Biomarkers of Brain Function in Psychosis and their Genetic Basis

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A thesis submitted to University College London
for the degree of Doctor of Philosophy

May 2016

Declaration

I, Siri Maria Ranlund, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:  Date: 18/05/2016

Abstract

Psychotic disorders, including schizophrenia and bipolar disorder, are amongst the most severe and enduring mental illnesses. Recent research has identified several genetic variants associated with an increased risk of developing psychosis; however, it remains largely unknown how these lead to the illness. This is where endophenotypes – heritable traits associated with the illness and observed in unaffected family members of patients – could be valuable. Endophenotypes are linked to the genetic underpinnings of disorders, and can help elucidate the functional effects of genetic risk variants.

This thesis investigates endophenotypes for psychosis, with the overall aim of identify such biological markers, as well as to examine the relationships between different endophenotypes and their associations with genetic risk for psychosis. A family design has been used throughout, including patients with psychosis, their unaffected first-degree relatives, as well as healthy controls.

In chapter 1, I review the endophenotype approach and those markers proposed for psychosis genetic research. Chapters 2 and 3 investigate whether different neurophysiological measures are potential endophenotypes for psychosis. In chapter 2, resting state EEG was studied and it was shown that risk groups, including unaffected relatives and people with an at-risk mental state, presented no abnormalities. This suggests that – rather than endophenotypes – the low frequency electrophysiological abnormalities seen in chronic patients in this study might be related to illness progression or long-term medication effects, and be more useful as biomarkers in non-genetic research.

In chapter 3, I used dynamic causal modelling to investigate effective connectivity – the influence that one neuronal system exerts over another – underlying the mismatch negativity evoked potential, a marker of pre-attentive auditory perception. Results indicate that, compared to controls, both patients and their

relatives show abnormalities of the excitability of superficial pyramidal cells in prefrontal cortex. Hence, this appears to be linked to the genetic aetiology of psychosis, and constitutes a potential endophenotype.

Chapters 4 and 5 investigate several pre-identified endophenotypes for psychosis: Electrophysiological (the P300 event related potential), cognitive (working memory, spatial visualisation, and verbal memory), and neuroanatomical (lateral ventricular volume). In chapter 4, the associations between these endophenotypes were examined. Results showed that the P300 amplitude and latency are independent measures; the former indexing attention and working memory and the latter possibly a correlate of basic speed of processing. Importantly, individuals with psychosis, their unaffected relatives, and healthy controls all showed similar patterns of associations between all pairs of endophenotypes, supporting the notion of a continuum of psychosis across the population.

Lastly, in chapter 5, polygenic risk scores – a measure of the combined effect of a large number of common genetic risk variants – were used to investigate the relationships between genetic risk for schizophrenia and bipolar disorder, and the endophenotypes studied in the previous chapter. Results showed that higher polygenic score for schizophrenia nominally predicts poorer performance on a spatial visualisation task; providing some evidence that the two traits share genetic risk variants as hypothesised. No other associations approached significance, possibly due to insufficient statistical power. However, as discovery samples grow, the use of polygenic scores is promising.

This thesis has thus contributed to the field of mental health research by investigating key electrophysiological, cognitive and imaging endophenotypes for psychosis, as well as their genetic influences. Well defined and reliably measured endophenotypes are valuable in mental health research by clarifying the functional effects of identified genetic risk factors, and by providing ways of identifying groups of people with similar abnormalities, both within and between current diagnostic categories.

Dissemination of Results

Published/accepted journal articles related to this thesis:

- **Ranlund**, Nottage, Shaikh, Dutt, Constante, Walshe, Hall, Friston, Murray, Bramon (2014). Resting EEG in psychosis and at-risk populations – A possible endophenotype? *Schizophrenia Research*, 153, 96-102.

  This paper forms chapter 2 of this thesis (and see Appendix A). My role: Literature review, study design, data management, EEG signal processing, data analysis and interpretation, manuscript writing and follow through until acceptance, dissemination of results at conferences.

- **Ranlund**, Adams, Díez, Constante, Dutt, Hall, Maestro Carbayo, McDonald, Petrella, Schulze, Shaikh, Walshe, Friston, Pinotsis, Bramon (2015). Impaired prefrontal synaptic gain in people with psychosis and their relatives during the mismatch negativity. *Human Brain Mapping*, in press.

  This paper forms chapter 3 of the thesis (and see Appendix B). My role: Literature review, study design, data management, EEG data processing, dynamic causal modelling analyses, interpretation of findings, writing manuscript and follow through until acceptance, dissemination of results at conferences.

- Shaikh, Dutt, Broome, Vozmediano, **Ranlund**, Diez, Caseiro, Lappin, Amakwa, Carletti, Fusar-Poli, Walshe, Hall, Howes, Ellett, Murray, McGuire, Valmaggia, Bramon (2015). Sensory gating deficits in the attenuated psychosis syndrome. *Schizophrenia Research*, 161, 277-282.

  My role: Contribution to data analyses and reviewing manuscript.

- Rapporteurs all performed equal work: Aas, Blokland, Chawner, Choin, Estrada, Forsingdal, Friedrich, Ganesham, Halli, Haslinger, Huckins, Loken, Malan-Müller, Martin, Misiewicz, Pagliaroli, Pardiñas, Pisanu, Quadri, Santoro, Shaw, **Ranlund**, Song, Tesli, Tropeano, van der Voetz, Wolfe, Cormack, DeLisi (2015) Summaries of plenary, symposia, and oral sessions at the XXII World Congress of Psychiatric Genetics, Copenhagen, Denmark, 12–16 October 2014. *Psychiatric Genetics,* in press.

  My role: Summarising sessions during the conference, writing and reviewing manuscript.

Journal articles related to this thesis in preparation:

- Joint first author: Blakey, **Ranlund**, Thygesen, Calafato, Lin, Psychosis Endophenotypes International Consortium (PEIC), The Wellcome Trust Case-Control Consortium 2 (WTCCC2), Colizzi, Crespo-Facorro, Díez, Di Forti, Iyegbe, Jablensky, Hall, Kahn, Kalaydjieva, Kravariti, McIntosh, McQuillin, Picchioni, Prata, Rujescu, Schulze, Shaikh, Toulopoulou, Van Haren, Van Os, Walshe, Lewis, Powell, Bramon (*in preparation*). Endophenotypes for psychosis and their interrelationships: A large scale family study.

  This paper forms chapter 4 of the thesis. My role: Study design, data management, writing manuscript, supervised during literature review, statistical analyses, and interpretation of findings.

- **Ranlund**, Thygesen, Calafato, Lin, Psychosis Endophenotypes International Consortium (PEIC), The Wellcome Trust Case-Control Consortium 2 (WTCCC2), Colizzi, Crespo-Facorro, Díez, Di Forti, Iyegbe, Jablensky, Hall, Kahn, Kalaydjieva, Kravariti, McIntosh, McQuillin, Picchioni, Prata, Rujescu, Schulze, Shaikh, Toulopoulou, Van Haren, Van Os, Walshe, Lewis, Powell, Bramon (*in preparation*). A Polygenic Risk Score Analysis of Psychosis Endophenotypes.

  This paper forms chapter 5 of the thesis. My role: Literature review, study design, data management, calculation of polygenic scores, statistical analyses, interpretation of findings, writing manuscript, dissemination of results at conferences.

- Díez, Adams, **Ranlund**, Constante, Dutt, Hall, Maestro Carbayo, McDonald, Petrella, Schulze, Shaikh, Walshe, Friston, Pinotsis, Bramon (*in preparation*). Effective connectivity underlying the P300 event related potential in schizophrenia.

  My role: Contribution to study design and data analyses, reading of manuscript drafts.

Conference poster/oral presentations:

- Poster award finalist: **Ranlund**, Calafato, Lin, Arranz, Bakker, Collier, Crespo-Facorro et al. A polygenic risk score analysis of psychosis endophenotypes. *XXIInd World Congress of Psychiatric Genetics (WCPG)*, Copenhagen, Denmark, 12-16 October, 2014.
- Poster presentation: **Ranlund**, Diez, Adams, Walshe, Murray, Friston, Pinotsis, Bramon. Effective Connectivity in Schizophrenia – Dynamic Causal Modelling of the Mismatch Negativity. *4th Schizophrenia International Research Society (SIRS) Conference*, Florence, Italy, 5-9 April, 2014.
- Selected oral presentation: **Ranlund**, Nottage, Walshe, Constante, Dutt, Shaikh, Murray, Bramon. Resting EEG in psychosis and at-risk populations – possible endophenotypes? *Biomarkers for Brain Disorders: Challenges and Opportunities*, Cambridge, UK, February, 2013.

Declaration of Contributions

During this PhD, I have been involved in setting up a new EEG laboratory at UCL as part of a collaborative project between my supervisor (Dr Elvira Bramon) at the Division of Psychiatry and Dr Oliver Mason from the Division of Psychology and Language Sciences. This work included learning how to collect EEG data, testing the equipment, designing EEG experiments and conducting EEG data collection to ensure recordings were of sufficient quality. This was done during rest in an anechoic chamber, both during sensory deprivation and in a control condition. However, the data acquired in this new laboratory was not included in my thesis because the process of setting this up took a long time. Also, as with any new laboratory, the number of participants with a high quality EEG recording recruited so far do not constitute a large enough sample to of a publishable size. Instead, for my thesis I have used pre-existing data-sets collected by colleagues collaborating with my supervisors and me.

Therefore, I would like to thank Elvira Bramon, Miguel Constante, Anirban Dutt, Madiha Shaikh, and Ian Williams, as well as our collaborators in the Psychosis Endophenotypes International Consortium (PEIC), for providing access to data that they have collected.

Throughout this work I have received supervision and advice from my supervisors and colleagues, including statistical advice from statisticians at UCL (including Dr Rebecca Jones). I wrote chapter 1 (introduction) and chapter 6 (general discussion). Below is an outline of my contribution to each of the four experimental chapters in this thesis.

Chapter 2: I was involved in the study design discussion together with Elvira Bramon, and I conducted the literature review. I set up the database and undertook the quality control of all the EEG and clinical data, liaising with those who collected the data where necessary. I conducted the EEG signal processing, with hands-on

training from Judith Nottage. I led the statistical analyses and interpreted the findings, and I wrote up the chapter and manuscript. I followed the manuscript though during the review process, including responding to reviewers' comments. I organised for the paper to have open access (as per UCL policy). I disseminated the paper by presenting it at the Biomarkers for Brain Disorders: Challenges and Opportunities conference (February 2013) organised by the Wellcome Trust, where I was selected to give an oral presentation. I also presented this paper at the UCL Neuroscience Symposium (June 2013).

Chapter 3: I designed this study together with my supervisors Elvira Bramon, Dimitris Pinotsis and Karl Friston. I conducted the literature review, database management and preparation for analysis. I conducted all EEG data pre-processing, dynamic causal modelling analyses, and interpretation of findings. This was completed with training and advice from Alvaro Diez, Rick Adams and Dimitris Pinotsis. I also wrote the thesis chapter and manuscript, I followed the manuscript through during the review process and responded to reviewers' comments. I organised for the paper to have open access. I disseminated the paper by presenting it at the Schizophrenia International Research Society Conference (April 2014). I applied for and received a travel grant from the UCL Graduate School to attend this conference. I also presented these findings at the UCL Neuroscience Symposium (June 2014).

Chapter 4: For this chapter, I was involved in the study design discussion with Elvira Bramon. I managed the database – including collating information from multiple research centres, locating missing data, and undertaking all the quality control of the data. Processing of MRI scans and EEG data was done locally at the respective research centres and I liaised with all individual centres to ensure the data were compatible and that consistent methods had been used. I supervised our MSc student Rachel Blakey during the literature review, data analyses and interpretations of findings. I wrote up the chapter for this thesis and the manuscript that I am finalising for submission to a peer-reviewed journal.

Chapter 5: I designed the study together with Elvira Bramon. Quality control of all DNA samples and all genotyping were conducted at the Wellcome Trust Sanger Institute (Cambridge, United Kingdom). Once the genotyping data were sent back to us I was involved in the data quality control together with Kuang Lin (bioinformatician) and Elvira Bramon. I conducted the literature review and database management (using a subset of data from chapter 4). I calculated the polygenic risk scores, with training and advice from Stella Calafato and Johan Thygesen. I conducted all the statistical analyses and interpreted the findings. I also wrote the thesis chapter and the manuscript that I am preparing for submission to a peer-reviewed journal. I have presented these findings at the World Congress of Psychiatric Genetics (October 2014). I applied for and received a travel grant from the Guarantors of Brain to attend this conference. I also presented this study at the UCL Neuroscience Symposium (June 2015).

I have also contributed to teaching in the Division, including supervision of one BSc and one MSc student, and lecturing for MRC Psychiatry (neurophysiology in psychiatry) and MSc (EEG methodology and its use in psychiatry) courses. I have also been closely involved in grant applications, including for the BMA Margaret Temple and the BRC fast track grants.

Acknowledgements

I would like to thank my supervisor, Elvira Bramon, for always being generous with her time, and for her invaluable advice, guidance and support throughout. I have also been supervised by Dimitris Pinotsis and Karl Friston, and would like to thank them for most useful advice, and insightful comments and discussions during the course of this work.

Without the hard work of those who collected the data I have had the privilege to use, this thesis would not have been possible, so I am extremely thankful to Miguel Constante, Anirban Dutt, Madiha Shaikh, Ian Williams and Elvira Bramon, as well as our collaborators in the Psychosis Endophenotypes International Consortium (PEIC).

I am most grateful to Alvaro Diez, Johan Thygesen, Rick Adams, Stella Calafato, Muriel Walshe, Judith Nottage and Kuang Lin for their help and support throughout this work, and for all the useful discussions of all aspects of this research and beyond. I want to thank Mei-Hua Hall and Andy McQuillin for their thoughtful and thorough comments on drafts.

I would also like to thank others in the Division and at UCL more widely that made working here during these years so enjoyable – including the many lunches at the Farmers' market! Finally, I would like to thank my mum and Leon for being there for me during the highs and lows of this work.

Contents

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Chapter 1: Introduction

1.1 Psychosis

Psychotic disorders are amongst the most severe and enduring mental illnesses, characterised by a distorted sense of reality; an inability to distinguish subjective experiences from objective reality. Disorders where psychosis is commonly experienced include, amongst others, schizophrenia, bipolar disorder, and schizoaffective disorder. The lifetime prevalence of psychotic illnesses is approximately 4% (Bogren *et al.*, 2009; Kendler, 1996; Perälä *et al.*, 2007), and the typical age of onset is in adolescence or early adulthood (Messias *et al.*, 2007). These disorders are disruptive and often life-long, and associated with great personal, familial and societal costs (Knapp *et al.*, 2004; Saunders, 2003; WHO, 2008). Psychosis is considered amongst the leading causes of disease burden, accounting for 2.5% of the total disability-adjusted life years and 4.5% of the total years lost due to disability in 15-44 year olds (WHO, 2001). Individuals with psychotic illnesses have between 10 and 20 years reduced life expectancy compared to the general population, due to both physical health problems and suicide (Chang *et al.*, 2011; Hannerz *et al.*, 2001; Healy *et al.*, 2012; Laursen *et al.*, 2012).

Psychotic disorders are characterised by significant abnormalities in perception, cognition, speech, affect, behaviour, and insight (NICE, 2014) – which leads to a range of symptoms such as hallucinations and delusions (i.e. positive symptoms),

cognitive deficits, as well as a lack of motivation and interest (i.e. negative symptoms) (APA, 2013; Crow, 1981; NIMH, 2009). These symptoms are seen in several psychotic illnesses, including schizophrenia and bipolar disorder, and although certain features of these illnesses are distinct, there is ample evidence of many shared epidemiological and genetic risk factors (Bramon and Sham, 2001; Lee *et al.*, 2013; Murray *et al.*, 2004; Smoller *et al.*, 2013). Hence, in this thesis, I will use the term 'psychosis' to include a broadly defined phenotype, comprising patients diagnosed with a psychotic illness – including, but not limited to, schizophrenia, bipolar disorder, and schizoaffective disorder. All patients studied here have experienced symptoms of psychosis as part of their illness.

Despite extensive research over the past 20 years, the understanding of the aetiology of psychotic disorders remains limited (Jablensky, 2010; Matheson *et al.*, 2014). Consequently, there is a lack of objective diagnostic tests, and diagnoses are today still made based on descriptive clinical criteria (APA, 2013; Insel, 2010; Light and Makeig, 2015; WHO, 1992). Furthermore, although current antipsychotic drugs often manage positive symptoms, they frequently have distressing side effects (Leucht *et al.*, 2012; Staring *et al.*, 2009) and only limited benefits towards negative symptoms (Lieberman *et al.*, 2005; NICE, 2014). Hence, there is a pressing need to improve our understanding of the biological basis of psychosis, to be able to develop treatments that are more effective, as well as better diagnostic tools and earlier detection of these illnesses.

