and P300 ERPs. Therefore, their responses

were already dampened down. This might mean that any small effects which might have been present in the case group might have weakened. Another factor might have been the effect of medication and its disruption to these measures in cases. A healthy control sample plays a valuable role in elucidating the molecular biology of cortical activity due to their being unburdened by any potential medication effects on the neural substrates of information processing picked up by ERPs with atypical anti-psychotic medications such as clozapine and quetiapine (Umbricht et al., 1998). In future research it would be interesting to follow up this study with a larger independent case sample and also with a sub-set of medication-free-cases where possible. Perhaps the most likely reason why the difference in genotype groups did not extend to cases, however, is because the case sample was underpowered. The case sample in the current study consists of 41 for the P1 and 29 for the P300. In a previous P1 genetic study (Donohoe et al., 2008) a case sample consisting of 26 individuals was sufficient to show a strong difference between genotype groups. In the case of NRGN however, the effect size associated with this variant may have been smaller and hence harder to determine in a modest sample size. For the Dysbindin study, the effect size was d=.89, which constitutes a large effect size according to the criteria of Cohen. In the current study, the effect size between cases for NRGN was more moderate (with an average effect size of d=.51).

5.6.1. NRGN: Molecular mechanisms and functional implications

The implicated SNP rs12807809 is located in a non-coding region, 3,457 bases upstream from the NRGN gene. Based on the HapMap CEU Phase III data, there were five proxy markers for rs12807809 with d'>.8. One of these, rs12792040 alters amino acid structure of a gene endothelial cell-selective adhesion molecule (ESM). The data also indicated that rs12807809 was in linkage disequilibrium with just one other SNP, rs1939214. In silico data from the UCSC genome browser does not indicate an obvious functional role for these SNPs. Therefore, these are not variants with manifest functional consequences- they do nothing to alter the amino-acid sequence of the protein, effect expression or alter splicing of the gene. It remains to be determined how these SNPs affect NRGN functioning. Functional assays will be needed to analyse the specific impact of the rs12807809 polymorphism on NRGN expression in further detail.

There was strong a priori evidence that NRGN may influence cognition which may be picked up at the level of cortical synaptic activity. NRGN is involved in synaptic potentiation, requiring the activation of NMDA receptors and CaMKII. Neurons expressing NRGN result in the triggering of Ca^{2+} and the induction of long-term-potentiation, the most noted characterization of synaptic plasticity (Alkon & Nelson, 1990; Bliss & Collingridge, 1993; Chen & Tonegawa, 1997; Baudry, 1998; Elgersma & Silva, 1999; Martin et al., 2000; Maren, 2005).

Evidence of the role of NRGN in cognition comes from animal and human studies. Mohn, Gainetdinov, Caron & Koller (1999) developed a mouse line that expressed 5-10% of normal levels of the NR1 subunit of NMDA receptors. They found that these mice exhibited behavioural changes which were intended to mimic some of the symptoms of SZ such as stereotypy and increased locomotion. Following treatment with the anti-psychotics haloperidol and clozapine, it was found that these behavioural patterns were considerably ameliorated. Levels of the NMDA receptor antagonists kynurenic acid have been found to be higher in the cerebro-spinal-fluid of cases with SZ with increased levels being associated with working memory impairments (Chess & Bucci, 2006; Chess, Landers & Bucci, 2009; Erhardt, Schwieler, Emanuelsson & Geyer, 2004; Shepard, Joy, Clerkin & Schwarcz, 2003).

Several lines of evidence point to links between SZ and abnormal plasticity involved in mechanisms underlying cognitive functioning. One such example is dendritic spine abnormalities and their association with long-term-potentiation. LTP and dendritic spine structure have been demonstrated by the finding that the size of the post-synaptic density is related to the size of the spine head (Harris et al., 1992); spine enlargements are associated with LTP in single identified spines (Matsuzaki et al., 2004) and evidence that LTP induces structural plasticity in dendritic spines (Bastrikova et al., 2008; Kopec et al., 2006; Lang et al., 2004; Okada et al., 2009; Okamoto et al., 2004; Otmakhov et al., 2004; Nagerl et al., 2004; Segal et al., 2005; Zhou et al., 2004). Interestingly, NRGN accumulates in dendritic spines of neurons within the cerebral cortex, hippocampus, striatum, and

amygdala, all cortical areas associated with memory, attention, concept formation, problem solving and association (Neuner-Jehle et al., 1996; Watson et al., 1992). Altered NRGN activity could ultimately result in the dendritic spine loss described in SZ because NRGN is concentrated in dendritic spines which happen to be where the majority of excitatory synapses are located (Broadbelt et al., 2002; Garey et al., 1998; Glantz & Lewis, 2000; Zhong et al., 2009).

5.6.2. NRGN & the glutamatergic hypofunctioning hypothesis in SZ

NRGN has been described as rather a new player in the glutamatergic hypothesis of SZ's known molecular biology. NRGN is at the centre of the glutamatergic pathway and is a downstream target of glutamate neurotransmission because of the link between NMDA receptors, calcium influx and NRGN's binding to calmodulin in synaptic transmission (see Figure 5.6. for an illustration of the role of NRGN in NMDA functioning from Ruano et al., 2008). As previously outlined, NRGN is a post-synaptic calmodulin-binding protein. During synaptic transmission, the large increase in calcium concentrations activate a Ca^{2+}/calmodulin-dependent-protein-kinase-II, leading to the induction of LTP. Where there are mutations to NRG, the capability to release calmodulin and perform synaptic plasticity is disrupted. If there are changes to NRGN, these may have consequences for determining the availability of calmodulin which is bound to neurogranin (Gerendasy & Sutcliffe, 1997).

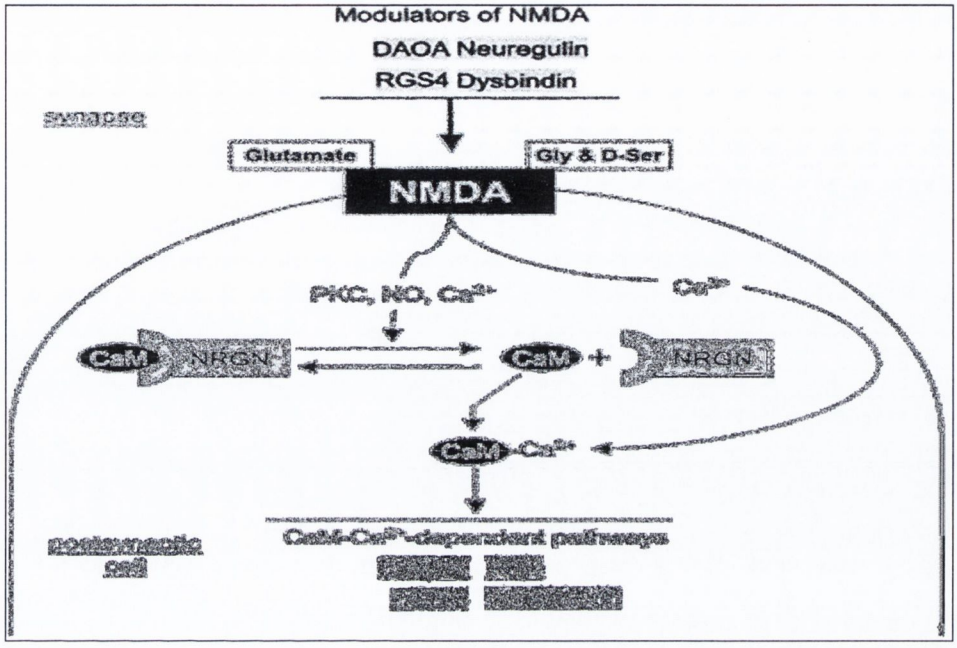

Figure 5.6. Summary of the relationship of NRGN with the glutamatergic hypothesis of schizophrenia adapted from Ruano et al., (2008). In neurons, NRGN targets CaM and enhances the probability of inducing long-term-potentiation.