It is well known that psychosis is highly heritable; twin studies show that the estimated heritability lies between 60-85% (Cardno and Gottesman, 2000; Smoller and Finn, 2003; Sullivan *et al.*, 2003), and population-based studies show around 65% heritability (Lichtenstein *et al.*, 2009; Wray and Gottesman, 2012). This clearly suggests that the aetiology of psychosis is partly due to genetic risk variants (in combination, of course, with numerous interacting environmental factors); however, unravelling the complex genetics of psychosis has proven more challenging than first anticipated (Hardy *et al.*, 2008; Maher, 2008; Manolio *et al.*, 2009).

Nonetheless, with great technological advances and large international collaborations, recent research has identified several genetic loci associated with an increased risk of psychosis (Doherty *et al.*, 2012; Geschwind and Flint, 2015; Sullivan *et al.*, 2012). This includes a large number of common single subunit changes in the DNA sequence (i.e. single nucleotide polymorphisms; SNPs) of very small individual effects (Lee *et al.*, 2013; Purcell *et al.*, 2009; Ripke *et al.*, 2013, 2014; Sklar *et al.*, 2011), as well as rare risk factors like structural changes of the DNA (such as copy number variants; CNVs) of larger effects (Green *et al.*, 2015; Grozeva *et al.*, 2011; Stefansson *et al.*, 2008; Stone *et al.*, 2008; Walsh *et al.*, 2008; Xu *et al.*, 2008).

Although efforts are underway (e.g. O'Dushlaine *et al.*, 2015; Ripke *et al.*, 2014), it is still largely unknown exactly how these genetic risk factors lead to the illness and what mechanisms are involved that lead to an increased risk of developing a psychotic illness. An important goal of psychiatric genetic research is therefore to clarify the functional effects of the genetic risk variants that have been identified (Geschwind and Flint, 2015; Gurung and Prata, 2015; Hall and Smoller, 2010).

1.2 Endophenotypes

The use of endophenotypes can help bridge this gap, and has been proposed as an alternative solution for increasing the understanding of complex disorders including psychosis, by providing intermediate phenotypes potentially linking genetic risk variants to the illness (Figure 1-1) (Geschwind and Flint, 2015; Gottesman and Shields, 1973; Hall and Smoller, 2010; Wickham and Murray, 1997).

Gottesman and Gould (2003) defined endophenotypes as heritable traits that are associated with the illness, state independent (i.e. observed in an individual regardless of whether the illness is active of not), co-segregated with the illness within families, and observed in non-affected family members at a higher rate than in the general population. Hence, endophenotypes can be considered a subset of biological markers that are linked to the genetic underpinnings of disorders (Gottesman and Gould, 2003). They are quantitative measures that are objectively

and reliably obtained with laboratory-based methods rather than using clinical observations (Braff *et al.*, 2007; Glahn *et al.*, 2014).

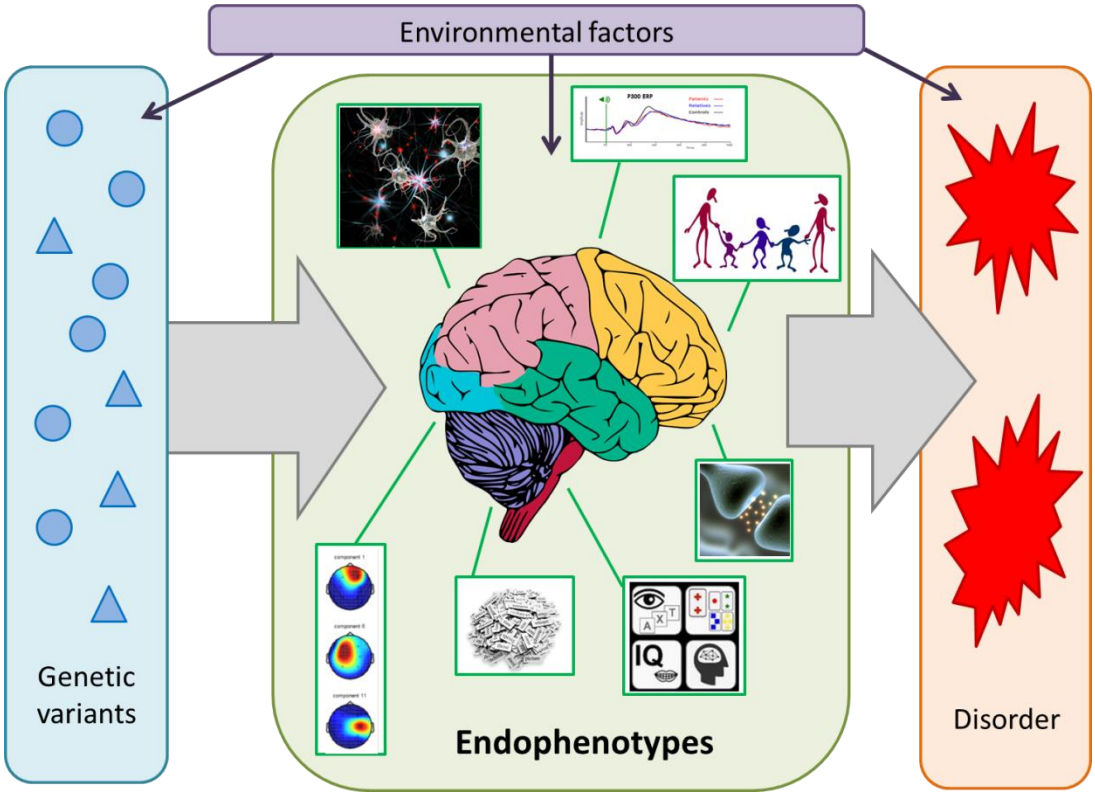

Figure 1-1. Endophenotypes.

Endophenotypes are quantitative traits on the pathway between genetic risk variants and the disorder.

These measures are thought to lie on the pathway between genes and behaviours, and are potentially a more direct expression of gene effects than the disorder itself (Gottesman and Shields, 1973; Light *et al.*, 2014). It was originally proposed that endophenotypes might be influenced by fewer genetic variants compared to the disorder, and that identifying reliable endophenotypes could facilitate the search for risk genes (Gottesman and Gould, 2003). This approach has been successful in other complex diseases such as obesity (e.g. Willer *et al.*, 2009), diabetes (e.g. Mitchell *et al.*, 2000), as well as in gene identification for alcoholism (Dick *et al.*, 2006).

In psychosis, however, endophenotypes have been of little use in identifying novel risk genes (Glahn *et al.*, 2014), and it is now clear that the genetic architecture of

endophenotypes most commonly studied in psychiatric research – such as neuroimaging and cognitive measures – are likely to be just as complex as that of the disorder (Davies *et al.*, 2015; de Geus, 2010; Munafò and Flint, 2014; Preston and Weinberger, 2005; Walters and Owen, 2007). Indeed, results from the Minnesota Twin Family study investigating several psychophysiological endophenotypes indicate that these are polygenic in nature, likely involving a large number of both common and rare genetic risk variants, similarly to psychiatric disorders themselves (Iacono *et al.*, 2014; Malone *et al.*, 2014a, 2014b). However, as mentioned above, with several genetic variants now identified that increase the risk of developing psychosis, the endophenotype approach can be useful in providing insight into the mechanisms linking these genetic risk variants to the disorder (Flint *et al.*, 2014; de Geus, 2010; Glahn *et al.*, 2014; Hall and Smoller, 2010; Iacono *et al.*, 2014; Meyer-Lindenberg and Weinberger, 2006; Munafò and Flint, 2014). For example, investigating associations between identified risk genes for schizophrenia and endophenotypes, Lencz et al (2010) found an association between the ZNF804A gene and brain volume in healthy individuals, and Hall and colleagues (2014) saw an association between the TCF4 gene and the P300 event related potential in a sample of patients with psychosis and controls.

Identifying reliable endophenotypes can also help define more homogenous subgroups within diagnostic classes, as well as groups of patients with similar characteristics across different diagnostic categories (Braff, 2015). This could in future lead to an enhanced understanding of the molecular and genetic aetiology of disorders, and to improved treatment options (by identifying novel treatment targets), as well as to better prediction of treatment outcomes (for both pharmacological and psychological treatments), earlier identification of risk groups, and improved diagnostic tools (Berrettini, 2005; Braff *et al.*, 2007; Hall and Smoller, 2010; Preston and Weinberger, 2005).

Candidate endophenotypes for psychosis include a wide range of measures – the most common being neuroanatomical, cognitive and electrophysiological – that have been found to be heritable, and abnormal in patients as well as in their

unaffected first degree relatives. This includes, for example, changes in grey and white matter volumes (Baaré *et al.*, 2001; Hasler *et al.*, 2006; McDonald *et al.*, 2004), neuropsychological abnormalities of executive functioning, working memory and attention (Burdick *et al.*, 2006; Glahn *et al.*, 2004; Horan *et al.*, 2008; Snitz *et al.*, 2006), as well as neurophysiological measures such as event related potentials (Bramon *et al.*, 2005; Ethridge *et al.*, 2015; Hall *et al.*, 2009; Olincy *et al.*, 2010; Schulze *et al.*, 2007; Thaker, 2008).

In this thesis, several of these will be discussed. However, the focus will be on the latter, neurophysiological endophenotypes identified using electroencephalography (EEG).

1.3 Electroencephalography (EEG)

Following on from pioneering work in animals by Richard Caton (1842-1926), the human EEG was first recorded in 1924 by the German psychiatrist Hans Berger (1873-1941), who described different brain rhythms such as alpha and beta waves, as well as the major features of normal, abnormal and sleep EEG (Berger, 1929, 1969). Since the 1930s, EEG has been key for the clinical diagnoses of seizure disorders (Gibbs *et al.*, 1935), and is today still widely used in clinical practice to also, for example, monitor sleep disorders and response to anaesthesia (Emerson and Pedley, 2012).

EEG is a direct measure of ongoing electrical brain activity resulting from neuronal communication. Since the electrical field quickly becomes weaker over distance, scalp electrodes are thought to measure activity originating from cortical neurons (Kropotov, 2009; Whittington *et al.*, 2000). Furthermore, the activity of a single neuron is too weak to be picked up, so the activity measured by EEG is thought to reflect the synchronous activity of thousands or even millions of neurons. Specifically, superficial pyramidal cells are thought to be the main generators of scalp EEG activity; because these neurons are large with an elongated shape that creates an electrical dipole, and they are aligned in parallel to each other, creating

an electrical field that can be detected on the scalp. In contrast, the electrical fields of spherically shaped dendritic trees of, for example, interneurons will cancel out because of the random orientation of the dipoles (Baldeweg and Boyd, 2008; Cohen, 2014; David and Friston, 2003; Lopes da Silva, 2013; Luck, 2005). Hence, when superficial pyramidal neurons fire synchronously the electrical signal gets amplified and can be detected by electrodes on the scalp (see Figure 1-2).

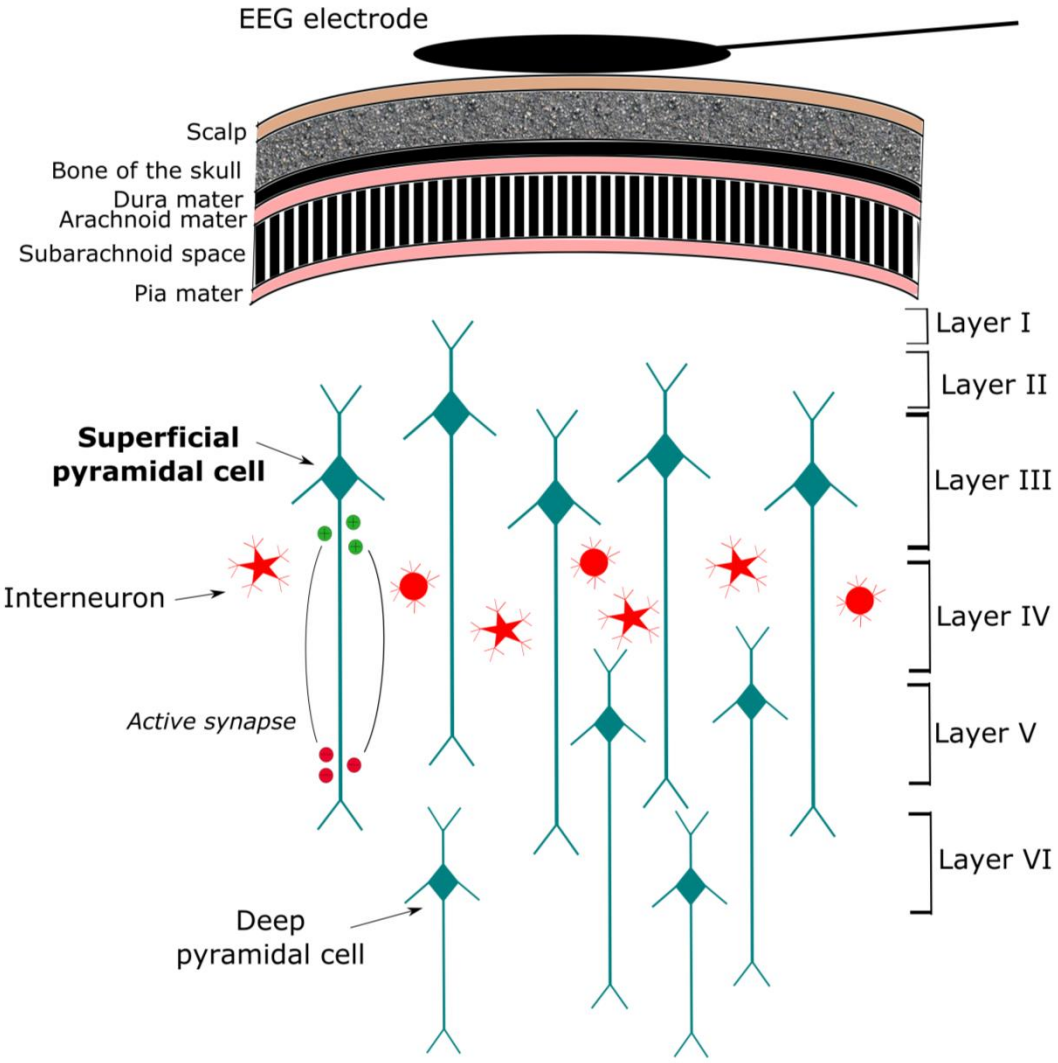

Figure 1-2. Scalp recorded EEG activity.

Superficial pyramidal cells are thought to be the main generators of scalp recorded EEG activity.

EEG activity is often measured in terms of the amplitude of oscillations at different frequencies – ranging from 0 to 100 Hz, commonly grouped into specific bands – or

the amplitude and latency of activity that is time and phased locked to a particular stimulus (i.e. event related potentials; ERPs). Changes of such measures are associated with variations in overall arousal levels, as well as with perceptual and cognitive processes (Baldeweg and Boyd, 2008; Buzsaki, 2006).

Importantly, EEG has excellent temporal resolution. Because electricity travels very fast, nearly at the speed of light, the activity recorded at the scalp represents brain activity at that moment in time (Cohen, 2014; Luck, 2005). For this reason, EEG is well suited to study the rapidly changing neural activity related to human cognition (Baldeweg and Boyd, 2008; Phillips and Uhlhaas, 2015). Other advantages of EEG include the relative ease with which it is assessed, the cost-effectiveness of the technique, and the fact the EEG can be obtained in a wide variety of clinical settings. Further, EEG is non-invasive, safe, and well tolerated by most patients (McLoughlin *et al.*, 2014; Winterer *et al.*, 2001). Because of these advantages, EEG is well-suited for studying brain activity in individuals who might be vulnerable, including psychiatric populations, as well as infants (Boutros, 2013; De Haan, 2013; Hoehl and Wahl, 2012; Saby and Marshall, 2012).

A limitation of EEG is its spatial resolution. It is well established that electrical fields in the brain do not flow directly upwards but get distorted and spread, and that each scalp electrode picks up the summed activity not only from spatially close cortical sources, but from nearly every source area in the brain (Baldeweg and Boyd, 2008; Light and Makeig, 2015; Luck, 2005). Hence, each pattern of scalp activity can originate from a large number of possible sources, making the reconstruction of cortical generators difficult. However, with high-density EEG recordings and novel analysis methods, there are now ways of reducing this problem, and high quality source localisation is now possible with EEG data (Bathelt *et al.*, 2014; Cohen, 2014; Michel and Murray, 2012; Phillips and Uhlhaas, 2015).

1.4 EEG measures as endophenotypes

As discussed above, candidate endophenotypes should be reliably measured and heritable (Glahn *et al.*, 2014; Gottesman and Gould, 2003). Research has found EEG measurements to have strong psychometric properties, with high test-retest (i.e. stability over time[1]) and split-half (i.e. internal consistency) reliabilities (Boyd *et al.*, 2014; Gudmundsson *et al.*, 2007; Hall *et al.*, 2006; Hämmerer *et al.*, 2013; Kondacs and Szabo, 1999; Salinsky *et al.*, 1991). Furthermore, individual differences in EEG parameters have been shown to be highly heritable, with estimates of up to 80% (van Beijsterveldt and van Baal, 2002; Enoch *et al.*, 2008; Hall *et al.*, 2009; Smit *et al.*, 2005).

Several EEG parameters have been shown to be promising endophenotypes for various psychiatric disorders, including psychosis, with measures associated with the illness and observed in unaffected relatives of probands. Many of these are not specific to diagnostic categories, but common amongst several illnesses. An example is the P300 event-related potential, which is elicited using an oddball paradigm, where the person is asked to respond to an infrequent target stimuli embedded in a series of frequent non-targets. The P300 is thought to reflect attention and working memory processes, and is a candidate endophenotype for substance use disorder (Euser *et al.*, 2012; Singh and Basu, 2009) as well as for psychosis (Bestelmeyer *et al.*, 2009; Bramon *et al.*, 2005; Schulze *et al.*, 2008).

As mentioned, endophenotypes should be observed in unaffected relatives of patients as well as in probands themselves, and to confirm whether this is the case, an experimental design including families is thus required. An important aspect of this thesis is that the sample studied here includes patients as well as their unaffected first degree relatives.

[1] Stability over time is mostly measured across several weeks, or up to 2-5 years. However, there are significant ageing effects in EEG measures, with great changes during development and across the lifespan (e.g. Kok, 2000; Kügler *et al.*, 1993).

It is advantageous to study unaffected family members for several reasons. First, since they are related to the patient they have an increased genetic risk for the disorder; patients and relatives will share some genetic risk factors that might influence the phenotype of interest. It is generally expected that relatives will show abnormalities that are intermediate between patients and healthy controls, which indicates a genetic basis of that phenotype (Cannon, 2005). Second, and importantly, because these individuals are unaffected they are not prescribed psychotropic medication. These drugs are known to alter brain function (Goozée *et al.*, 2014; Radua *et al.*, 2012), and this significant confounder can thus be eliminated by studying unaffected family members of patients. In short, studying unaffected relatives of patients allows us to examine the effect of carrying increased genetic risk without the confounding effects of the disease itself.

1.5 Thesis aims and hypotheses

This thesis aims to identify new psychosis endophenotypes, explore how established endophenotypes co-relate and to investigate their genetic influences. All studies presented here use EEG to investigate brain function, and all include unaffected family members of patients as well as probands themselves.

There are four specific aims of this thesis, which correspond to four experimental chapters. These are:

i) To investigate whether power of different frequency bands obtained during resting state EEG are suitable endophenotypes for psychosis genetic research (chapter 2);

ii) To investigate neural connectivity underlying the mismatch negativity event related potential, using dynamic causal modelling, and whether these measures qualify as potential endophenotypes for psychosis (chapter 3);

iii) To investigate the associations between different endophenotypes for psychosis – including electrophysiological, neuroanatomical and neurocognitive – and especially to characterise sub-components of the P300 event-related potential (chapter 4);

iv) To investigate the associations between genetic risk for schizophrenia and bipolar disorder and several multi-modal endophenotypes for psychosis, using polygenic risk scores (chapter 5).

The following hypotheses will be tested:

1) Compared to controls, resting state EEG activity of delta and theta activity will be increased, alpha activity will be reduced, and beta activity will be altered in patients with psychosis and to a lesser degree in at-risk populations.

2) Compared to controls, both individuals with psychosis and (to a lesser extent) their first degree relatives will show altered effective connectivity (specifically, the excitability of superficial pyramidal cells) in response to the mismatch negativity paradigm.

3) A range of multi-modal endophenotypes will be associated with each other: (i) All cognitive measures will be positively correlated; (ii) higher cognitive performance will be associated with larger P300 amplitude and shorter P300 latency; (iii) larger P300 amplitude will be associated with shorter P300 latency and; (iv) larger lateral ventricular volumes will be associated with poorer performance on the cognitive tasks and more impaired P300 (reduced amplitude and longer latency).

4) Higher polygenic risk scores for both schizophrenia and bipolar disorder will be associated with (i) poorer cognition, (ii) altered brain anatomy (larger lateral ventricular volume), and (iii) impaired P300 (reduced amplitude and delayed latency).

Chapter 2: Resting EEG in psychosis – a possible endophenotype?

2.1 Introduction

This chapter will investigate resting state EEG activity, aiming to explore whether this could act as a potential endophenotype for psychosis. Background EEG oscillations have been associated with overall arousal levels, and with perceptual and cognitive processing as well as task performance (Baldeweg and Boyd, 2008; Finnigan and Robertson, 2011; Kam *et al.*, 2013; Malone *et al.*, 2014a; Stam *et al.*, 2002). Hence, abnormal resting state EEG activity could lead to disturbances in perceptual and cognitive processing and is important to study.

The human EEG measures the brain's spontaneous electrical activity, which contains signals with a range of frequency bands. The slowest EEG frequencies in humans – delta (1-4Hz) and theta (4-8Hz) activity – are important in infancy and during deep sleep in adults (Baldeweg and Boyd, 2008; Hong *et al.*, 2012b). The functional significance of resting state delta and theta activity in the waking brain is not yet fully understood, although it is thought to be a measure of neural inhibition (Spironelli et al., 2011). Delta oscillations are also thought to be involved in motivation, and have been found to be increased during hunger and sexual arousal in healthy individuals, as well as in substance users (Knyazev, 2012). Further, increased delta activity has been associated with salience detection and attention.

All such processes are thought to be evolutionary old and basic, and in adults who are awake, delta and theta oscillations may be overshadowed by higher frequency EEG activity associated with higher cognitive functions (Baldeweg and Boyd, 2008). This includes alpha activity (8-13Hz), which has been associated with a state of relaxation without attention or concentration (Niedermeyer, 1999). Alpha activity is the most prominent human EEG rhythm during wakefulness and is best observed with eyes closed (Knyazev and Slobodskaya, 2003). With mental activation and attention, alpha activity is usually reduced, and higher frequencies such as beta oscillations (13-21Hz) become more prominent (Knyazev, 2012). Beta activity is seen in most healthy adults, and has been associated with active thinking and attention, a focus on the outside world, and problem solving (Niedermeyer, 1999). Beta activity is, thus, important in many higher cognitive processes, as well as attention, and cognitive integration and communication between spatially distinct areas of the brain (Benchenane et al., 2011; Brenner et al., 2003).

Resting EEG is heritable, with estimates of around 80% (van Beijsterveldt *et al.*, 1996; Enoch *et al.*, 2008; Malone *et al.*, 2014a; Smit *et al.*, 2005; Tang *et al.*, 2007), and psychiatric populations often show subtle alterations of background activity compared to healthy controls (Boutros *et al.*, 2008; Hughes and John, 1999). Patients with psychosis generally exhibit increased slow wave activity in the delta and theta bands and decreased alpha activity (Begić *et al.*, 2011; Galderisi *et al.*, 2009; Gattaz *et al.*, 1992; Harris *et al.*, 2006; Hong *et al.*, 2012b; Karson *et al.*, 1988; Kirino, 2004; Sponheim *et al.*, 1994, 2000; Venables *et al.*, 2009; Winterer *et al.*, 2001). In terms of resting beta activity, studies have reported both decreased (John *et al.*, 1994) and increased (Begić *et al.*, 2011; Wuebben and Winterer, 2001) activity, as well as no abnormalities in patients with psychosis (Hong *et al.*, 2012b; Mientus *et al.*, 2002; Sponheim *et al.*, 1994; Winterer *et al.*, 2001). Abnormalities in psychosis, furthermore, are not specific to these illnesses, but also observed in other psychiatric disorders such as depression and attention deficit disorder (e.g. Barry *et al.*, 2003; Begić *et al.*, 2011; Gauthier *et al.*, 2009; Saletu *et al.*, 2010).

When it comes to studies investigating resting state EEG activity in populations at-risk for psychosis, including unaffected family members of patients, relatively little research has been conducted and results have been inconsistent and sometimes even contradictory. Increased activity of all frequency bands have been observed, as well as no alterations compared to controls (Alfimova and Uvarova, 2003; Clementz *et al.*, 1994; Hong *et al.*, 2012b; Itil, 1977; Narayanan *et al.*, 2014; Venables *et al.*, 2009; Winterer *et al.*, 2001). Hence, although resting EEG activity appears to be heritable, and there are abnormalities in patients – particularly of the lower frequencies – it is unclear whether resting EEG represents a useful endophenotype for psychosis, which speaks to the need for further research in this area.

The aim of this study was to investigate the role resting EEG abnormalities play in the aetiology of psychosis, and whether it can provide an endophenotype for the illness. Quantitative EEG amplitudes at rest were compared across four frequency bands (delta, theta, alpha and beta), between five groups; chronic patients with psychosis, first episode patients, individuals at-risk of developing psychosis, unaffected relatives of patients, and healthy controls.

Based on past findings, it was hypothesised that amplitudes in delta and theta frequency bands would be increased, and amplitude in the alpha band would be reduced, in patients with psychosis as well as in populations at risk, compared to healthy controls. In the beta frequency band, no direction of abnormalities was predicted. Impairments were predicted to be most severe in patients.

2.2 Methods

2.2.1 Sample and clinical assessments

The total sample of 279 participants was recruited from the South London and Maudsley NHS Foundation Trust (including "Outreach and Support in South London" and the Lambeth Early Psychosis Intervention service), as well as through

collaboration with the charity Re-Think (www.rethink.org), and advertisements in the local and national media.

All participants were clinically interviewed to confirm or exclude a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; APA, 1994) diagnosis. The interview instruments used were the Structured Clinical Interview for DSM Disorders (SCID; First *et al.*, 1995) or the Schedule of Affective Disorders and Schizophrenia Lifetime Version (SADS-L; Endicott and Spitzer, 1978), and the Positive and Negative Syndrome Scale (PANSS; Kay *et al.*, 1987). Information regarding psychiatric diagnoses of family members not directly assessed was collected from the most reliable informant(s) with the Family Interview for Genetic Studies (FIGS; Maxwell, 1992). Additional information was collected from medical notes where available. Participants were excluded if they had a diagnosis of alcohol or substance dependence in the 12 months preceding study entry, any neurological disorders, or head injury with loss of consciousness for more than a few minutes.

Information regarding ethnicity and education for each participant was collected as part of our extensive semi-structured clinical interviews that were conducted by trainee or qualified psychiatrists. These measures were thus self-report in nature as is common in similar studies, including in previous publications from the group (Bramon *et al.*, 2005; Dutt *et al.*, 2011; Schulze *et al.*, 2008; Shaikh *et al.*, 2013).

The total sample included five groups. At the time of testing, chronic patients (N=48) had been ill for more than three years, and first episode patients (N=46) less than three years. The cut-off of 3 years reflects the maximum amount of time the local Early Intervention Service – where the first episode patients were recruited from – followed up their patients. This is comparable to other early psychosis research (Saleem *et al.*, 2013; Singh *et al.*, 2011). A full breakdown of the diagnoses in these two patient groups can be found in Table 2-1. Individuals with an "at risk mental state" (ARMS, N=33) were assessed using criteria in the Comprehensive Assessment for At Risk Mental State (Morrison *et al.*, 2006; Yung *et al.*, 2005). In this sample, 67% had attenuated psychotic symptoms, 10% brief limited intermittent psychotic symptoms (BLIPS), 10% BLIPS and attenuated symptoms, 3%

genetic risk with a decline in function, and 10% genetic risk with a decline in function and attenuated symptoms.

Unaffected first-degree relatives of chronic patients (N=45) had no personal history of any psychosis spectrum illness. Healthy controls (N=107) had no personal or family history of any psychotic disorders. Having a personal history of other non-psychotic psychiatric illnesses did not constitute an exclusion criteria for relatives or controls, provided they were well and not taking any psychotropic medication at the time of testing and for the preceding 12 months. This was to avoid recruiting biased control groups, unrepresentative of the local population.

After a complete description of the study, all participants gave their written informed consent. The study was approved by the Research Ethics Committee at the Institute of Psychiatry, King's College London.

2.2.2 EEG data acquisition

Resting EEG data was collected using either a 64-channel Synamps or a 40-channel Nuamps amplifier and respectively 64 or 40 channel quick caps with sintered silver/silver-chloride electrodes, placed according to the International 10/20 system (Jasper, 1958). All data were continuously digitised at 1000 Hz, with a 0–200 Hz band-pass filter. Electrode impedances were kept below 5 kΩ (Bramon *et al.*, 2008; Shaikh *et al.*, 2013).

For EEG data collected from 40 channels, unipolar electrodes placed on the outer canthi of both eyes, and above and below the left eye monitored eye movements. Linked ear lobes served as reference, and FPZ was the ground (Frangou *et al.*, 1997a). For EEG data collected using 64 channels, bipolar vertical and horizontal electro-oculographs monitored eye movements. Bilateral mastoids served as reference, and AFZ was the ground (Bramon *et al.*, 2008; Shaikh *et al.*, 2012).

EEG recordings were collected in a quiet room with participants sitting down comfortably. They were asked to keep their eyes closed for 20 seconds and then

open for 20 seconds, during a total of 5 minutes. Resting EEG data collection was followed by other EEG procedures reported elsewhere (e.g. Dutt *et al.*, 2012; Schulze *et al.*, 2008; Shaikh *et al.*, 2011).

2.2.3 EEG data processing

Signal processing was conducted using Neuroscan 4.3 software and MATLAB. Sequential epochs of 2048 ms were created from the continuous EEG files, separately for eyes-open and eyes-closed conditions. Automatic artefact detection rejected sweeps with activity exceeding ±100 μV (Reinhart *et al.*, 2011). EEG amplitude (μV) was calculated using the Fast Fourier Transformation using a Hanning window with 10% taper length. To suppress the effect of ocular artefacts, only the EEG segments acquired under eyes-closed conditions were included in further statistical analyses (Lavoie *et al.*, 2012; Zimmermann *et al.*, 2010). After artefact rejection and exclusion of eyes open data, on average 101 seconds remained per subject for analysis (mean = 101.20, SD = 29.33). This did not differ between groups.

Amplitude was analysed for four individual segments of the EEG spectrum; delta (1.95–3.90 Hz), theta (4.39–7.32 Hz), alpha (8.30–12.70 Hz), and beta (13.20–21.00 Hz). These frequency bands are typical of similar research (Boutros *et al.*, 2008), except that frequencies above 21 Hz were not analysed. This was due to accumulating evidence that frequencies above 21 Hz can still be substantially contaminated by scalp electromyogram activity (EMG), even after rejection of large EMG bursts (Nottage *et al.*, 2013; Shackman *et al.*, 2010; Whitham *et al.*, 2007).

For data-reduction purposes (to minimize type I error), only the three midline EEG channels, frontal (FZ), central (CZ), and parietal (PZ), were chosen for statistical analysis (Harris *et al.*, 2006).

2.2.4 Statistical analysis

Mixed effects linear regression models were used to examine EEG amplitude (log transformed to ensure normality), separately for each frequency band, with fixed effects of clinical group and scalp site, and random effects of family and subject. Hence, correlations between members of the same family were modelled, to maintain correct type 1 error rates. The dependent variable was EEG amplitude at each of the four frequency bands (delta, theta, alpha, and beta). The independent variables were participant group – a between-subjects variable with five levels (chronic patients, first episode patients, ARMS, relatives, and controls), and region – a within-subjects variable with three levels (FZ, CZ, and PZ). Age and gender were controlled for (as nuisance regressors) in all analyses. Since EEG data were collected using two different laboratories, due to an upgrade of the EEG equipment, this was also controlled for by including a binary regressor in the analysis. The control group and FZ were used as reference categories in all inferential tests.

A Bonferroni correction for four tests (delta, theta, alpha, and beta frequency bands) was applied, with the significance threshold thus set to $p = 0.05/4 = 0.0125$. Statistical analyses were performed using STATA version 11.2 and SPSS version 17.1.

2.3 Results

2.3.1 Sample characteristics

Demographic data for the entire sample is provided in Table 2-1. T tests showed that each group differed significantly from the control group in mean age, with the chronic patients and relatives being older (both groups $p<0.001$), and the first episodes and at-risk mental state (ARMS) individuals being younger ($p<0.001$) than controls. Chi square tests indicated that there were significantly more males in the first episode group in comparison to the control group ($p=0.05$). No other group differed in gender distribution compared to controls. To control for any age or gender effects on the resting EEG, these effects were included as covariates in all

analyses. As described in Table 2-1, the majority of chronic and first episode patients were taking antipsychotic medication at the time of testing, whereas the relatives, ARMS and controls were free of any psychotropic medication at the time of testing.

The mean EEG amplitudes (μV) for each group, in the four frequency bands, are shown in Table 2-2. Correlations between EEG amplitude in the four frequency bands and the three scalp sites were all significant, with correlation coefficients ranging between 0.28 and 0.99 (see Appendix A). Nevertheless, all analyses were adjusted for multiple testing (4 tests).

Most participants (first episodes, ARMS, and controls) were recruited individually, but the chronic patients and their relatives were recruited as part of a family study. Of the 279 participants, 174 (62.37%) were singletons, 72 (25.81%) were part of families with two members in the study, 21 (7.53%) were in three-person families, and 12 (4.30%) were part of families with four members participating.

Table 2-1. Sample demographics (N=279).