NMDA hypofunction has been implicated for some time in the pathophysiology of SZ (Goff & Coyle, 2001). Connections between corticocortical, corticolimbic and corticothalamic projections are predominantly glutamatergic with connections to corticolimbic regions such as the hippocampus and the amygdala, all areas which are found to have altered neuropathology in SZ (Harrison, 2004; Lewis et al., 2003; Weinberger, 1999). There is evidence supporting altered glutamate functioning in the pathophysiology of SZ.

Firstly, antagonists of NMDA receptors induce many of the symptoms of SZ, with these inducements being attenuated by anti-psychotics. NMDA antagonists such as phencyclide and

ketamine reliably induce the cognitive deficits associated with SZ including working memory, attention, short and long term memory and executive functioning deficits (Krystal et al., 2005; Malhotra et al., 1996; Stoet & Snyder, 2005). Secondly, in addition to these cognitive deficits, these NMDA antagonists are also found to induce positive and negative symptoms associated with SZ (Bruins, Slot, Klevn & Newman-Tancredi, 2005; Lee, Brady, Shapiro, Dorsa & Koenig, 2005; Murai et al., 2007; Sams-Dodd, 1996; Snigdha & Neill, 2008). Thirdly, these inducements have been demonstrated to be attenuated by anti-psychotic drugs (Grayson, Idris & Neill, 2007). The NMDA receptor agonist D-serine has been found to improve positive, negative and cognitive symptoms in SZ further supporting the role for NMDA receptor hypofunction in SZ (Tsai, Yang, Chung, Lang & Coyle, 1998). Fourthly, NRGN may influence NMDA functioning via its role in synaptic potentiation. During de-polarisation, magnesium first becomes dissociated from its binding site within the NMDA receptor, allowing calcium to enter the spine. The local increase in calcium within the spine allows calmodulin to be in its calcium binding conformation and activates subsequent targets. NMDA receptors are most pervious to calcium ions, thus providing the post-synapse with high amounts of calcium, activating further processes lending to the expression of LTP (Riedel & Reymann, 1996).

The role of NMDA in plasticity is most especially associated with developmental stages, with neurodevelopmental theories of SZ increasingly focusing on NMDA antagonism in the consequent disruption of normal neuronal development, migration and differentiation (Lipska & Weinberger, 2000). For example, NMDA

receptors regulate pruning of cortical connections during adolescence, making them a critical component of developmental processes whose malfunction may lead to SZ (Goldberg et al., 2006). NRGN joins the list of several modulators of NMDA receptor activity, implicated in SZ such as the genes Dysbindin, Neuregulin-1, DAOA and RGS-4. These are all involved in the regulation of glutamate signalling. These genes could be exerting their effect on glutamate receptors perhaps even by altering NRGN activity. These genes, Dysbindin, Neuregulin-1, DAOA & RGS-4, are all strong candidates in the pathophysiology of SZ and glutamate is a site of action they share (Harrison & Owen, 2003).

5.7. Conclusion

The current study sought to elucidate the impact of the identified risk variant rs12807809 on indices of cortical synaptic function. Differences between "TT" and "CC/CT" carriers in a healthy control group following post-hoc analysis for both the P1 and P300 ERPs were observed. This finding indicated that this variant was influencing both automatic sensory and higher cognitively mediated levels of processing as indexed by the P1 and the P300 in controls but not in cases. It is likely that the direction of results did not extend to cases because the case sample was underpowered to demonstrate the effect. This finding that homozygous risk carriers demonstrated greater cortical responses suggest that this could be a risk variant which may not be increasing SZ risk via its deleterious effects on cognition. The current study afforded the opportunity to confirm the effects of the risk variant rs12807809 associated with increased disease risk to further characterise how this variant

may be affecting individual aspects of gene function. The current finding in healthy participants is consistent with the known biology of NRGN and its role in calcium-calmodulin binding pathways and NMDA receptor functioning. Once functional assays are available for this gene, it will be interesting to see specifically how the rs12807809 polymorphisms is impacting calmodulin and NMDA receptor functioning in the etiology of SZ. It seems likely that NRGN could be mediating its effect on SZ via its role in synaptic plasticity based on healthy control data. Evidence that NRGN plays a role in both sensory processing and memory/attentional mechanisms in conjunction with our knowledge about the biology of this gene in synaptic function suggests that NRGN is likely to be relevant not just to SZ pathophysiology but to normal variation in cognitive functioning as well.

Chapter 6

General Discussion

6.1. Introduction

As originally conceived, the use of endophenotypes was proposed as a strategy for reducing the genetic complexity of the broader illness phenotype, thus facilitating identification of genes of small effect. Since then, the intermediate phenotype strategy has moved away from gene discovery (as first envisaged by Gottesman & Gould, 2003) and has instead focused on confirming the effects on individual brain systems of variants showing statistical association with illness. Assuming that clinical behaviour is, among other things, a consequence of alterations to biological brain traits due to common variants, these endophentoypes, in theory, may mediate the neural effects of risk variants on clinical behaviour. Central to this is the assumption that individual gene effects are stronger at the level of the endophenotype e.g., the ERP, than the broader illness phenotype. This set of studies has contributed to this field in a number of ways, addressing both methodological aspects of using ERPs as endophenotypes in SZ research, and also the utility of ERPs for interrogating the neural contribution of SZ risk variants.

6.2. Summary of Findings

Firstly, this research tested the reliability of ERPs purported to measure executive functioning. These ERP components, elicited

during the build-up to pre-switch and switch stimuli during a task, proved to be less than satisfactory in meeting the preliminary criteria of an endophenotype by failing to reliably distinguish between cases and controls. Secondly, this series of studies provided more evidence that the P1 and the P300, indices of both visual perception and cognitive processing respectively are good electrophysiological cortical indicators of visual perception and attentional processing and offer a good platform from which to examine how risk variants in SZ may be impacting cortical function. Thirdly, these studies are important for understanding the functionality of risk genes associated with SZ and cognition, namely NOS1, NRGN and ZNF804A. An association between the P1, the P300 and already identified risk alleles were observed. By this estimate, there is some evidence that these endophenotypes may actually lie "on the disease pathway."