	Chronic patients	First episode patients	"At-risk mental state"	Relatives	Controls
N (%)	48 (17.2%)	46 (16.5%)	33 (11.8%)	45 (16.1%)	107 (38.4%)
Age (mean years ±SD)	41.8 ±11.3	25.0 ±3.9	23.8 ±4.0	48.8±16.1	31.6 ±13.3
Statistics[a]	t=-4.6 p<0.001	t=4.7 p<0.001	t=5.4 p<0.001	t=-6.3 p<0.001	-
Gender (% female)	35.4%	30.4%	39.4%	55.6%	48.6%
Statistics[a]	χ^2=2.3 p=0.16	χ^2=4.3 p=0.05	χ^2=0.9 p=0.43	χ^2=0.6 p=0.48	-
Diagnoses (N, %)					
Schizophrenia	33 (68.8%)	12 (26.1%)	-	-	-
Schizoaffective disorder	8 (16.7%)	1 (2.2%)	-	-	-
Brief psychotic disorder	1 (2.1%)	-	-	-	-
Schizophreniform psych.	-	26 (56.5%)	-	-	-
Bipolar I Disorder	5 (10.4%)	4 (8.7%)	-	-	-
Psychotic disorder NOS	1 (2.1%)	3 (6.5%)	-	-	-
ARMS	-	-	33 (100%)	-	-
Depressive illness	-	-	9 (27.3%)	17 (37.8%)	7 (6.5%)
Anxiety disorder	-	-	3 (9.1%)	5 (11.1%)	-
Substance Abuse	-	-	4 (12.1%)	-	1 (0.1%)
Personality Disorder	-	-	2 (6.1%)	-	-
No psychiatric illness	-	-	-	23 (51.1%)	99 (92.5%)
Medication (N, %)[b]					
No psychotropic medication	5 (10.4%)	6 (17.1%)	33 (100%)	45 (100%)	107 (100%)
Amisulpiride	5 (10.4%)	1 (2.9%)	-	-	-
Aripiprazole	4 (8.3%)	5 (14.3%)	-	-	-
Clozapine	7 (14.6%)	-	-	-	-
Flupentixol	4 (8.3%)	-	-	-	-
Olanzapine	14 (29.2%)	10 (28.6%)	-	-	-
Quetiapine	3 (6.3%)	1 (2.9%)	-	-	-
Risperidone	5 (10.4%)	11 (31.4%)	-	-	-
Other antipsychotic	9 (18.8%)	1 (2.9%)	-	-	-
Lithium or Sodium Valproate	9 (18.8%)	6 (17.1%)	-	-	-
Antidepressant	17 (35.4)	4 (11.4%)			
Education (mean years ±SD)[c]	12.9 ± 2.2	14.4 ± 2.9	14.1 ± 3.1	12.5 ± 2.2	14.4 ± 2.6
Ethnicity (N, %)					
Caucasian	44 (91.7%)	8 (17.4%)	20 (60.6%)	43 (95.6%)	76 (71.0%)
African/Caribbean	2 (4.2%)	30 (65.2%	8 (24.2%)	1 (2.2%)	25 (23.5%)
Other/Mixed	2 (4.2%)	8 (17.4%)	5 (15.2%)	1 (2.2%)	6 (5.6%)

SD = Standard Deviation; ARMS = At risk mental state; NOS = not otherwise specified; [a] t-tests for age and χ^2 tests for gender, each group compared against controls; [b] Data available for 76.1% of first episode group, % of those with information available reported; [c] Data available for 78.9% of the total sample.

Table 2-2. Average resting EEG amplitudes.

	Chronic patients	First episode patients	At risk mental state (ARMS)	Unaffected relatives	Controls
Delta	9.03 ± 2.63	8.08 ± 2.34	8.29 ± 2.05	7.17 ± 1.65	8.00 ± 1.94
Theta	12.10 ± 5.28	9.57 ± 3.72	9.38 ± 3.29	8.49 ± 3.24	8.95 ± 2.81
Alpha	8.57 ± 3.04	8.78 ± 4.44	8.60 ± 5.06	7.51 ± 3.84	8.95 ± 4.13
Beta	11.73 ± 3.49	9.21 ± 3.30	10.23 ± 3.65	11.23 ± 5.46	10.56 ± 3.35

Average resting EEG amplitudes (micro volts ± standard deviations) across FZ, CZ and PZ, for all participant groups and frequency bands, uncorrected for covariates.

2.3.2 Mixed effects linear regression

Four mixed effects linear regression models were analysed, see Table 2-3 and Figure 2-1. In the delta band, chronic patients had on average 0.208 μV greater amplitude than controls, which was statistically significant ($p<0.001$). No other group differed significantly from the control group in resting delta EEG amplitude. In the theta frequency band chronic patients had significantly greater resting amplitude compared to controls ($p<0.001$), with a 0.368 μV average increase in amplitude. No other group differed significantly from the controls in resting theta activity.

In the alpha and beta frequency bands, the control group did not differ significantly from any other group in resting EEG amplitude. Full details of these results, including main effects of covariates, can be found in Appendix A. Importantly, the effect of the two different EEG laboratories used for data collection was not significant in any frequency band, justifying pooling the two datasets in one analysis.

Table 2-3. Linear regression results.

Delta frequency band				
Controls vs.	β	p-value	95% confidence interval	
Unaffected Relatives	0.001	0.746	-0.033	0.046
"At-Risk Mental State"	-0.011	0.621	-0.053	0.032
First Episode Patients	0.005	0.800	-0.034	0.044
Chronic Patients	0.082	**<0.001**	0.045	0.119
Theta frequency band				
Controls vs.	β	p-value	95% confidence interval	
Unaffected Relatives	0.013	0.637	-0.044	0.072
"At-Risk Mental State"	0.004	0.891	-0.056	0.064
First Episode Patients	0.012	0.679	-0.044	0.067
Chronic Patients	0.136	**<0.001**	0.083	0.190
Alpha frequency band				
Controls vs.	β	p-value	95% confidence interval	
Unaffected Relatives	-0.026	0.486	-0.100	0.048
"At-Risk Mental State"	-0.045	0.254	-0.122	0.032
First Episode Patients	0.008	0.829	-0.063	0.079
Chronic Patients	0.035	0.310	-0.034	0.104
Beta frequency band				
Controls vs.	β	p-value	95% confidence interval	
Unaffected Relatives	0.034	0.232	-0.022	0.089
"At-Risk Mental State"	-0.022	0.457	-0.079	0.034
First Episode Patients	-0.013	0.644	-0.066	0.041
Chronic Patients	0.062	0.018	0.010	0.113

Mixed effects linear regression models on log transformed amplitudes with group (patient, relative, controls) and scalp site (FZ, CZ, PZ) as fixed effects, and family and subject as random effects. Covariates of age, gender and EEG laboratory included.

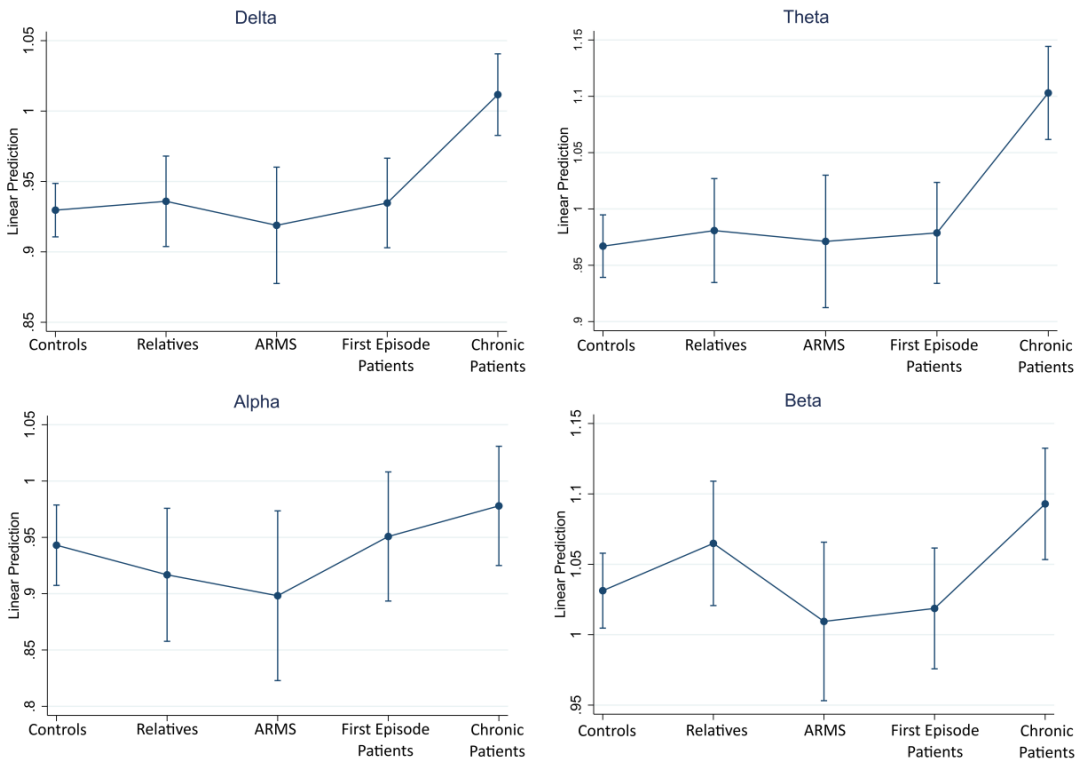

Figure 2-1. Resting EEG amplitudes.

Estimated mean resting EEG amplitudes (log transformed) with 95% confidence intervals, in the four frequency bands and the five participant groups. Adjusted for covariates of age, gender and EEG laboratory.

Since a broad definition of psychosis was used in this study, the analyses were repeated using a narrow definition of schizophrenia and schizophreniform psychosis, to investigate whether this would affect the results. Patients were excluded is they had a diagnosis of schizoaffective disorder, brief psychotic disorder, bipolar I disorder, and psychotic disorder not otherwise specified (15 chronic and 8 first episode patients), as well as their relatives (14). These analyses led to results very similar to those using the full dataset, and have not been reported further.

To further investigate potential differences in resting EEG between the groups, the 4 regression models were repeated post-hoc, using the chronic patient group as the reference category. This did not change the overall conclusions, and results are presented in Appendix A.

2.4 Discussion

The aim of this study was to compare EEG activity at rest in four frequency bands, in patients with psychosis, two populations at-risk of the disease, and healthy controls, to investigate whether these measures could be used as possible endophenotypes for the illness. The a-priori hypotheses were partly supported; chronic patients showed significantly increased resting delta and theta activity compared to healthy controls. However, first episode patients, individuals with an at-risk mental state (ARMS), and unaffected relatives of chronic patients did not differ from controls in these frequencies. Furthermore, there were no significant group differences in resting alpha or beta EEG activity.

Increased slow wave resting EEG activity in delta and theta bands in chronic patients with psychosis appears to be well replicated across studies (Begić *et al.*, 2011; Boutros *et al.*, 2008; Galderisi *et al.*, 2009; Harris *et al.*, 2006; Hong *et al.*, 2012b; Kim *et al.*, 2015b; Kirino, 2004; Narayanan *et al.*, 2014; Omori *et al.*, 1995; Sponheim *et al.*, 2000, 1994; Winterer *et al.*, 2001), and supported by these current results. However, this study did not find any significant differences in delta or theta resting activity between the control group and first episode patients or at-risk populations (including both clinically at-risk and genetically predisposed groups). Previous studies on such groups are limited, with inconclusive findings. Abnormalities similar to chronic patients have been observed in first episode patients (Clementz *et al.*, 1994; Sponheim *et al.*, 1994), ARMS (Gschwandtner *et al.*, 2009) and unaffected relatives (Alfimova and Uvarova, 2003), but several studies have also failed to show abnormalities in these populations (Harris *et al.*, 2006; Winterer *et al.*, 2001; Wuebben and Winterer, 2001). John et al (1994) found, similarly to current results, that chronic but not first episode schizophrenic patients had increased delta and theta resting activity.

In comparison to the slower frequencies, less research has been conducted on resting alpha EEG activity in psychosis. As in this study, Mientus et al. (2002) reported no evidence of alpha impairments in patients. However, several previous

studies on resting alpha have found a decrease in activity in psychotic patients compared to healthy controls (Begić *et al.*, 2011; Harris *et al.*, 2006; Omori *et al.*, 1995; Sponheim *et al.*, 2003). Reduced alpha activity has been associated with negative symptoms of schizophrenia (Merrin and Floyd, 1996), although the clinical significance of altered alpha activity is not well understood (Sponheim et al., 2000). Similarly to delta and theta EEG activity, abnormalities in alpha activity are not specific to psychosis, but commonly found in other disorders, for example in depression (Begić et al., 2011).

One potential reason for the lack of significant findings in this study might be that alpha activity is most prominent during eyes closed, and here participants were asked to keep their eyes open for 20 seconds, then closed for 20 seconds, and this was repeated during 10 minutes. This approach was taken to prevent participants from falling asleep during the experiment. Previous studies finding reduced alpha activity (Begić *et al.*, 2011; Harris *et al.*, 2006; Omori *et al.*, 1995; Sponheim *et al.*, 2003) asked participants to keep their eyes closed for the duration of the recording. This difference in methodology might explain our lack of findings in the alpha band. Future studies should investigate this further by conducting resting EEG experiments in large samples, including at-risk populations, and using methodology fully comparable to past findings.

In the beta frequency band, no significant group differences were found in resting EEG activity. However, a slight increase of activity was observed in chronic patients compared to controls (not reaching significance after correction for multiple testing), and post-hoc comparison between chronic and first episode patients revealed a slight increase of beta activity in the former group. Together this might indicate an abnormality in chronic psychotic patients, although more research is needed to confirm if this is the case. Whereas negative symptoms of psychosis have been largely associated with slow wave EEG activity, positive symptoms may be closer related to fast wave beta activity (Lavoie et al., 2012). Beta activity is thought to be involved in the synchronisation of activity of spatially distant brain regions; in functional connectivity (Whittington et al., 2011). Further, beta activity is thought to

be involved in a range of cognitive functions that are known to be impaired in psychotic disorders, such as attention, memory, and primary sensory processing (Kwon et al., 1999; Whittington et al., 2011).

The literature on resting beta activity in psychosis is inconsistent, with several studies reporting no resting beta abnormalities in psychotic patients (Hong *et al.*, 2012b; Mientus *et al.*, 2002; Sponheim *et al.*, 1994; Winterer *et al.*, 2001), although both decreased (John *et al.*, 1994) and increased (Begić *et al.*, 2011; Wuebben and Winterer, 2001) activity has also been observed. Finally, this study did not find any differences in beta amplitude between controls and first episode patients or at-risk populations. Past research on such populations has also largely failed to find significant impairments in these groups (Harris *et al.*, 2006; Hong *et al.*, 2012b; Sponheim *et al.*, 1994; Winterer *et al.*, 2001).

Taken together, the current results did not show any statistically significant differences in resting EEG activity of any frequency band between controls and first episode patients or at-risk populations, including ARMS and unaffected relatives of patients with psychosis. This indicates, as also argued by Winterer et al. (2001), that low frequency EEG abnormalities seen in chronic psychotic patients are likely related to the illness process, or to long-term effects of treatments, rather than to genetic risk for the disorder. Hence, resting EEG activity (of the four frequency bands examined) does not appear to be promising candidate endophenotypes for genetic research in psychosis.

Nevertheless, low frequency resting EEG abnormalities, in the delta and theta bands, were observed in chronic psychotic patients compared to healthy controls. Increased low frequency activity has been linked to negative symptoms of psychosis (Lavoie et al., 2012), as well as to cognitive deficits (Spironelli et al., 2011). It has been hypothesised that an increase in slow wave activity in psychosis could reflect a lack of motivation and anhedonia (Knyazev, 2012), since this type of brain activity has been shown to be important in such information processing in healthy individuals (Hong *et al.*, 2012b; Knyazev, 2012).

This could then be a useful biomarker in non-genetic research, perhaps investigating chronicity of the illness or cognitive deficits characterising psychosis, which are often associated with an enduring illness (Hyman and Fenton, 2003; Insel, 2010), or research into prediction of medication-responses. More research is needed to investigate this.

From an aetiological perspective, these findings of increased low frequency activity (and previous reports of similar abnormalities) are consistent with recent theoretical treatments of psychosis as false perceptual inference (Adams *et al.*, 2013; Fletcher and Frith, 2009). In this formulation, acute psychotic symptoms are regarded as a compensation for a failure of sensory attenuation. In other words, psychotic symptoms arise due to assigning too much salience or precision to high level representations to compensate for precise sensory (low level) inputs (c.f., aberrant salience; Howes and Kapur, 2009). In this setting, negative symptoms or chronic states are seen as a decompensation, with a relative loss of precision at higher levels of the neuronal hierarchy. In this context, precision corresponds to the post-synaptic gain of pyramidal cells reporting prediction errors in hierarchical predictive coding (Adams *et al.*, 2013; Bastos *et al.*, 2012). This is important because a decrease in postsynaptic gain or efficacy leads to a preponderance of lower frequencies relative to higher frequencies in endogenous or resting state activity (Kilner *et al.*, 2005). In short, the chronic group in this sample may be evidencing reduced synaptic gain at higher hierarchical levels and a shift in the characteristic frequencies of neuronal fluctuations to lower frequencies. Whether this is a primary aetiological factor, a characteristic part of the disease process, or a response to medication remains an open question.