6.3. What these endophenotype studies tell us about the mechanism of disease risk.

6.3.1. Multiple genes-multiple phenotypes

Sometimes there are simple relationships between genes and phenotypes e.g., Huntington's disease. However, in complex traits such as SZ, many genes can influence many phenotypes and conversely, one phenotype can be influenced by many genes. Already it is known that the genes in the current studies probably influence many different phenotypes. For example, NRGN is associated with bipolar disorder (Williams et al., 2010), and thyroid hormone function (de Arrieta, Morte, Coloma &

Bernal, 1999; Iniguez, Rodriguez-Pena, Ibarrola, Moreale de Eseobar, 1992). Likewise, ZNF804A has been found to be associated with bipolar disorder (Williams et al., 2010), and a number of neuroanatomical and neurocognitive phenotypes (Esslinger et al., 2009; Esslinger et al., 2010; Donohoe et al., 2010; Lencz et al., 2010; Walter et al., 2010). Similarly, NOS1 has been associated with asthma (Grasemann, Yandava & Drazen, 1999; Leung et al., 2005) and with restless leg syndrome (Winkelmann et al., 2008). As the study of neuropsychiatric genetics of SZ continues to evolve it seems likely that the current findings will align themselves to this complex relationship between multiple genes affecting multiple phenotypes (Kendler, 2005). It is likely that a huge number of variants impact the ERPs in the current studies. For example, there is evidence that NOS1 and NRGN may be involved in LTP through their role in glutamatergic and calmodulin functioning. It is worth noting that Sanes & Lichtmann (1999) observed that about *one-hundred genes* were involved in LTP. The current studies contribute to informing how connecting genes and connecting networks combine to contribute to the broader phenotype.

6.3.2. Common genes of small effect

Clearly the strength of the association between the genes in the current studies and behavioural phenotypes are weak at best, accounting very little for overall vulnerability. As a complex disease the odds ratios in SZ, which measure the risk for a particular outcome are very low. Unlike other areas of research, such as lung cancer, mesothelioma and depression which have odds ratios ranging from 12-15 (Agudo et al., 2000; Kendler,

2001; Khuder, 2001), meta-analyses of genetic association studies suggest that the magnitude of association between individual genes and psychiatric illnesses has a much smaller odds ratios, ranging from 1.1 to 1.6 (Owen, Williams & O' Donovan, 2004; Schwab et al., 2003; Williams et al., 2004). The effect sizes of the variants in the current studies are no exception. The odds ratio for NOS1 rs6490121 is 1.03, for ZNF804A rs1344706 is 1.1 and for NRGN rs12807809 is 1.15. These odds ratios fit into the general range for psychiatric illnesses. It still leaves the impact of these individual genes as very minor pre-determinants of disease risk.

Pearlson & Folley (2008) argue that the combination of singly occurring SNPs such as rs1344709, rs6490121 and rs12807809 owing to their small effect on SZ are generally speaking, probably not even disadvantageous enough to be selected against. Although the P1 and P300 ERPs were found to be associated with SZ risk genotypes, variation in these genes doesn't exclusively influence these neurophysiological markers because i) these variants are affecting other phenotypes ii) these phenotypes are being influenced by many other genes and iii) these genes are sensitive to the impact of both genetic but also environmental background (Flint, Greenspan & Kendler, 2010). Indeed, although a model of multiple pleiotrophy [single genes influencing multiple possibly unrelated traits] may explain how some of these risk genes may be mediating risk, it is highly unlikely that they are all of equal importance. Some may partly mediate risk whereas some may be entirely irrelevant (Flint et al., 2010).

One of the association studies in the current research has been NOS1, which aside from its original identification by O' Donovan et al., (2008), has not been identified in subsequent genome-wide-association studies as achieving genome-wide significance (ISC, 2009; Stefansson et al., 2008; Walshe et al., 2008). NOS1, because of this problem, may well be influencing cognitive ability without being causally involved in the clinical manifestation of the disorder. There are other examples of this in the literature. One such example is D-amino-acid-oxidase-activator (DAOA) which has been found to be associated with both SZ and also better semantic fluency (Opgen-Rhein et al., 2008). Another example is protein-phosphate-1-regulatory-inhibitor-subunit-IB (PP1R1B) which has been found to be associated with both SZ but also with better intra-striatal processing (Meyer-Lindenberg et al., 2007). It could be that only above a certain threshold does the culmination of SNPs and deficits ultimately give rise to clinical symptoms.

6.4. Do we know more about these genes than we did?

By their nature, endophenotypes lend themselves to being a good means of interpreting the underlying gene-disease pathway in SZ because they are simple in structure, are easily quantifiable and lie closer to the gene. The current studies help to pinpoint the neurophysiological responses these genes are influencing. Where a known gene maps onto a particular brain system which regulates a specific function, there is the potential to understand an actual brain pathway which may be disrupted in SZ.

6.4.1. The intronic nature of these SNPs

One thing that all the implicated SNPs in these studies have in common is that they are intronic- their effects are likely to be at the level of alterations in transcription regulation rather than amino acid changes (Buonocore et al., 2010). It is interesting to explore what has thus far been discovered about the functionality of these genes and how they may be involved in affecting neuronal activity. Foremost, ZNF probably plays numerous roles in cellular function (Williams et al., 2010). Zinc finger proteins are extremely common in eukaryotes with 15,000 domains existing in 1,000 different proteins (Rubin et al., 2000). The family of ZNFs was originally characterised as DNA-binding domains but recent evidence suggests that they may be involved in protein recognition (Gamsjaeger, Liew, Loughlin, Crossley & Mackay, 2007). This would indicate that there is some involvement in the regulation of gene expression. We have seen that the risk variant for ZNF804A rs1344706 has been associated with transcription factor expression in the human brain, with higher mRNA expression and with cis-acting effects, all involved in gene expression (Buonocore et al., 2010; Riley et al., 2009; Williams et al., 2010). Recent evidence (Hill & Bray, 2011) suggests that rs1344706 may be a functional SNP, finding that this variant altered DNA-protein interaction.

The NOS1 and NRGN SNPs are also intronic. Unlike ZNF804A, these genes seem to converge on glutamatergic receptor and calcium signalling domains. Nitric oxide strongly influences glutamate neurotransmission via NMDA receptor interaction (Akyol et al., 2004; Brenman & Bredt, 1997) and NRGN is the

main post-synaptic protein regulating the availability of calmodulin, which is a calcium-binding protein involved in synaptic plasticity and long-term-potentiation. The role of glutamate in SZ has been very well documented, stemming from the observations from NMDA antagonists which closely mimic the symptoms of SZ (Javitt & Zukin, 1991; Rosenbaum, Cohen, Luby, Gottlieb & Yelen, 1959; Yesavage & Freman, 1978). The current findings with respect to NOS1 and NRGN are interesting because the role of NMDA and calcium in SZ are not mutually exclusive. Indeed, reductions in NMDA result in an increase in calcium (Olney, Newcomer & Farber, 1999; Schwartz, Wagner, Yu & Martin, 1994) and bi-directionally, increases in calcium inhibit NMDA receptors (Krupp, Vissel, Thomas, Heinemann & Westbrook, 1999, 2002).

6.4.2. Relationship between lower and higher levels of cognition

The risk variants in the current study have been found to have a direct influence on both sensory processing and cognitive cortical responses. ZNF804A seems to confer a relative advantage for carriers in cortical processes relevant to stimulus evaluation, and this finding extends previous work which found this risk variant made for relatively less impaired memory functioning in cases. In the case of NRGN, it was observed that risk carriers in the healthy control group demonstrated greater cortical responses for both the P1 and the P300. In the current studies, NOS1 was associated with impaired P1 responses. The P1 response predicted SWM task performance and NOS1 continued to predict variance in P1 response even after the

variance associated with SWM was accounted for. The combination of both the findings from the current set of studies and our previous studies may suggest a reciprocal relationship between early sensory processing as measured by EEG and higher cognitive functioning. By implication, there may be "bottom up" effects of ZNF804A, NOS1 and NRGN to other areas of cognition. Alternatively, these findings may represent multiple pleiotropic effects on both sensory and cognitive processes by these genetic variants. Bottom-up versus top-down effects are an area of cognitive neuropsychology continually open to discussion. There is evidence from the current studies that these risk variants are influencing both basic sensory processing and higher areas of cognition.

6.4.3. Do these genetic associations represent domain-specific or general factor effects?

Although it is possible that deficits at the level of sensory processing may be influencing effects in higher cognitive processes, this is difficult to establish. One problem is that the separable dimensions of cognition are in fact highly correlated, particularly those measured by neuropsychological-behavioural assessment, reflecting a "common" cognitive ability factor, often referred to as "g" or the general factor of intelligence (Jensen, 2002). Dickinson, Ragland, Gold & Gur (2008) address how generalised deficits are a challenge to domain-specific interpretations of neuropsychological findings in studies of SZ genetics. SZ is directly associated with generalised poor performance on all areas of cognition, with more specific deficits e.g., deficits in the P300, being trumped by the over-arching

"general factor effect", with cognitive deficits encompassing a large number of domains. These specific deficits may well be independent of one another or be entirely inter-twined in a common generalised deficit. Genetic markers in SZ may be influencing these specific domains or any number of specific domains e.g., the influence of NOS1 on both visual perception and spatial-working-memory: the P1 response was found to predict spatial-working-memory performance but there was insufficient power to determine whether NOS1's effect on spatial-working-memory was mediated by P1 performance.

The current studies have contributed to advancements in linking genetic risk markers in SZ to very precise cortical evoked responses. It is as yet unclear whether these findings will ultimately link up with common ability factor or "g" in neuropsychiatric genetics or whether the specific electrophysiological responses would continue to be a very specific domain for future genetic studies. If the current studies are to be understood in the context of a generalised effect of illness, rather than multiple domain-specific effects, then they may be just another area of cognition which is enfeebled in SZ. On the other hand, impairment at the most preliminary engagement of cortical response may have an impact on all later cognitive processes i.e., deficits in encoding, resulting in the clinical presentation of cognitive impairment consistent with this disorder (Dias, Butler, Hoptman & Javitt, 2011; Javitt, 2009; Javitt, Rabinowicz, Silipo & Dias, 2007). The current studies have been informative in contributing to our understanding of how a specific "lesion" in SZ e.g., the P1 visual evoked response could impact higher cognitive functioning via the mechanisms of

underlying genetic-neurobiological pathways as in the case of NOS1.

Indeed, at the whole organism level, one area through which these genetic variants may be impacting many levels of cognitive processing is memory function. Firstly, NRGN has been shown to influence the P300, a neurocortical measure associated with stimulus evaluation and engagement of structures associated with memory processing. Secondly, risk variance for NOS1 has been associated with deficits in working memory and in the current studies we were able to once more explore the relationship between NOS1 and spatial-working-memory. Thirdly, ZNF804A has been shown to influence episodic memory and working memory and brain regions associated with memory and in the current study, with the P300. These studies elucidate the shared genetic component in both neural and behavioural processes wherein NOS1, ZNF804A and NRGN impact both sensory and higher levels of cognitive processing.

6.5. Shortcomings of this research

6.5.1. Reductionism

The current studies could be subjected to some general criticisms of biological psychiatry research. Firstly, the genetic basis of SZ has not been scientifically established- a potential fundamental flaw of neuropsychiatric genetics is the assumption that there are genetic imperfections involved in the etiology of SZ in the first instance. It is a great presumption that coinciding with clinical presentation are biological parameters underlying

this behaviour. This is a theory which has been broadly accepted without acknowledging that in reality, at most, one can really only proclaim there to be a polygenetic predisposition to psychiatric disorders generally. Aside from co-varying for age, gender and medication, the role of non-genetic factors i.e., environment has been somewhat disregarded. The current studies place little or no emphasis on psycho-social variables which may well be hugely involved in the etiology of SZ. Ross & Alvin (1995) for example, points out that the 1% incidence of SZ in the world is always cited as "evidence" that SZ is a biomedical, genetically driven, evenly distributed disease, rather than that this is evidence of something more specific to society and culture. The assumption that psychiatric disorders have a large genetic component has been extensively criticised, chiefly for becoming axiomatical (Bentall, 2009). This criticism is deserving of consideration- there is a lot of evidence that environmental factors play a role in the etiopathogenesis of SZ and it is commonplace to overlook these in genetic studies. However, a lack of discourse between research fields should not be confused with geneticists disregarding environmental factors and environmental-psychologists disregarding genetic factors. If anything, it may be a reflection of the lack of partnership between these fields. Any successful model of SZ must account for the roles of gene-environment interaction, genetic variants and environmental exposure. Each of these is likely to be individually necessary but not sufficient to cause SZ (Brown, 2011). Better methods could be implemented to combine environmental and genetic influences going forward. There have already been several very successful attempts at exploring gene-

environment interaction (Clarke, Janskanen, Huttunen, Whittaker & Cannon, 2009; Ibi et al., 2010).

6.5.2. Problems with a diagnosis of SZ

The cases in this study are assumed to be part of a homogeneous group. This also pertains to the cases in the genome-wide-association studies. The DSM-IV diagnostic criteria, from which the diagnostic category of SZ is used as the phenotype in genetic studies is not delineated by its homogeneity. Although it undoubtedly most useful in a clinical sense to arrive at a diagnosis based on behavioural presentation, this may not necessarily guarantee that the underlying neurobiology culminating in clinical presentation is not vastly heterogeneous, comprised of inter-individual differences which may change over time. As pointed out by Jablensky (2009: 42) "as no symptom is pathognomic or necessary, and variable sub-sets of symptoms can be sufficient for the diagnosis, patients may be allocated to the diagnostic category of SZ without sharing a single symptom, sign or type of impairment." This scenario results in the large samples in genetic-association-studies comprising multiple aetiological pathways. The endophenotype approach affords the opportunity to reduce the complexity of the broad phenotype by earmarking distinct subtypes of SZ, negotiating issues of etiological heterogeneity to help resolve the abyss between primary symptoms and underlying biology (Gerlai, 2002; Moldin, 1994; Tan, Callicott & Weinberger, 2008).