Importantly, since antipsychotic drugs cross the blood–brain barrier and influence many parameters of brain function (e.g. Joutsiniemi et al., 2001; Knott et al., 2001), it is possible that these medications contribute or lead to resting EEG abnormalities observed in psychotic patients. In fact, several studies have found that the use of antipsychotic medication, especially clozapine, might lead to a slowing in the EEG signal, with increased low frequency (delta and theta) activity (Centorrino *et al.*,

2002; Hubl *et al.*, 2001; Hyun *et al.*, 2011; Joutsiniemi *et al.*, 2001; Knott *et al.*, 2001). This could be an important confounder in these current findings, suggesting that true illness-related effects on resting EEG are nuanced by medication. However, it has also been argued that antipsychotics are unlikely to account for EEG abnormalities seen in chronic patients, since such alterations have also been found in unmedicated patients (Boutros *et al.*, 2008; Kim *et al.*, 2015b; Merrin and Floyd, 1996; Omori *et al.*, 1995; Wuebben and Winterer, 2001). Since both the chronic and the first episode patient groups were medicated in the current sample, medication effects alone do not appear to fully explain why no abnormalities were observed in the latter group. Nevertheless, with my cross-sectional design it is difficult to disentangle true illness effects form effects of medication, and it is possible that the long-term effect of treatment is a confounding factor when interpreting these results. The effects of antipsychotic drugs on resting EEG activity need further investigation in longitudinal studies. However, such studies are very difficult to conduct since it is difficult to obtain EEG recordings from unmedicated patients who are often agitated and anxious. To delay treatment to allow EEG testing would have obvious ethical and practical challenges, and be hard to conduct, especially in the UK where patients are treated rapidly and efficiently.

Important considerations of statistical power need to be acknowledged. Calculations of effect sizes are hampered by the few studies available looking at populations at-risk of developing psychosis. Deficits in such populations are likely to be subtler than those in chronic patients. This has been shown to be true for, for example, the P300 event related potential (ERP) peak amplitude (Bramon *et al.*, 2005) and the error-related negativity ERP (Simmonite *et al.*, 2012), and electrophysiological measures of cortical inhibition (Hasan *et al.*, 2012). Furthermore, only a minority of individuals with an at-risk mental state will go on to develop psychosis (Fusar-Poli *et al.*, 2012a; Morrison *et al.*, 2012; Simon *et al.*, 2011), making abnormalities in this population difficult to detect. This was clearly observed in a study by Bodatsch et al. (2011) where only at-risk individuals who later converted to psychosis showed EEG abnormalities compared to healthy controls, whereas, similarly to these findings, the overall at-risk group did not differ

from controls. Hence, it may be assumed that effect sizes for possible resting EEG abnormalities in at-risk populations are smaller than those in patients. This, in turn, suggests that the current study might have been underpowered to detect true yet subtle differences between healthy controls and at-risk groups. Furthermore, this might also be true for previous studies investigating resting state EEG in at-risk populations, and it can be argued that findings of no abnormalities in such groups should not be interpreted as true until further research has been conducted. Future studies should address this issue by including large samples of individuals at-risk, including unaffected relatives, and by including comprehensive power calculations prior to conducting the study. At risk individuals are not easy to recruit and mega-analyses and meta-analyses offer a solution to increase sample sizes and integrate the growing number of small studies available.

In conclusion, the aim of this study was to characterise resting EEG oscillations in psychosis and populations at risk for this disease and particularly, whether such measures could act as endophenotypes for the illness. These results provide evidence that chronic psychotic patients exhibit resting EEG abnormalities in low frequencies. However, no abnormalities were observed in first episode patients or at-risk populations, suggesting that resting EEG activity is not likely to be related to genetic risk for the illness. Instead, abnormalities observed in chronic patients may be related to the illness process, or to long-term effects of treatment. Hence, results from this study indicate that resting EEG activity is not an appropriate candidate endophenotype for genetic research in psychosis, although low frequency activity could be a potential biomarker for non-genetic research, for example as prognostic or medication-response predictors.

Chapter 3: Effective connectivity underlying the mismatch negativity – a psychosis endophenotype?

3.1 Introduction

This chapter will investigate brain connectivity underlying the mismatch negativity (MMN) event related potential and whether this could act as an endophenotype for psychosis. The MMN is a pre-attentive brain response to a discriminable change in auditory stimulation (Duncan *et al.*, 2009; Näätänen, 1992; Todd *et al.*, 2013; Umbricht *et al.*, 2005). Reduced MMN amplitude is one of the most reliable findings in schizophrenia research, and since the first publication by Shelley et al (1991) over 100 papers have commented on this reduced amplitude (e.g. Baldeweg and Hirsch, 2015; Shaikh *et al.*, 2012; Todd *et al.*, 2013), with a mean effect size of 0.99 (Umbricht *et al.*, 2005). The MMN is abnormal in clinical risk groups as well as in patients, and is a promising biomarker for psychosis prediction (Bodatsch *et al.*, 2014; Nagai *et al.*, 2013). Furthermore, the MMN has been proposed as a potential endophenotype, because it is heritable (Hall *et al.*, 2006, 2009; Hong *et al.*, 2012a), and abnormal in first degree relatives of patients, who have an increased genetic risk for psychosis (Jessen *et al.*, 2001; Michie *et al.*, 2002). However, not all studies in unaffected relatives have found MMN abnormalities (Bramon *et al.*, 2004; Hong *et al.*, 2012a; Kim *et al.*, 2014).

Most previous studies of the MMN use classical EEG analysis methods that investigate the observed amplitude of the event related potential at the sensor level. However, abnormal functional integration among brain regions, or 'dysconnection', has been proposed as a core pathology of psychosis (Friston, 1998; Stephan *et al.*, 2006). Motivated by this hypothesis, the MMN was investigated in terms of the underlying neuronal connectivity. Dynamic causal modelling (DCM) was used, which explains EEG data using a hierarchical network of dynamically coupled sources, and estimates effective connectivity – the influence that one neuronal system exerts over another – using Bayesian model comparison and inversion (David *et al.*, 2006; Friston *et al.*, 2003). Several previous DCM studies have found abnormal effective connectivity in psychosis, both using EEG/MEG (Dima *et al.*, 2010, 2012; Fogelson *et al.*, 2014; Roiser *et al.*, 2013) and fMRI methods (Crossley *et al.*, 2009; Deserno *et al.*, 2012; Dima *et al.*, 2009; Mechelli *et al.*, 2007; Schmidt *et al.*, 2014). However, this was the first DCM study investigating the MMN paradigm in patients as well their unaffected relatives, with a view to examine whether abnormal effective connectivity (and its modulation) could act as an endophenotype for psychosis.

The hypothesis is based on current theories of psychosis that implicate the neuromodulation of postsynaptic excitability, or cortical gain control (Harrison *et al.*, 2011; Lisman *et al.*, 2008; Phillips and Silverstein, 2013; Stephan *et al.*, 2006). The most ubiquitous neurotransmitter receptor involved in gain modulation is the glutamatergic N-methyl-D-aspartate receptor (NMDA-R), which is expressed more densely in superficial cortical layers (Friston, 1998; Gonzalez-Burgos and Lewis, 2012; Lakhan *et al.*, 2013). NMDA-R hypofunction is known to be associated with psychosis; it is for example well established that NMDA-R antagonists such as ketamine or phencyclidine produce psychotomimetic symptoms in healthy individuals and worsen symptoms in patients with schizophrenia (Gilmour *et al.*, 2012; Javitt and Zukin, 1991; Kantrowitz and Javitt, 2010; Krystal *et al.*, 1994; Lahti *et al.*, 1995; Malhotra *et al.*, 1996; Pilowsky *et al.*, 2006). Recent genetic association studies also implicate the NMDA-R and its post-synaptic signalling cascade in the disorder (Purcell *et al.*, 2014; Ripke *et al.*, 2014). Furthermore, the hypofunctioning

of NMDA-Rs on inhibitory GABAergic interneurons is also thought to contribute to a loss of balance between excitation and inhibition, which has been implicated in the neuropathology of psychosis (Gonzalez-Burgos and Lewis, 2012). Lastly, reduced MMN amplitudes have been observed in healthy volunteers after NMDA-R blockade, for example by administration of ketamine (Javitt *et al.*, 1996; Näätänen *et al.*, 2012; Schmidt *et al.*, 2012a; Umbricht *et al.*, 2000). From a theoretical perspective, this loss of gain control or excitation-inhibition balance fits comfortably with hierarchical predictive coding models of psychosis and false inference – that rest on the abnormal encoding of uncertainty or precision by the gain of (superficial pyramidal) cells reporting prediction errors (Adams *et al.*, 2013).

Given the prominence of NMDA-Rs in superficial cortical layers, it is unsurprising that the gain of superficial pyramidal cell populations is strongly affected by NMDA-R function (Fox *et al.*, 1990; Pinotsis *et al.*, 2014). In DCM, this gain is parameterized as the inhibitory self-connectivity (or 'intrinsic connectivity') of superficial pyramidal cells within a cortical source (Friston, 2008). The aim of this study was to investigate group differences in MMN responses of patients with psychosis, their unaffected relatives, and healthy controls, and test whether these are best explained by modulations of synaptic gain at different levels of the cortical hierarchy. It was hypothesised that – compared to controls – both individuals with psychosis and (to a lesser extent) their first degree relatives would show abnormal cortical gain control.

3.2 Methods

3.2.1 Sample and clinical assessment

The total sample of 84 participants included 24 patients with a psychotic illness (75% schizophrenia, no comorbid diagnoses; see breakdown in Table 3-1), 25 unaffected first degree relatives of psychosis sufferers (without any personal history of a psychotic illness), and 35 unrelated controls (without any personal or family history of psychotic illnesses).

A personal history of non-psychotic psychiatric illnesses did not constitute an exclusion criterion for relatives or controls, provided they were well and not taking any psychotropic medication at the time of testing and for the preceding 12 months. This was to avoid recruiting biased control groups, unrepresentative of the general and local populations. 3 relatives (12%) and 1 control (3%) had a history of major depressive disorder.

Patients with psychosis and relatives were recruited through voluntary organisations, advertisements in the local press and from clinical teams at the South London and Maudsley NHS Foundation Trust. Controls were recruited by advertisements in the local press and job centres. Participants were excluded if they had a diagnosis of alcohol or substance dependence in the last 12 months, neurological disorders, or a previous head injury with loss of consciousness longer than a few minutes.

All participants were clinically interviewed to confirm or exclude a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; APA, 1994) diagnosis. Instruments used included the Schedule for Affective Disorders and Schizophrenia – Lifetime version (SADS-L; Endicott and Spitzer, 1978) and the Positive and Negative Syndrome Scale (PANSS; Kay *et al.*, 1987). Information regarding psychiatric diagnoses of family members not directly assessed was collected from the most reliable informant(s) with the Family Interview for Genetic Studies (FIGS; Maxwell, 1992).

All participants gave informed written consent to participate, and the study was approved by the Institute of Psychiatry Research Ethics Committee, conforming to the standards set by the Declaration of Helsinki. This sample is part of the larger Maudsley Family Study of Psychosis (e.g. Dutt *et al.*, 2012; Ranlund *et al.*, 2014; Schulze *et al.*, 2008; Shaikh *et al.*, 2013).

3.2.2 EEG data acquisition

Electroencephalogram (EEG) was collected from 17 scalp sites according to the 10/20 International system (FP1, FP2, F7, F8, F3, F4, C3, C4, P3, P4, FZ, CZ, PZ, T3, T4, T5, T6), grounded at Fpz using silver/silver-chloride electrodes (Jasper, 1958). Vertical, horizontal, and radial electro-oculographs monitored eye movements, and the left ear lobe served as reference. Data were continuously digitised at 500 Hz with a 0.03–120 Hz band-pass filter (24 dB/octave roll-off). Impedances were kept below 5kΩ (Bramon *et al.*, 2004, 2005).

3.2.3 MMN paradigm

This was a duration-deviant auditory two tone paradigm. The stimuli were 1200 tones (80 dB, 1000 Hz, 5 ms rise/fall time), with a 300 ms inter-stimulus interval, presented in three blocks of 400 stimuli through bilateral intra-aural earphones. 85% of the tones were “standards” (25 ms duration), and 15% were “deviants” (50 ms duration). Participants were sitting comfortably in an armchair, and were instructed to keep their eyes open, fixate on a point in front of them, and disregard the sounds presented. The total duration of the experiment was about 10 minutes (Hall *et al.*, 2009; Shaikh *et al.*, 2012).

The classical group comparisons of the MMN amplitude in this sample have been reported in a previous study (Bramon *et al.*, 2004). Here a new analysis of effective connectivity during the MMN task was conducted.

3.2.4 EEG data pre-processing

Signal processing was conducted using SPM 12b (Litvak *et al.*, 2011) and FieldTrip (Oostenveld *et al.*, 2011) in MATLAB R2013b.

The raw EEG data were converted to SPM format, and re-referenced to the common average. A high-pass filter of 0.5 Hz was applied, followed by a low-pass 70 Hz filter. A stop-pass (49-50 Hz) filter was also applied, to remove line noise. The

data were then downsampled to 200 Hz, and epoched with a peristimulus window of -100 to 300 ms. Baseline correction was performed using the 100 ms before stimulus onset.

Independent Component Analysis was used to correct for ocular artefacts in the data, and the EEG activity was decomposed into 17 independent components. When inspecting the ICA components for each participant, more than 2 that clearly corresponded to eye movements were not observed for any subject. For the majority of participants, 1 component was rejected, and for 8 participants (9.5%), two components were rejected. Additional automatic artefact rejection was then conducted, removing any trials whose activity exceeded ±70 μV across all channels. This resulted in an average of 45 trials (3.7%) being rejected per participant, which did not differ between the three groups ($F(2,81)=1.1, p=0.3$).

The EEG data were then averaged using robust averaging in SPM. This procedure produces the best estimate of the average by weighting data points as a function of their distance from the sample mean, so that outlier values have less influence on the overall mean (Wager *et al.*, 2005). This was followed by an additional low-pass filter of 70 Hz, as recommended with robust averaging (Litvak *et al.*, 2011).

The grand average event related potential waveforms across subjects were computed for patients, relatives and controls separately. The use of grand average waveforms ensures cleaner (almost noiseless) data for each group and condition. Grand averages retain features that are conserved within groups, and suppress individual differences (Fogelson *et al.*, 2014). These grand averages constitute 6 event related potentials – one for each group and stimulus condition (standard and deviant tones) – that were characterised in the subsequent DCM analysis.

3.2.5 Dynamic causal modelling

Dynamic causal modelling (DCM) explains measured data using a hierarchical network of dynamically interacting sources, and estimates effective connectivity (the influence that one neuronal system exerts over another), using Bayesian model

inversion (Friston *et al.*, 2007). DCM was originally developed for fMRI (Friston *et al.*, 2003) and was subsequently generalised to other modalities, including evoked responses measured by EEG (David *et al.*, 2006).

DCM permits source reconstruction whilst incorporating biological constraints on neuronal dynamics and coupling (David *et al.*, 2005; Kiebel *et al.*, 2009; Pinotsis *et al.*, 2012). The neuronal model makes predictions about the dynamics of each source based on the underlying anatomy and biology. The canonical microcircuit neural mass model (Bastos *et al.*, 2012) was used, in which each neural source comprises four cell populations: Superficial and deep pyramidal cells, spiny stellate cells and inhibitory interneurons. Each source is connected to other sources via extrinsic excitatory connections, and cell populations within sources are connected to each other via intrinsic connections (Pinotsis *et al.*, 2013). The focus of this study was the self-inhibition of superficial pyramidal cell populations (see Appendix B), because the strength of this connection reflects the gain (or excitability) of this population, which is linked to NMDA-R function.

Each source (i.e. each node in the network) was modelled with a single equivalent current dipole under bilateral symmetry assumptions (Kiebel *et al.*, 2006). A boundary elements head model was used (Fuchs *et al.*, 2001) to approximate the brain, cerebrospinal fluid, skull and scalp surfaces. A canonical MRI head model was used, and coregistration of electrode positions and head model was performed for each subject to map the Montreal Neurological Institute coordinates to points on the head.

Following standard practice, the EEG data were projected onto eight spatial modes to ensure more robust model inversion and dynamical stability. These are the eight principal components or modes of the prior predictive covariance in sensor space (Fastenrath *et al.*, 2009). Responses from 0 to 250 ms post stimulus onset were modelled, to ensure selective modelling of the MMN response *per se*, rather than later components (Garrido *et al.*, 2008).

3.2.6 DCM specification

In DCM, Bayesian inference is used to optimise neural source dipoles based on *a priori* information about their locations. This information is available from studies investigating the sources underlying the MMN – using fMRI (Molholm *et al.*, 2005; Rinne *et al.*, 2005; Schönwiesner *et al.*, 2007), PET (Dittmann-Balçar *et al.*, 2001; Müller *et al.*, 2002), EEG/MEG (Deouell *et al.*, 1998; Fulham *et al.*, 2014; Jemel *et al.*, 2002; Rinne *et al.*, 2000; Tiitinen *et al.*, 2006), and DCM (Garrido *et al.*, 2007, 2008, 2009a) – showing that the MMN is generated by temporal and frontal sources. Using DCM, the model with the most evidence consists of a three-level hierarchy comprising bilateral primary auditory cortices (Heschl's gyrus, A1), bilateral superior temporal gyri (STG), and the right inferior frontal gyrus (rIFG). The frontal source is lateralised to the right hemisphere for auditory paradigms (Garrido *et al.*, 2009a; Levanen *et al.*, 1996).

Following Garrido et al (2008), the following five sources were included, with prior source locations in the DCM analysis (in Montreal Neurological Institute coordinates): Left A1 (-42, -22, 7), right A1 (46, -14, 8), left STG (-61, -32, 8), right STG (59, -25, 8), and right IFG (46, 20, 8), illustrated in Figure 3-1A. DCM incorporates source reconstruction, and the inversion algorithm provides efficient Bayesian estimates of dipole sources that optimises these (David *et al.*, 2005; Kiebel *et al.*, 2009).

The DCM model used here assumes the existence of extrinsic (forward and backward) connections between, and intrinsic (inter- and intra-laminar) connections within the specified sources. This has been supported by previous MMN research (Dietz *et al.*, 2014; Garrido *et al.*, 2007, 2008, 2009a). Lateral connections linking left and right A1 and STG were also included (Schmidt *et al.*, 2012b). Auditory stimuli were modelled as direct input, entering bilateral A1. This model is shown in Figure 3-1B.

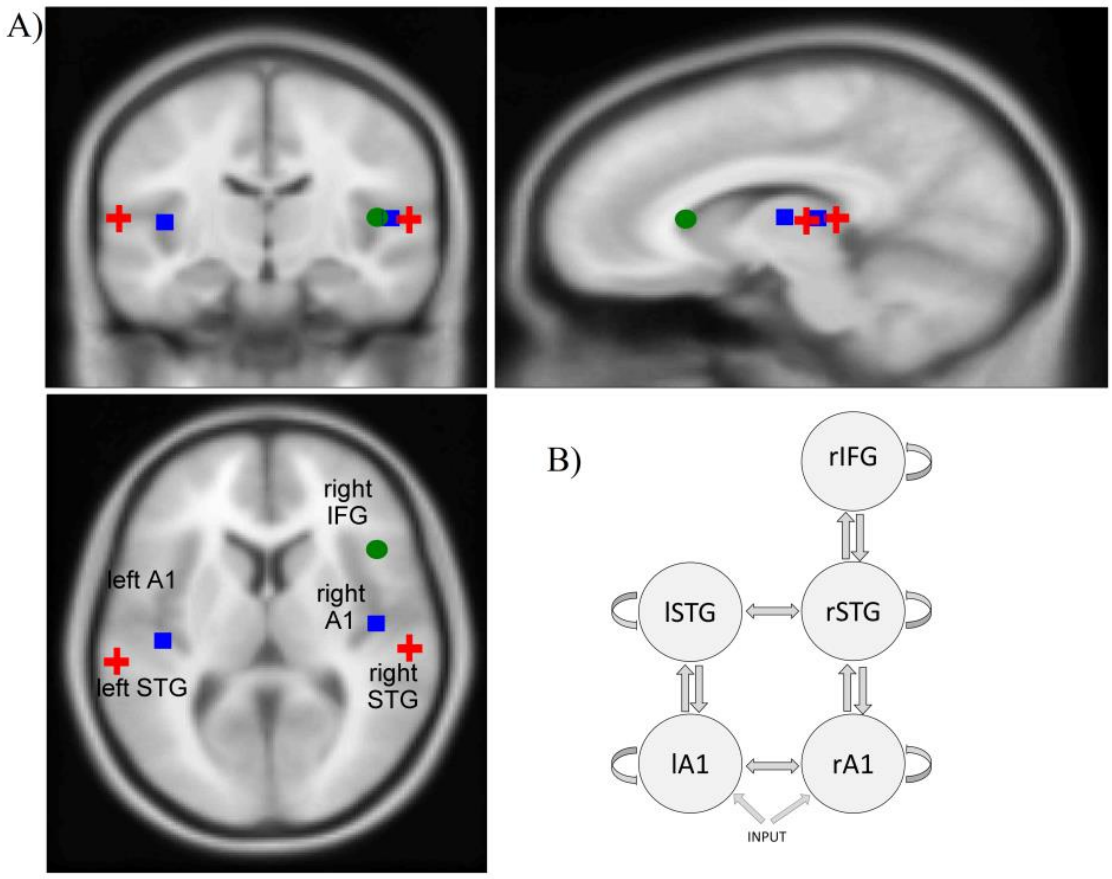

Figure 3-1. Dynamic Causal Modelling specifications.

Image showing A) the prior source locations (overlaid on an MRI image of a standard brain), and B) the structural model used for dynamic causal modelling. The sources are linked by extrinsic (forward, backward and lateral) connections, and each source has intrinsic inhibitory self-connections. A1 = primary auditory cortex; STG = superior temporal gyrus; IFG = inferior frontal gyrus; l = left hemisphere; r = right hemisphere.

3.2.7 Experimental effects

Condition-specific grand averaged data over all subjects within each group was used, allowing testing of the effect of group directly, as well as the effect of condition by group interactions (e.g. Fogelson *et al.*, 2014; Kiebel *et al.*, 2007). In other words, the grand averages were treated as the six cells of a 2 x 3 factorial design, with two levels of 'condition' (standard and deviant tones) and three levels of 'group' (controls, relatives and patients with psychosis).

Group effects were defined as i) having a genetic risk for psychosis (controls versus relatives and patients combined) and ii) having a diagnosis of a psychotic illness, irrespective of genetic risk (relatives versus patients). Main effects of diagnosis and genetic risk on effective connectivity were investigated, and their interactions with the effect of condition (standard versus deviant tones). The interactions reflect a diagnosis or risk effect on deviant-related changes in effective connectivity or postsynaptic sensitivity.

Bayesian model selection was used to find the model with the largest (free energy approximation to the) log model evidence, among the models tested, where models are penalised for increased complexity (Penny *et al.*, 2004). A difference in log evidence of three or more is considered strong evidence in favour of a model, corresponding to an odds ratio of about 20:1 (Friston and Penny, 2011).

Before testing for the effects of genetic risk and diagnosis, the best model to explain the effect of the deviant stimulus across all three groups was established. Eight candidate models were considered, with modulations of forward, backward and/or intrinsic connections. The model that allowed for modulations of intrinsic connections (self-inhibition of superficial pyramidal populations) only had the highest evidence, and was used in all subsequent analyses (see Appendix B).

To study the effects of genetic risk and diagnosis Bayesian model selection was used to establish where in the hierarchy synaptic gain – intrinsic (self-inhibitory) connectivity – was modulated. The model space consisted of models with modulations of intrinsic connections at each of the hierarchical levels (A1, STG, rIFG), and all combinations of these. A total of 8 models were thus compared, shown in Figure 3-2.

Having established the model with the greatest evidence, the posterior estimates of the effective connectivity under this model were examined (Friston and Penny, 2011). The focus was on changes in intrinsic connectivity induced by the mismatch negativity, to identify any differences between patients with psychosis, unaffected relatives and controls.

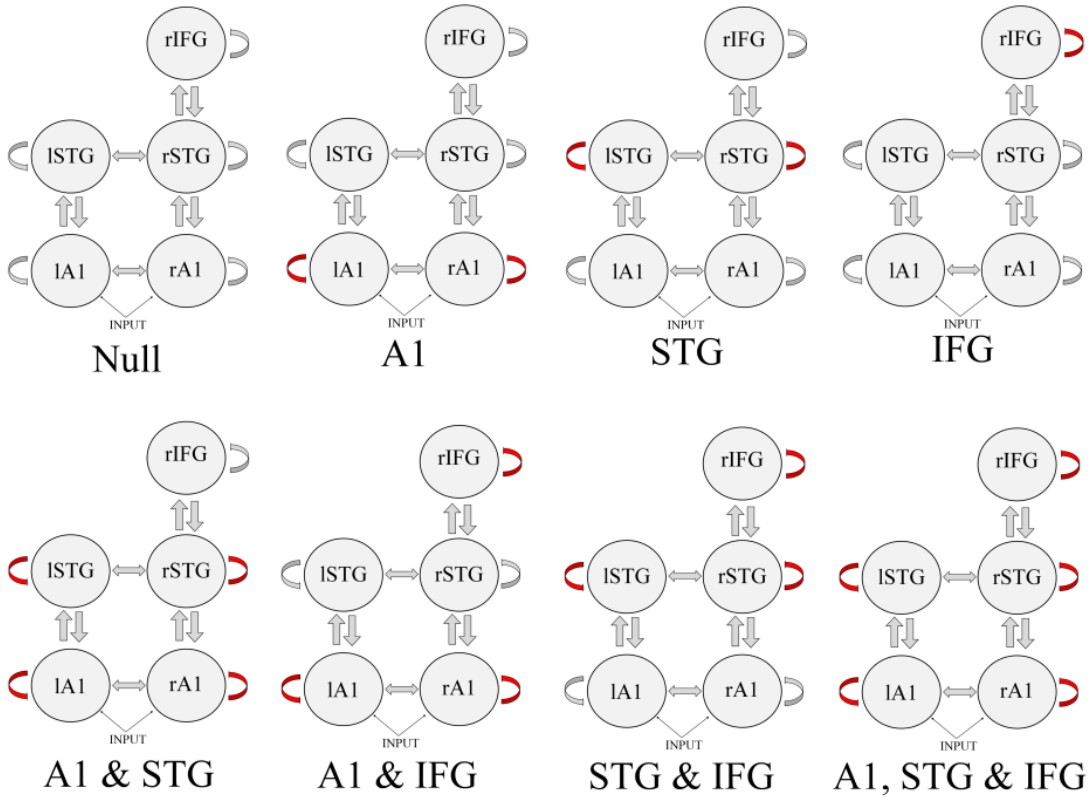

Figure 3-2. Dynamic Casual Modelling model space.

Dynamic Causal Modelling model space; identifying group differences in intrinsic (self-inhibitory) connectivity. Red arrows indicate a modulated connection. A1 = primary auditory cortex; STG = superior temporal gyrus; IFG = inferior frontal gyrus; l = left hemisphere; r = right hemisphere.

3.3 Results

3.3.1 Sample demographics

The demographic and clinical characteristics of the sample are detailed in Table 3-1. All participants were of European Caucasian ethnicity. Patients were significantly younger than controls (t=2.14, p=0.04) and relatives (t=2.60, p=0.01), and this group also contained more males compared to controls (χ^2=4.1, p=0.04) and relatives (χ^2=3.8, p=0.05). Controls and relatives did not differ significantly in age (t=0.51, p=0.61) or gender (χ^2=0.002, p=0.97) distributions. Importantly, patients and relatives together (i.e. the genetic risk group) did not differ from controls in age (t = -0.83, p=0.41) or gender (χ^2=1.33, p=0.27) distributions. Years in education did not differ between groups (F=0.40, p=0.67).

Table 3-1. Sample demographics (N=84).

	Patients with Psychosis N=24	Unaffected Relatives N=25	Controls N=35
Mean age (years, ±SD)	34.6 (±9.3)	43.7 (±14.5)	41.8 (±14.5)
Age range (years)	23 – 54	16 - 62	19 - 69
Gender (% female)	25%	52%	51%
Education (mean years, ±SD)	13.6 (±2.8)	14.0 (±3.1)	14.4 (±3.7)
Diagnosis (N, %)			
Schizophrenia	18 (75%)	-	-
Schizoaffective disorder	3 (13%)	-	-
Psychosis NOS	1 (4%)	-	-
Bipolar I disorder (w. psychosis)	2 (8%)	-	-
Major Depression	-	3 (12%)	1 (3%)
No psychiatric illness	-	22 (88%)	34 (97%)
Illness duration (mean years, SD)	12.1 (8.4)	NA	NA
Psychotropic medication (N, %)	23 (95.8%)	NA	NA
CPZ equivalent (mean, min-max)	549.4 (30-1100)	NA	NA
Years medicated (mean, ±SD)	10.6 (±8.6)	NA	NA
First medicated (mean years, ±SD)	24.4 (±7.2)	NA	NA
PANSS (mean, ±SD)[§]			
Positive	12.5 (±4.6)	7.2 (±0.6)	7.0 (±0.0)
Negative	14.9 (±5.5)	7.2 (±0.6)	7.0 (±0.0)
General	24.3 (±4.9)	17.5 (±2.0)	16.1 (±0.4)
Relationship to proband (N, %)			
Mother	NA	4 (16.0%)	NA
Father	NA	9 (36.0%)	NA
Sister	NA	8 (32.0%)	NA
Brother	NA	3 (12.0%)	NA
Daughter	NA	1 (4.0%)	NA

NA = not applicable; SD = standard deviation; NOS = not otherwise specified; CPZ equivalent = average chlorpromazine equivalent dosage (mg) for those taking antipsychotic medication (N=18); [§]PANSS = Positive and Negative Syndrome scale, positive and negative scores range from 7 to 49, PANSS general scores range from 16 to 112

The sample comprised 63 families, each including between 1 and 4 individuals. 49 participants (58.3%) were singletons, 18 (21.4%) were part of families with two members in the study, 9 (10.7%) were in three-person families, and 8 (9.5%) were part of families with four members participating. All unaffected relatives had a first-degree relative with a psychotic illness, although 8 (32%) did not have a proband participating in this study.

3.3.2 *Mismatch negativity group differences*

The grand averaged event related potential waves for patients, relatives and controls are shown in Figure 3-3. Group differences in the amplitude of the MMN wave of this sample have been reported in a previous paper (Bramon *et al.*, 2004): Patients with psychosis had significantly reduced MMN amplitude compared to both relatives and controls. The relatives did not differ significantly in MMN amplitude compared to the controls.

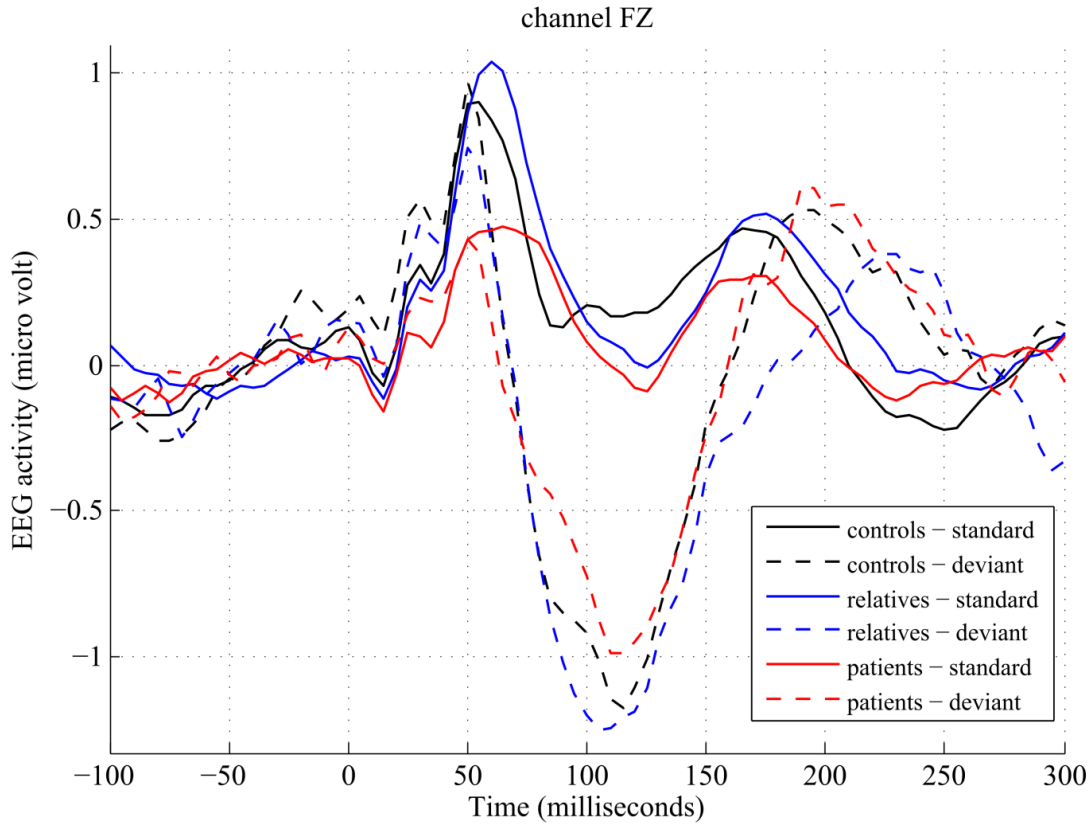

Figure 3-3. EEG activity to standard and deviant tones.

Grand average (across subjects) EEG amplitudes to standard and deviant tones for each group (patients, relatives, and controls), at channel FZ.