Furthermore, the DSM-IV on which diagnosis of SZ is based considers SZ as a pre-emptive diagnosis, ruling out the

concurrent diagnosis of co-morbid conditions. In reality, SZ is often co-morbid with numerous conditions: it is often co-morbid with anxiety disorders (Braga et al., 2004; Ciapparelli et al., 2007; Craig et al., 2002; Goodwin et al., 2003; Muller et al., 2004); intellectual disability (Bhaumik et al., 2008; Morgan et al., 2008) substance abuse and increased occurrence of psychotic symptoms in the presence of substance abuse (Green et al., 2007; Westermeyer, 2006). Additionally, SZ cases present with a whole cohort of other medical conditions (Carney et al., 2006; Goff et al., 2005; Iacovides & Siamouli, 2008; Meyer & Nasrallah, 2009). Some of these co-morbidities could be occurring because of the experience of having SZ itself e.g., the development of a social phobia; they could be parallel unique disorders with their own common risk factors; or they could share genetic-pathophysiology with SZ (First, 2005). Additionally, although these ERP endophenotypes may reliably distinguish between healthy controls and cases, to be truly clinically meaningful they must apply to finer gradations of illness. Future research, with an anticipated decrease in the boundaries imposed by the DSM-IV may take concurrent diagnoses into consideration and the probable overlap with numerous psychiatric disorders (see Craddock & Owen, 2007; Guilmatre et al., 2009). Cognitive neuro-genetics will co-evolve with the movement away from categorical interpretations of mental illnesses.

6.5.3. The sample

Finally, the opportunistic sample method employed in the recruitment and testing of cases and controls has its limitations. This has been referred to throughout this thesis. This sampling

strategy was employed to maximise recruitment under the constraints of time,. Almost all approaches to recruitment are biased: our approach (recruiting through media adverts, volunteer websites, campus advertisements etc) appears to have been biased to attracting controls who are of a higher IQ bracket, eager to participate in scientific studies in a university surrounding, and cases who are in regular communication with their mental health team and are well enough to participate in this type of research. This sampling method has been employed in most other studies such as this to date. However, it is not ideal, and future research in this area would benefit from a sample drawn randomly from the general patient and control population. Another shortcoming of the sampling method was that there were insufficient numbers to power a comparison of all possible genotypes. Therefore, it made a lot of sense to group the lowest allele groups with heterozygous groups who carried one risk allele and one non-risk allele i.e., [AG/GG in NOS1, AC/CC in ZNF804A and CC/CT in NRGN]. This was a strategy we have used before and is commonly found in the literature. Due to this, there was a low representation of one or other of the paired allele groups individually. Future replication studies could also include a sample where these genotype groups are better individually represented.

6.6. Future directions & concluding remarks

6.6.1. Resolving functionality

Cognitive neuro-genetics researchers have been limited to date in translating association into a direct causation owing to the

paucity of knowledge about the function of risk variants. An important step is to understand how variation in these association genes increases the risk of developing a condition so that we can understand just how a gene is having an impact. Functional assays will help to understand how genes are functioning and interacting and how the gene is transcribed and translated through genetic interaction-mapping, understanding the expression patterns of genes, protein-protein interactions using such techniques as expression profiling, large-scale mutagenesis and protein-interaction analysis (Twyman, 2009a, b). Since the commencement of this thesis, rare variants have become increasingly relevant to neuropsychiatric genetics (Gershon, Alliey-Rodriguez & Liu, 2011). Although these rare variants do not appear to be solely responsible for the presentation of SZ (nor indeed are the culmination of common variants) it will be interesting to see how ERPs in SZ will be impacted in individuals who are carriers of these rare variants. Either way, once the causative DNA markers have been identified, be they either SNPs or CNVs, their biological relevance on the molecular biological level will be important. As a neurodevelopmental disorder, the temporal expression of risk genes will also be a noteworthy avenue of investigation (Owen, O' Donovan, Thaper & Craddock, 2011). EEG could be one of many useful measures in charting the course of gene expression and how it may be burdening the developing neuron.

6.6.2. EEG as part of larger cognitive-neuroscience batteries

One way to examine the different levels at which risk variants may be impacting is through cross-discipline work looking at

partnerships within the different techniques available to cognitive neuroscientists. As we know, EEG is accurate when it comes to temporal information on the fluctuations in brain activity but it lacks spatial specifications awarded by imaging techniques such as fMRI and PET. The combination of ERPs with imaging data can provide spatio-temporal resolution that neither alone can provide (Hopfinger, Khoe & Song, 2005). With extensive batteries on cases, healthy controls and first-degree relatives including behavioural tests, structural and functional imaging and electrophysiological data, this will greatly influence how extensively each risk variant's impact may be investigated. Gerlai (2002) recommends that such batteries should be organised hierarchically, starting from broader, less specific tests covering larger domains of cognition e.g., memory and then proceeding to increasingly focused tests e.g., a specific mechanism of memory such as visual tracking during a spatial-working-memory task.

6.6.3. SZ endophenotypes as treatment targets

The outstanding hope for neurocognitive approaches to neuropsychiatric genetics is to translate behavioural and genetic research into better diagnosis prognosis and treatment of SZ with the aim of ameliorating symptoms at the level where they present to a clinic. Although this is a far-sighted vision it remains an important ambition in treating this highly disabling condition. Although there is no clear-cut example of how an individual's risk of developing a particular disorder aids medical treatment in psychiatry at present, endophenotypes may emerge as a focus of pharmacotherapeutic intervention most especially because they

are potential targets for pathophysiological disturbance rather than something more over-arching such as hearing voices (Deutsch et al., 2009). Considering that these endophenotypes are also relevant to unaffected relatives, and even variation in the population at large, the rewards of such therapies would be far reaching. As previously outlined in chapter 1, the ą7 nAChR receptor in SZ underlies impairment in sensory gating (DeLuca et al., 2004; Freedman et al., 1997; Gray et al., 1996; Leonard et al. 1996; Stassen et al., 2000; Vidal & Changeux, 1993; Xu et al., 2001). Recently, pharmacological treatment targets for the P50 gating deficit in SZ have been addressed (see Morten et al., 2010 for a review). These recent studies have attempted to counter-act the gating deficits by improving the binding of choline and channel openings using citicoline and galantamine (Deutsch et al., 2008a; Deutsch et al., 2008b). It is also often useful to look to other fields of medicine to see what symptoms and genetic risk factors have combined to create avenues for treatment targets. One example comes from Alzheimer's disease where the E4 polymorphisms on Apolipoprotein E (ApoE4) are the largest known genetic risk factors for early-onset Alzheimer's disease (Corder et al., 1993; Kim, Basak & Holtzman, 2009; Strittmatter et al., 1993). The structure of ApoE4 is a much researched area for potential therapeutic targets whereby the detrimental effects of ApoE4 may be alleviated by genetic and pharmacological resistance to ApoE4 (Chen et al., 2011).