3.3.3 *Dynamic causal modelling results*

The Bayesian model selection results are presented in Figure 3-4A, showing model evidences relative to the null model (with no intrinsic modulations). The model that best explained the differences between groups allowed modulations of intrinsic

connectivity in bilateral A1 and rIFG. The difference in model evidence between the winning model and the runner-up was 80. This is significant seeing as a difference of 3 (corresponding to an odds ratio of 20:1) is considered strong evidence in favour of the winning model (Friston and Penny, 2011).

Figure 3-4B shows the posterior estimates of the modulations of intrinsic connectivity in the winning model for each group (controls, relatives, and patients) and condition (standard and deviant trials). Note that because the intrinsic self-connectivity is inhibitory, increased values correspond to reduced neural excitability, and *vice versa*. Posterior estimates of the modulations are also shown in Figure 3-5, for each source and experimental effect.

The largest effects are observed at the high-level frontal source (rIFG), where there are striking group differences. First, both relatives and patients show reduced self-inhibition (increased excitability) across task conditions compared to controls (i.e. a main effect of having a genetic risk for psychosis). Second, patients with psychosis show an additional reduction in self-inhibition compared to relatives, across task conditions (i.e. a main effect of diagnosis).

Third, there is a clear interaction between having a genetic risk for psychosis and task condition in rIFG; both relatives and patients show the opposite pattern of responses to the task compared to controls. While controls demonstrate reduced inhibition (i.e. increased excitability) in response to deviants compared to standard tones, the two groups with a genetic risk showed decreased excitability in response to changes in stimulus regularities.

At the sensory level (left and right primary auditory cortices, A1), all three groups show similar responses to the MMN task conditions: Increased excitability in response to deviant compared to standard tones.

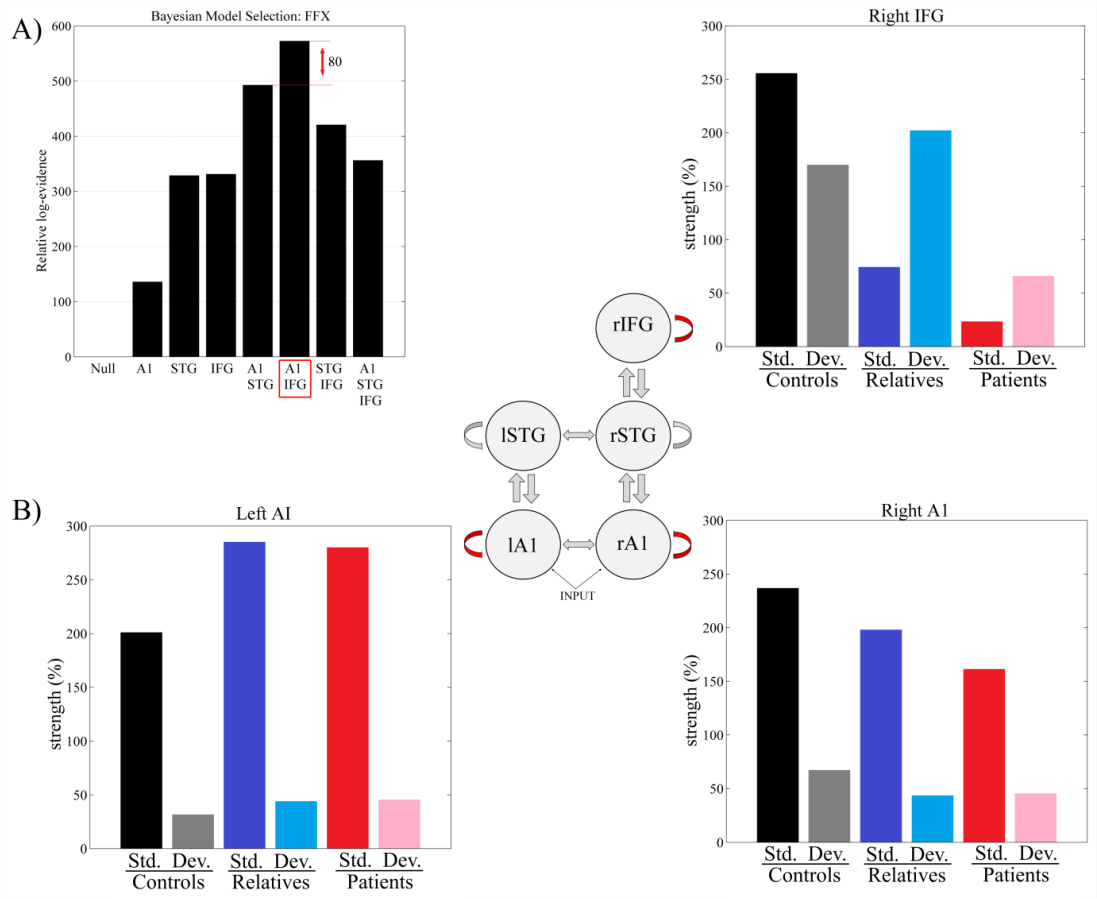

Figure 3-4. Dynamic Causal Modelling results.

A) Bayesian model selection results investigating intrinsic (inhibitory) modulations at different levels of the hierarchy. Log model evidences relative to the null model are shown. The winning model has modulations at A1 and IFG, and the difference in log evidence between this and the runner-up is 80. B) Changes in intrinsic connectivity strengths under the winning model, at each source, for patients, relatives and controls, and for standard (std.) and deviant (dev.) trials. A1 = primary auditory cortex; STG = superior temporal gyrus; IFG = inferior frontal gyrus; l = left hemisphere; r = right hemisphere.

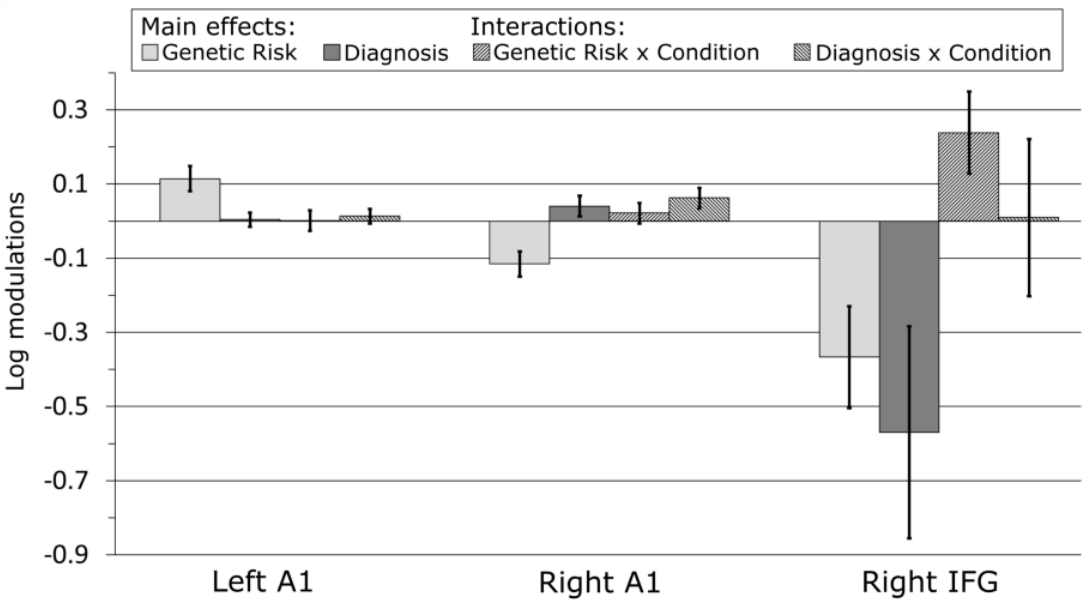

Figure 3-5. Posterior estimates of intrinsic connectivity.

Posterior estimates of the (log scaling of) intrinsic connection parameters and their 95% confidence intervals, for each source and experimental effect investigated. A1 = primary auditory cortex; IFG = inferior frontal gyrus.

3.4 Discussion

The aim of this study was to investigate whether, compared to controls, patients with psychosis and/or their unaffected relatives show altered cortical gain control (intrinsic connectivity) within cortical sources during the mismatch negativity (MMN) paradigm. DCM was used, where intrinsic connectivity is a parameterisation of the (to some extent NMDA-R mediated) excitability of superficial pyramidal cells, which is thought to be abnormal in psychosis (Stephan *et al.*, 2006).

The main findings were that; i) the largest differences in cortical responses between controls and the other groups were expressed at the top of the cortical hierarchy in the right inferior frontal gyrus (rIFG), rather than in primary sensory areas (A1); ii) in rIFG, both groups with an increased genetic risk for psychosis (patients and their relatives) demonstrated an increase in cortical excitability across task conditions (with an additional increase in patients compared to relatives); iii) the two groups with a genetic risk for psychosis also showed a *reversal* of the normal pattern of increased excitability to deviant tones in rIFG.

The finding of reduced self-inhibition within rIFG across task conditions in those with a genetic risk for psychosis – as well as an additional reduction in patients with psychosis compared to relatives – is in line with theories of NMDA-R hypofunction in psychosis (Abi-Saab *et al.*, 1998; Corlett *et al.*, 2011; Goff and Coyle, 2001; Olney *et al.*, 1999; Stephan *et al.*, 2006). Specifically, NMDA-R hypofunction on parvalbumin positive inhibitory interneurons results in decreased inhibitory γ-aminobutyric acid (GABA) input to (and therefore disinhibition of) pyramidal cells and hence a loss of balance between excitation and inhibition in prefrontal cortex (Lewis *et al.*, 2012; Murray *et al.*, 2014; Pinotsis *et al.*, 2014). These abnormalities may be linked to neurophysiological disorganisation (Díez *et al.*, 2014), cognitive dysfunction, and the development of symptoms of psychosis (Ahn *et al.*, 2011; Lewis *et al.*, 2008; Spencer *et al.*, 2004).

Crucially, patients with psychosis and relatives show the opposite pattern of rIFG responses to deviant and standard tones, compared to controls. Controls show reduced self-inhibition (increased excitability) in response to deviants, whereas both patients and relatives show a reduction in excitability in this condition. This indicates that those with an increased genetic risk for psychosis (including both relatives and patients) fail to adjust or optimise the excitability of superficial pyramidal cells in response to changes of stimulus regularities.

In a visual target detection task, in which subjects had to respond to target appearances that were either predictable or unpredictable, Fogelson et al (2014) also investigated differences in intrinsic connectivity in patients with schizophrenia and healthy controls using EEG and DCM. They found that changes in intrinsic self-inhibition in response to predictable stimuli were significantly attenuated in patients; this is further evidence that patients with schizophrenia fail to adjust neuronal connectivity in response to the context of incoming stimuli.

These results can be interpreted in the context of predictive coding theories of brain function, in which the brain infers the causes of its sensory data using Bayesian inference by minimising prediction errors throughout the cortical hierarchy (Friston, 2008; Rao and Ballard, 1999). Predictive coding can be

implemented neurobiologically by deep pyramidal cells sending top-down predictions about lower level representations, and superficial pyramidal cells sending bottom-up prediction errors (the difference between the actual and predicted activity) back up the hierarchy, in order to update the higher level representations (Friston, 2008). These neurobiological details are important, because superficial pyramidal cells – i.e. prediction error units – make the primary contribution to event related potentials (Garrido *et al.*, 2009b; Lieder *et al.*, 2013). Crucially, the influence of ascending prediction errors on higher representations depends upon their precision, which is thought to be encoded by the gain or excitability of superficial pyramidal cells. In this setting, precision (inverse variance) corresponds to the confidence or reliability attributed to prediction errors at each level of the cortical hierarchy (Adams *et al.*, 2013; Feldman and Friston, 2010).

In this MMN data, controls show increased synaptic gain (diminished intrinsic self-inhibition) in all cortical sources in the deviant condition – i.e. their prediction error responses to deviant tones are processed as being unduly precise and are therefore less easily suppressed. This is also the case for all individuals with a genetic risk for psychosis at the primary sensory level, but in rIFG the opposite pattern is seen. This indicates an abnormal influence of context on prediction error responses in this group, as has been seen not only in perceptual paradigms like the MMN, but also in reward learning and causal inference paradigms (Corlett *et al.*, 2007; Murray *et al.*, 2008). This also links to reward learning and the aberrant salience hypothesis, where symptoms of psychosis are attributed to assigning attention or salience to irrelevant perceptions or experiences (Howes and Kapur, 2009; Kapur, 2003). Results from the current study suggest that controls show precise prediction error responses to deviant tones (i.e. they are attending to these unexpected events). However, both patients with psychosis and their unaffected relatives show abnormalities here, suggesting they are not assigning salience to events in the environment correctly.

In computational modelling work, it has been shown that a loss of precision at higher levels of a hierarchical model can explain a loss of influence of context

(Adams *et al.*, 2013). Predictive coding simulations show that aberrant precision or gain control can reproduce classic findings in the schizophrenia literature, including a reduced MMN response (Adams *et al.*, 2013). NMDA-R hypofunction could confound precision or gain control in two ways, either by directly lowering synaptic gain in superficial pyramidal cell populations, or by reducing the excitability of GABAergic interneurons, thereby impairing sustained oscillatory firing of pyramidal cells and reducing their influence on lower areas (Adams *et al.*, 2013). These current results lend more support to the latter mechanism, and it would be interesting to test this hypothesis directly by using DCM to assess the relative model evidences for psychosis altering the excitability of superficial pyramidal cell versus inhibitory interneuron populations.

Importantly, these results suggest that both patients and their first degree relatives have similar alterations in the excitability of superficial pyramidal cell populations, compared to controls. This indicates that these changes are linked to genetic risk factors, and are not merely a consequence of the illness state or antipsychotic medication. This alteration in the gain of superficial pyramidal cells could therefore be a potential endophenotype for psychosis. The use of endophenotypes might help clarify the functional effects of genetic risk variants identified (Bramon *et al.*, 2014; Hall and Smoller, 2010), and further research could investigate whether deviant-related changes in excitability can predict genotype; for example, looking at candidate genes linked to NMDA-R function. Other studies investigating effective connectivity in psychosis have also observed abnormalities in relatives of patients, including children of probands (Diwadkar *et al.*, 2012, 2014; Winterer *et al.*, 2003a), and a previous study by Dima et al (2013) observed associations between fMRI derived measures of effective connectivity and risk genes linked to GABAergic interneuron function in patients with bipolar disorder.

These results also suggest that patients show a further increase in excitability in rIFG across task conditions compared to unaffected relatives. This may indicate that – at least in prefrontal cortex – there are quantitative, rather than qualitative, differences between those with and without a diagnosis of a psychotic illness but at

elevated genetic risk. Alternatively, this difference could be due to the effects of antipsychotic medication, which is known to influence brain function (e.g. Joutsiniemi *et al.*, 2001; Knott *et al.*, 2001). The exact effects of psychotropic drugs on effective connectivity remain unclear; however, a study investigating effective connectivity in schizophrenia found abnormalities in an unmedicated at-risk group but not in first episode patients (prescribed antipsychotics), suggesting that medication might potentially normalise abnormalities (Schmidt *et al.*, 2013). Future longitudinal studies and research in unmedicated patient populations are needed to address this important issue.

It should be noted that the amplitude of the MMN wave did not differ between unaffected relatives and controls in this sample, as has been published previously (Bramon *et al.*, 2004). Findings in the literature are somewhat inconsistent with some reporting abnormalities in relatives (Jessen *et al.*, 2001; Michie *et al.*, 2002), where others do not (Hong *et al.*, 2012a; Kim *et al.*, 2014). It is also interesting to note that although the amplitude of the MMN wave at sensor level did not differ between unaffected relatives and controls in my sample, the latter group showed abnormal source level connectivity compared to controls. This might seem contradictory, however, these two analyses differ in some key aspects: Firstly, the source level analysis of the MMN wave takes into account activity from all electrodes, whereas the sensor level analysis only investigating activity at two frontal locations (F3 and F4). Secondly, this DCM analysis was conducted on the averaged activity across all individuals within each group (the peak of the averaged group wave), whereas the study by Bramon et al (2004) looked at the amplitude of the MMN wave for each individual separately (the average of individual peak MMN waves). These differences could contribute to the apparent discrepancy in the findings. Furthermore, because these analyses are focusing on very different aspects of the data, it is also entirely possible that although the amplitude of the wave at the sensor level does not differ between relatives and controls, the source level measure of connectivity – the excitability of superficial pyramidal cells – is abnormal in unaffected relatives. Taken together, based on findings from this sample (i.e. from both sensor and source level analyses) it can be hypothesised that

source level connectivity of the MMN might be a more sensitive endophenotype for psychosis compared to sensor level activity.

A limitation of the current study is that the groups differed slightly in age and gender distributions. There is evidence for both age (Cooper *et al.*, 2006; Cooray *et al.*, 2014; Kiang *et al.*, 2009; Näätänen *et al.*, 2012) and gender (Brossi *et al.*, 2007; Matsubayashi *et al.*, 2008) effects on MMN responses, although a DCM study did not find significant effects of aging on intrinsic connectivity (Moran *et al.*, 2014). Importantly, however, the most significant effects were found when comparing those with a genetic risk for psychosis (i.e. both relatives and patients) with controls, and since these two groups did not differ in age or gender distributions, the main findings of this study are unlikely to be influenced by such confounds.