6.7. Conclusion

Endophenotype research is just one of a number of approaches to discovering the relationship between genetic inheritance and SZ risk. The overall aim of this approach is to identify genetically

mediated aspects of cortical pathophysiology in SZ guided by hypotheses from neuroscience and molecular biology to that will ultimately improve diagnosis and treatment of patients through an improved understanding of the underlying neurobiology. The current studies measured very specific domains of cognition-executive functioning, visual perception and stimulus evaluation/processing. This set of studies sought to elucidate the influence of genome-wide-associated risk variants for SZ and demonstrate their utility in revealing how SZ risk genes may be affecting neural substrates of cognitive processing. These ERPs directly measured cognitive or perceptually relevant brain processes and how they varied in cases compared to healthy controls. This knowledge was also applied to converging evidence about gene function and connections to other areas of cognition. Hopefully progress in endophenotypes for SZ will directly benefit those affected by this illness by targeting pathophysiology rather than symptoms.

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Appendix A

Information letter & letter of consent

This research seeks to investigate the genetics of mental health. Our research group at Trinity College investigates whether genes thought to be involved in mental health have a specific role in brain function e.g. memory and attention. More specially, we are looking at the way in which the brain is influenced by genetics in relation to very early sensory information processing stages.

The current study uses a test which records the electrical activity of the brain. This is a non-invasive (does not penetrate the body) and safe measure. During the EEG recording, you will be seated in front of a computer screen, wearing a special kind of cap which contains sensors for picking up electrical activity from the. Each sensor will be conducted via water-based gel which washes out easily. This study involves the completion of some simple tasks. Basically these tasks require you to look at pictures of objects (such as an animal) and press a button when you see something you recognise. The purpose of this research is mainly to test people's ability to take in information through their senses. It won't require you to do anything as the equipment we use is very sensitive and picks up most responses automatically.

The preliminary stages of participation will involve preparing the equipment and fitting the head with the cap. This will take about 30-45 minutes. Thereafter, the actual completion of the tasks will take about 2hrs 15 mins. There will be short breaks interspersed. Thus the experiment will include: set-up, testing and finishing (washing the electrode gel from the hair).

CONSENT FORM

Name & Institution Leading the Research: Trinity College Dublin
Research Director: Dr. Gary Donohoe
Experimenter: Therese O' Donoghue.
Phone: 01-8962462
Email: odonogt@tcd.ie

I have read the above information sheet and the information has been explained to me to my satisfaction. I have had the opportunity to ask questions about the project and understand why the research is being done and any foreseeable risks or consequences involved.

I agree to partake of an EEG experiment for this study, which will take about 3 and a half hours. I understand how the sample will be collected, and that giving a sample for this research is voluntary and that I am free to withdraw my approval at any time.

I understand that all medical information pertaining to me will be protected by principles of confidentiality.

I understand that I will not benefit financially in any way and that this study is unlikely to benefit me personally.

Name of Participant (BLOCK CAPITALS) Date
Signature

_____ _____ _____

Name of Researcher (BLOCK CAPITALS) Date
Signature

_____ _____ _____

Participant Details

Participant Identification Number: _____

Date of Assessment: _____

Start time: _____ Finish time: _____

Name: _____

Gender: Male Female

Glasses Yes No

Age: _____ RA: _____

Date of Birth: _____

Cap size: L M

Handedness (EHS): _____

Vision: Normal Corrected to normal

Address:

_____

_____

Contact Telephone Number: _____

Email: _____

Educational Attainment:

a) finished primary school
b) completed inter-cert/ junior certificate
c) completed Leaving Certificate
d) certificate/plc
e) diploma
f) degree
g) post-graduate training/PhD etc.

Irish grandparents: yes no

Consultant: _____

Hospital: _____

Current medication:		Dosage:
a)	_____	_____
b)	_____	_____
c)	_____	_____
d)	_____	_____
e)	_____	_____
f)	_____	_____

Appendix B

Edinburgh Handedness Inventory

Please indicate your preferences in the use of hands in the following activities *by putting a check in the appropriate column.* Where the preference is so strong that you would never try to use the other hand, unless absolutely forced to, *put 2 checks.* If in any case you are really indifferent, *put a check in both columns.* Some of the activities listed below require the use of both hands. In these cases, the part of the task, or object, for which hand preference is wanted is indicated in parentheses. Please try and answer all of the questions, and only leave a blank if you have no experience at all with the object or task.

	Left	Right
1. Writing	☐ ☐	☐ ☐
2. Drawing	☐ ☐	☐ ☐
3. Throwing	☐ ☐	☐ ☐
4. Scissors	☐ ☐	☐ ☐
5. Toothbrush	☐ ☐	☐ ☐
6. Knife (without fork)	☐ ☐	☐ ☐
7. Spoon	☐ ☐	☐ ☐
8. Broom (upper hand)	☐ ☐	☐ ☐
9. Striking Match (match)	☐ ☐	☐ ☐
10. Opening box (lid)	☐ ☐	☐ ☐
TOTAL(count checks in both columns)		

Difference	Cumulative TOTAL	Result

Scoring:

Add up the number of checks in the "Left" and "Right" columns and enter in the "TOTAL" row for each column. Add the left total and the right total and enter in the "Cumulative TOTAL" cell. Subtract the left total from the right total and enter in the "Difference" cell. Divide the "Difference" cell by the "Cumulative TOTAL" cell (round to 2 digits if necessary) and multiply by 100; enter the result in the "Result" cell.

Interpretation (based on Result):

- below -40 = left-handed
- between -40 and +40 = ambidextrous
- above +40 = right-handed

Appendix C

Experimental paradigms

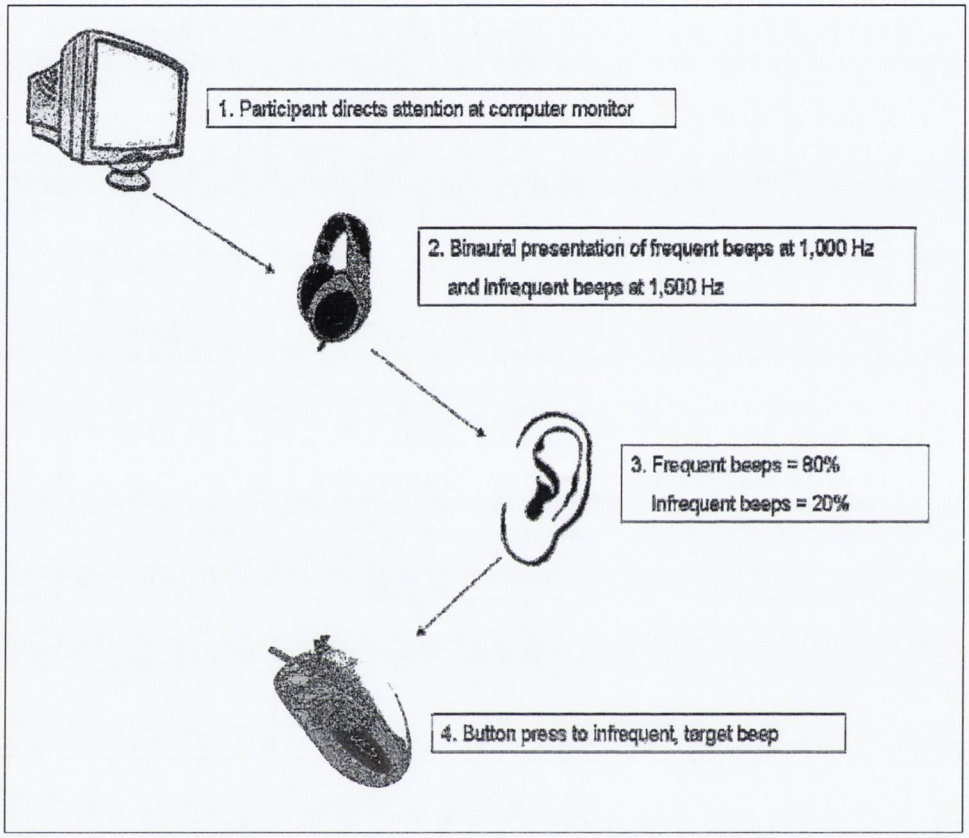

Figure C.1. The P300 was evoked by using an auditory oddball paradigm with pseudorandomised binaural presentation of frequent non-target (@ 1,000Hz) and rare target stimuli (at 1,500 Hz). Participants were directed to press the button on a computer mouse when they identified one of the target tones.

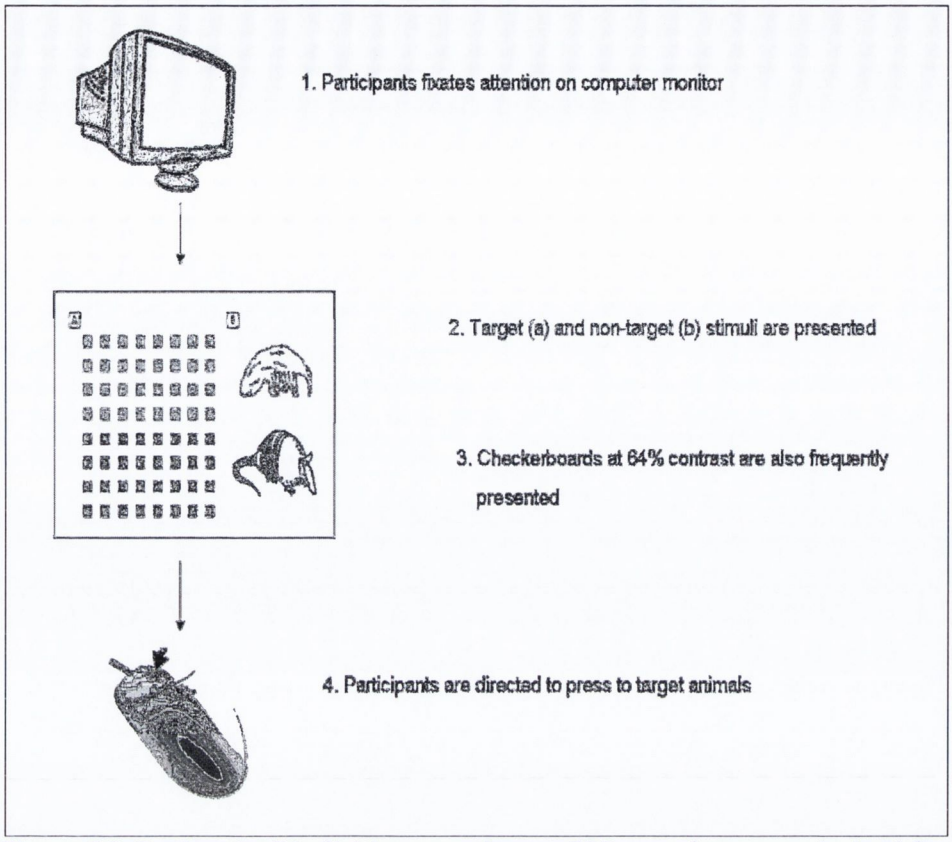

Figure C.2. During the P1 eliciting experiment, ERP waveforms are derived for the isolated check non-target stimulus. Participants are directed to perform target discrimination on the basis of infrequently presented animal line drawings, examples of which are (a) and (b).

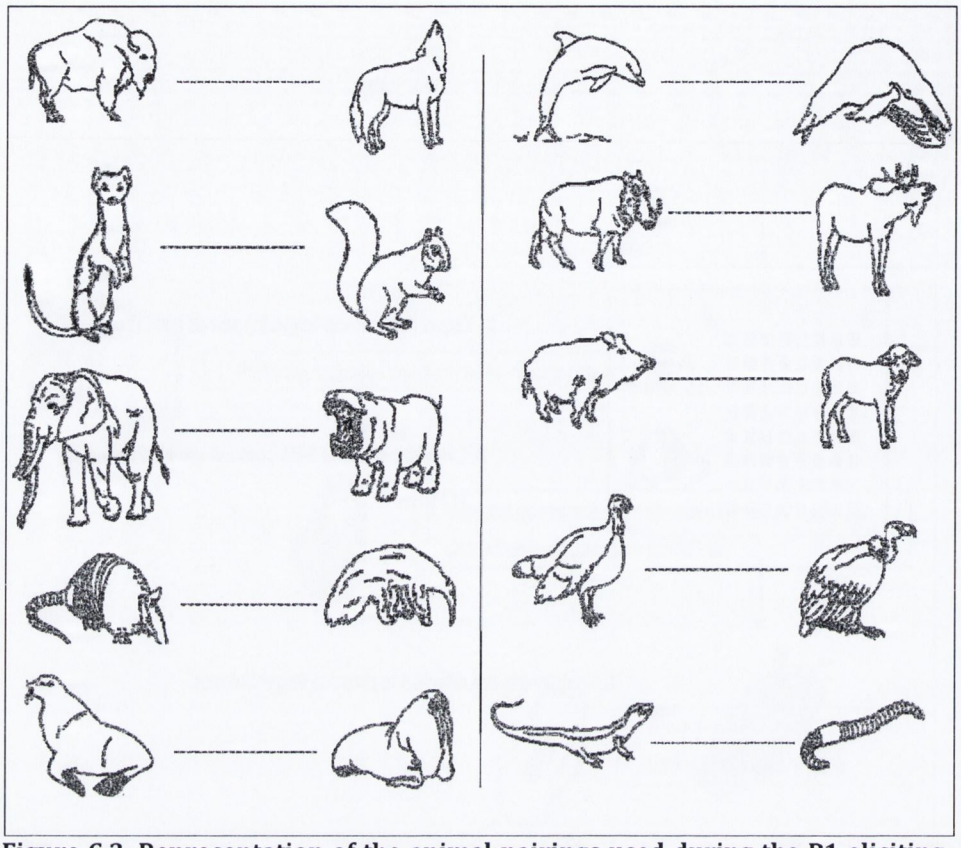

Figure C.3. Representation of the animal-pairings used during the P1 eliciting experiment. A different animal pair was presented for each block. These line drawings of two kinds of animals were presented on a white background. Participants were directed to respond to the target (either animal from each pair) by button press.

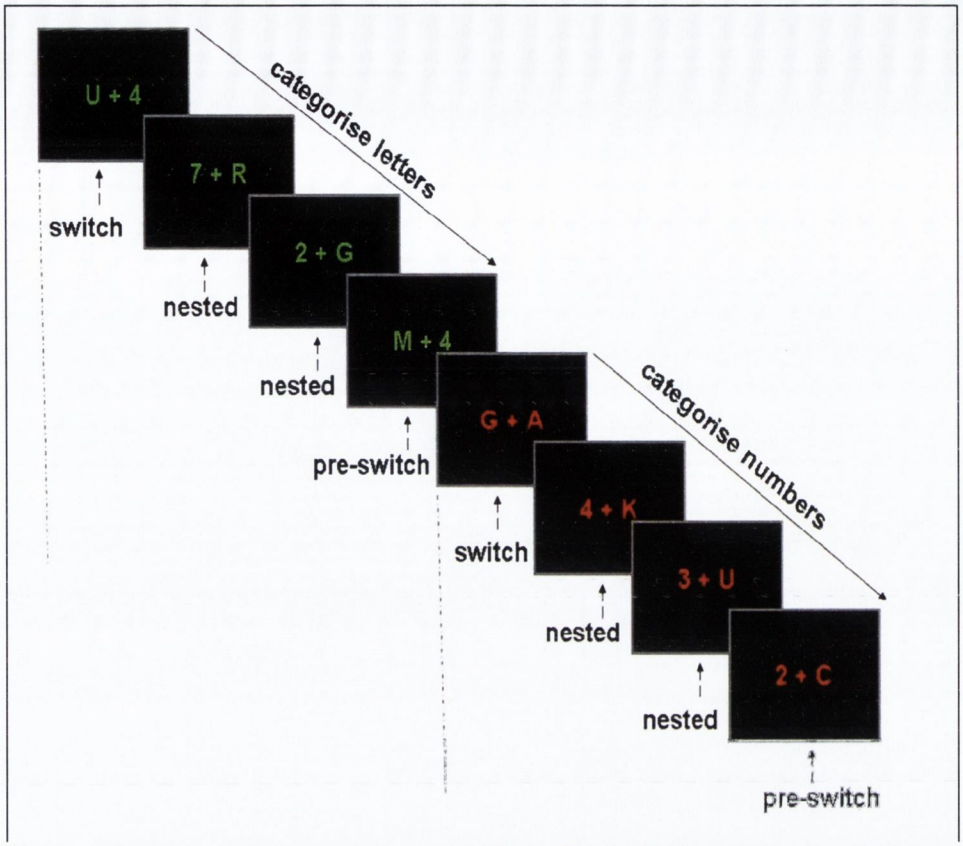

Figure C.4. Here, eight consecutive trials from the Switching-Attention-Task are shown. Participants were directed to perform one task (i.e., the letter task or the number task) when the stimuli were one colour (i.e., red or green). Participants always performed four trials of each task before switching to the other task.

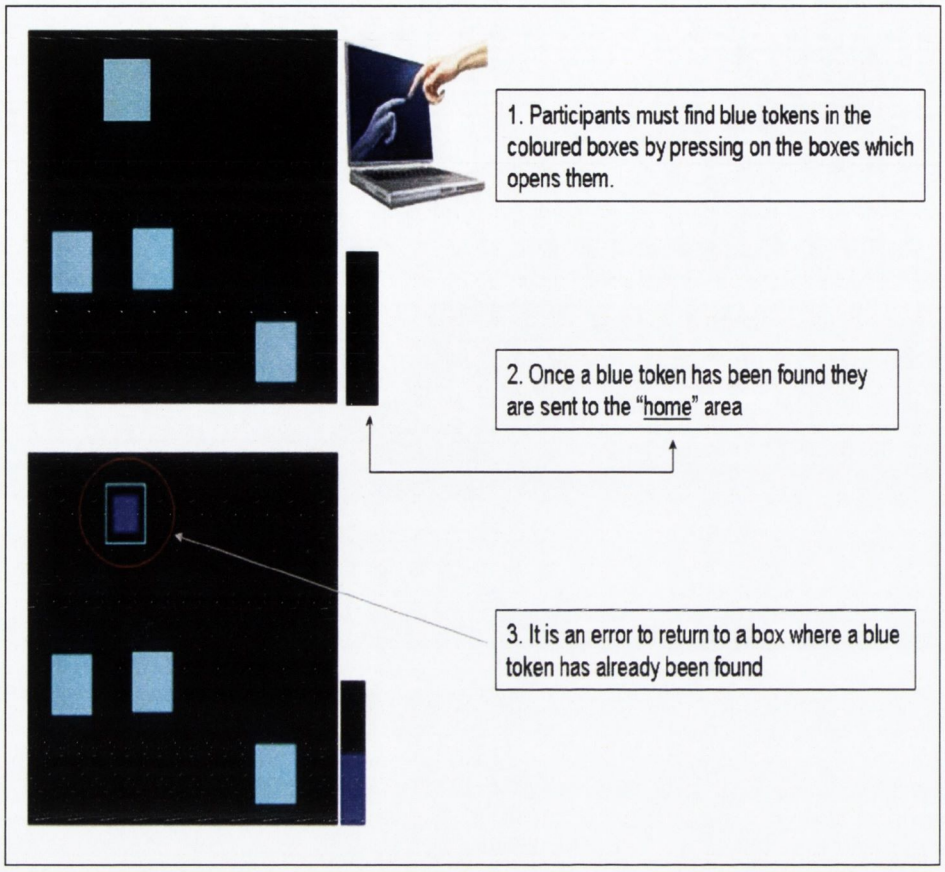

Figure C.5. A depiction of the Spatial Working Memory Task from the Cambridge Cognition Test Battery (CANTAB). Participants are directed to look for blue tokens in coloured boxes, send these tokens to "home" and remember never to return to a box from where a token has already been retrieved.

Appendix D

List of publications arising from this thesis

O' Donoghue, T., Morris, D., Fahey, C., Da Costa, A., Foxe, J., Horeld, D., Tropea, D., Gill, M., Corvin, A., Donohoe., G. (2011). A NOS1 variant implicated in cognitive performance influences evoked neural responses during a high density EEG study of early visual perception. *Human Brain Mapping (2011)*