Another potential limitation is the experimental procedure used to elicit the MMN response. Because the MMN is a pre-attentive response not depending on the person paying attention to the sounds, it has been suggested that using a distractor task (such as watching a silent video or reading a book) can be advantageous (Duncan *et al.*, 2009; Lang *et al.*, 1995). In this study no distractor task was administered, and participants were instructed to disregard the sounds presented to them. It was therefore not possible to control whether participants were paying attention to the task or not. Nevertheless, this distractor-free design has been used previously and has been shown to generate clear MMN responses (Bramon *et al.*, 2004; Haenschel *et al.*, 2000; Javitt *et al.*, 1998; Juckel *et al.*, 2007). Furthermore, attention has been found to modulate the MMN response suggesting this ERP might not actually be independent of attention (Auksztulewicz and Friston, 2015; Sussman *et al.*, 2014; Woldorff *et al.*, 1991).

Patients with psychosis consistently show alterations in brain volumes compared to healthy individuals, including increased ventricular volumes (Boos *et al.*, 2007; Crespo-Facorro *et al.*, 2009; Fannon *et al.*, 2000; Fusar-Poli *et al.*, 2013; Kempton *et al.*, 2010; Kumra *et al.*, 2014; McDonald *et al.*, 2002, 2006; Sharma *et al.*, 1998; Shenton *et al.*, 2001; Strasser *et al.*, 2005; Wright *et al.*, 2000). An issue that should be considered when interpreting findings from brain connectivity analyses such as

the ones presented here is if and how such differences between patients and controls might influence results. If patients have enlarged ventricles, then maybe the prior source locations defined are not as suitable for patients as they are for controls. However, it is important to note that DCM incorporates source reconstruction, and that the inversion algorithm provides efficient Bayesian estimates of the dipole sources that optimise these (David *et al.*, 2005; Kiebel *et al.*, 2009). Hence, should the prior source locations be inappropriate for some subjects, DCM is robust enough to deal with this. Furthermore, these results indicate that effective connectivity abnormalities are also present in unaffected relatives of patients, and although not directly investigated here, a meta-analysis found that enlarged ventricles are not observed in relatives of patients with schizophrenia (Boos *et al.*, 2007). This suggests that abnormalities of effective connectivity in this group are unlikely to be explained by changes in brain volume associated with psychosis, and support the conclusion that this is due to an underlying genetic liability. Nevertheless, this is an issue that should be explicitly investigated using DCM. Future studies should employ individual MRI images for each participant, rather than a template MRI image as used in this study.

A further potential limitation of this study is the use of the average reference with this data. The use of an average reference across all electrodes is only ideal if the head was a sphere and electrodes were placed all around it. However, with a relatively small number of electrodes (17 here), and furthermore when the occipital areas are not covered, the signal might be distorted with the use of the average reference (Kropotov, 2009; Luck, 2005). This would however distort the signal for all subjects equally, and will not have influenced the group differences observed.

The Bayesian model selection result indicates that both bilateral A1 and rIFG are important in explaining group differences in modulations of intrinsic connectivity in response to deviant tones. However, modulations of self-inhibition in STG do not seem to be so important (and were not included in the winning model). Importantly, this does not mean that the STG makes no contribution to group differences in responses, but merely suggests that including modulations in this

region did not increase the evidence for the model sufficiently to justify the increased complexity. These results furthermore suggest that group differences are most pronounced in rIFG. This is in line with past research suggesting that psychosis is associated with abnormalities at high hierarchical levels, including the prefrontal cortex (reviewed in Adams *et al.*, 2013; Harrison *et al.*, 2011).

In this study, condition-specific grand average responses for each group were calculated, an approach that has been used previously (e.g. Fogelson *et al.*, 2014). While this produces cleaner data features by reducing noise and enhancing features that are conserved over subjects, it eliminates potentially interesting individual differences. Future work could obtain subject-specific DCM estimates, allowing the investigation of individual differences within groups, and correlations between effective connectivity parameters and various clinical and cognitive measures, as well as with genotypes.

In summary, my main finding is that patients with psychosis as well as their unaffected first-degree relatives show increased excitability in the rIFG across task conditions, relative to controls, and crucially, a loss (reversal) of the normally increased excitability in deviant trials. Hence, these results suggest that psychosis is associated with abnormalities of the sensitivity (gain) control of superficial pyramidal cell populations, which might be influenced by NMDA-R hypofunction in prefrontal cortex. These results are in line with theories about the neuropathology and pathophysiology of psychosis. Importantly, abnormalities in unaffected relatives of patients suggest that these alterations are potentially related to genetic predisposition to psychosis, and are therefore potential endophenotypes for the illness.

Chapter 4: Associations between endophenotypes across brain functional, structural and cognitive domains

4.1 Introduction

Moving away from the identification of endophenotypes, in this chapter I will investigate a range of known endophenotypes for psychosis, obtained through different techniques. To optimise the use of these measures for future genetic analyses, they need to be carefully characterised, for example by assessing the relationships between different endophenotypes. Previous research has focused on investigating biomarkers within one method, especially the associations between different cognitive measures (Dickinson *et al.*, 2002, e.g. 2006; Gladsjo *et al.*, 2004; Seidman *et al.*, 2015; Sheffield *et al.*, 2014; Sullivan *et al.*, 2003; Toomey *et al.*, 1998), but there is a lack of literature examining brain structural – cognitive and physiological – cognitive pairings using multiple methods and across domains of brain function and structure. Crucially, the inclusion of unaffected relatives in these kinds of analyses has been rare, but the performance of relatives who carry increased genetic risk but have no illness or treatment confounding factors is crucial for establishing the utility of these markers in genetic studies.

In this study, the aim was to investigate the relationship between a range of multi-modal endophenotypes for psychosis genetic research, including

electrophysiological, neurocognitive, and neuroanatomical measures. These were selected as they are putative endophenotypes for psychosis and because they were compatible across centres reaching a substantial sample size. The endophenotypes included were:

- Changes in the P300 event-related potential measured by EEG: Reduced amplitude and prolonged latency of the P300 have consistently been found in patients with psychotic illnesses as well as in unaffected relatives, compared to controls (Bestelmeyer *et al.*, 2009; Blackwood *et al.*, 1991; Bramon *et al.*, 2005; Pierson *et al.*, 2000; Price *et al.*, 2006; Schulze *et al.*, 2008; Turetsky *et al.*, 2014; Weisbrod *et al.*, 1999; Winterer *et al.*, 2003b). The amplitude is thought to be a correlate of attention and working memory (Ford, 2014; Näätänen, 1990), and although the latency has been less precisely outlined, it is thought of as an index of classification speed (Polich, 2007, 2011). However, there is an increasingly recognised need for greater precision in the theoretical significance of electrophysiological markers including the P300 (Polich, 2011).

- Changes in cognition measured by neuropsychological tests: Deficits on the cognitive tests digit span (measuring working memory), block design (measuring spatial visualisation and problem solving abilities), and the Rey Auditory Verbal Learning Task (RAVLT) immediate and delayed recall (measuring short and longer term verbal memory, respectively) are common and persistent across psychotic illnesses (Bora and Pantelis, 2015; Bora *et al.*, 2009; Gur *et al.*, 2007; Heinrichs and Zakzanis, 1998; Kim *et al.*, 2015c). Abnormalities are often observed before the onset of the illness as well as in unaffected relatives (Birkett *et al.*, 2008; Forbes *et al.*, 2009; Glahn *et al.*, 2006; Ivleva *et al.*, 2012; Park and Gooding, 2014; Reichenberg *et al.*, 2010; Saperstein *et al.*, 2006; Snitz *et al.*, 2006).

- Changes in brain structure obtained by magnetic resonance imaging (MRI): Increased lateral ventricular volume is consistently found in patients with psychosis compared to controls (Boos *et al.*, 2007; Crespo-Facorro *et al.*, 2009;

Fannon *et al.*, 2000; Fusar-Poli *et al.*, 2013; Kempton *et al.*, 2010; Kumra *et al.*, 2014; McDonald *et al.*, 2002, 2006; Sharma *et al.*, 1998; Shenton *et al.*, 2001; Strasser *et al.*, 2005; Wright *et al.*, 2000). This enlargement has been attributed to neurodevelopmental difficulties, disease progression, or the effects of antipsychotic medications (Gogtay *et al.*, 2003; McDonald *et al.*, 2006; Pilowsky *et al.*, 1993). Lateral ventricular volume comparisons between unaffected relatives and controls have been less consistent, and the latest meta-analysis did not find an effect despite many other conflicting reports (Boos *et al.*, 2007).

The present study includes, to our knowledge, the largest sample of individuals with psychosis, their unaffected first-degree relatives, and controls to investigate the relationships between this wide range of multi-modal endophenotypes. The main objective is to facilitate the use of endophenotypes for genetic research into psychosis, which requires well defined and characterised measures. The aim of this study was therefore to examine the relationships between different endophenotype pairs, and in particular, to characterise sub-components of the P300 event related potential in the context of well-defined cognitive markers.

4.2 Methods

4.2.1 Sample and clinical assessments

The total sample included 8754 participants: 2212 individuals with a diagnosis of a psychotic disorder, 1487 of their unaffected first-degree relatives (with no personal history of psychosis), and 5055 healthy controls (with no personal or family history of a psychotic illness). Psychotic illnesses were defined broadly to include schizophrenia, schizoaffective disorder, bipolar disorder with psychotic symptoms and other less common forms of psychosis (see Table 4-1 for a breakdown of diagnoses, and see Appendix C for diagnoses across the participating study centres). Multiply affected families often include individuals with different diagnoses.

Relatives and controls were not excluded if they had a personal history of non-psychotic psychiatric illnesses (such as depression or anxiety), provided they were well and off psychotropic medication at the time of testing and for the preceding 12 months. This was to avoid recruiting biased control groups, unrepresentative of the general population.

To confirm or rule out a DSM-IV (APA, 1994) diagnosis, all participants underwent a structured clinical interview with either the Comprehensive Assessment of Symptoms and History (Andreasen *et al.*, 1992), the Structured Clinical Interview for DSM Disorders (Spitzer *et al.*, 1992), the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer, 1978) or the Schedule for Clinical Assessment in Neuropsychiatry, Version 2.0 (Wing *et al.*, 1990). Participants were excluded if they had a history of neurologic disease or a loss of consciousness due to a head injury.

Recruitment occurred across 11 locations in Australia and Europe (Germany, Holland, Spain, and United Kingdom). See Appendix C for a summary of the data collected from each site. Participants provided written informed consent, and the study was approved by the respective ethical committees at each of the 11 participating centres.

4.2.2 Neuropsychological assessments

Cognitive data were provided by 10 sites and full methodology for each is reported elsewhere (Crespo-Facorro *et al.*, 2007; González-Blanch *et al.*, 2007; Johnstone *et al.*, 2005; Korver *et al.*, 2012; Toulopoulou *et al.*, 2010; Walters *et al.*, 2010; Waters *et al.*, 2009).

The Wechsler Adult Intelligence Scale, revised version (WAIS-R; Wechsler, 1981) or third edition (WAIS-III; Wechsler, 1997), was administered to participants. Performance on two subtests was used for analyses; the forward and backward digit span (measuring attention and working memory) and block design (measuring

spatial visualisation). For both subtests, the percentage of the maximum score for each individual was calculated to correct for test version.

The Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964), assessing verbal memory, was also administered, including both immediate and delayed recall. Total scores, corrected for number of trials, were calculated for each individual, hence accounting for different test versions.

4.2.3 EEG data collection and processing

Electrophysiological data were obtained from three sites, the full methods for each site are reported elsewhere (Bramon *et al.*, 2005; Hall *et al.*, 2006; Price *et al.*, 2006; Waters *et al.*, 2009; Weisbrod *et al.*, 1999).

In summary, EEG was collected from 17 to 20 electrodes placed according to the International 10/20 system (Jasper, 1958). The P300 event related potential was obtained using a standard two-tone frequency deviant auditory oddball paradigm, with standard ('non target') tones of 1000Hz and rare ('target') tones of 1500Hz. The number of tones presented varied from 150 to 800, the tones were 80dB or 97dB, lasted for 20-50ms, and the inter-stimulus interval was between 1 and 2 seconds. The majority of participants (93.4%) were asked to press a button in response to 'target' stimuli, but a subset were asked to close their eyes and count 'target' stimuli in their heads.

The data were continuously recorded in one of three ways: 500Hz sampling rate and 0.03-120Hz band pass filter; 200Hz sampling rate and 0.05-30Hz band pass filter; or 400Hz sampling rate and 70Hz low-pass filter. Linked earlobes or mastoids were used as reference and vertical, and in most cases also horizontal, electro-oculographs were recorded at each site and used to correct for eye-blink artefacts using regression based weighting coefficients (Semlitsch *et al.*, 1986). After additional manual checks, artefact-free epochs were included and baseline corrected before averaging. The averaged waveforms to correctly detected targets were then filtered using 0.03 or 0.05 Hz high-pass and 30 or 45 Hz low-pass filters.

The peak amplitude and latency of the P300 were measured at electrode location PZ, within the range of 250-550ms post-stimulus.

4.2.4 MRI data collection and processing

MRI data acquisition and image processing varied between sites; methods for each are referenced and outlined briefly below. Lateral ventricular volumes were measured using automatic or semi-automatic region of interest analyses, and included the body, frontal, occipital and temporal horns.

Edinburgh

Scanner used: 1 Tesla (T) Siemens Magnetom (Erlangen, Germany). Acquisition sequence: Magnetisation prepared rapid acquisition gradient echo (MPRAGE). Acquisition protocol: Flip angle = 12°, repetition time (TR) = 10 ms, echo time (TE) = 4 ms. Images were analysed using a regions of interest analysis using the semi-automated programme Analyze, and lateral ventricular volume was defined by the autotrace and included frontal, occipital and temporal horns. For full details see (Lawrie *et al.*, 1999; Steel *et al.*, 2002; Whalley *et al.*, 1999).

Heidelberg

Scanner used: 1.5 T Phillips. Acquisition sequence: Magnetisation prepared rapid acquisition gradient echo (MPRAGE). Acquisition protocol: Flip angle = 15°, TR = 11.4 ms, TE = 4.4 ms. Images were analysed using a region of interest tool in the software Analyze, and lateral ventricular volume was defined according to borders described in the literature (Shenton *et al.*, 2001). For full details see (Wobrock *et al.*, 2009).

London

Scanner used: 1.5 T General Electric (USA) Signa System. Acquisition sequence: Spoiled gradient recall (SPGR) echo. One of the following acquisition protocols was used: Flip angle = 35°, TR = 35 ms, TE = 5 ms; Flip angle = 20°, TR = 14.7 ms, TE = 3.7

ms; Flip angle = 20°, TR = 9.8 ms, TE = 2.3 ms; or Flip angle = 20°, TR = 13.1 ms, TE = 5.8 ms. Images were analysed using MEASURE, an image analysis program that uses stereologically unbiased estimation of volume. Lateral ventricular volume included the body, frontal, occipital and temporal horns, and choroid plexus where visible. For full details see (Dutt *et al.*, 2009; Frangou *et al.*, 1997b; McDonald *et al.*, 2002; Schulze *et al.*, 2006).

Maastricht

Scanner used: 3 T Siemens (Erlangen, Germany). Acquisition sequence: Either a modified driven equilibrium Fourier transform (MDEFT), or a magnetization prepared rapid acquisition gradient echo (MPRAGE). Acquisition protocol either; i) Flip angle = 15°, TR = 7.92 ms, TE = 2.4 ms, or ii) Flip angle = 9°, TR = 2250 ms, TE = 2.6 ms. Images were analysed using Freesurfer. Automatic labelling of each MRI voxel was carried out based on probabilistic information derived from training on a manually labelled dataset (Fischl *et al.*, 2002). For full details see (Collip *et al.*, 2013; Habets *et al.*, 2011).

Santander

Scanner used: 1.5 T General Electric Signa System (GE Medical Systems, Milwaukee, WI). Acquisition sequence: Spoiled gradient-recalled acquisition in the steady state (GRASS) (SPGR). Acquisition protocol: Flip angle = 45°, TR = 24 ms, TE = 5 ms. Images were analysed using the software BRAINS2, including automatic measurements of brain areas. For full details see (Crespo-Facorro *et al.*, 2009; Mata *et al.*, 2009).

Utrecht

Scanner used: 1.5 T Philips NT. Acquisition sequence: Fast field echo (FFE). Acquisition protocol: Flip angle = 30°, TR = 30 ms, TE = 4.6 ms. Images were analysed using a Histogram method validated previously by the research group (Schnack *et al.*, 2001b). For full details see (Hulshoff Pol *et al.*, 2002; Schnack *et al.*, 2001a).

4.2.5 Statistical methods

Endophenotype measures were standardised for each site separately (using the overall means and standard deviations within each site) to control for differences between the centres.

First, regression analyses were used to establish if there were differences between the three clinical groups on the endophenotypes. Each regression model had "group" as a categorical predictor with three levels (patient, relative, control). The outcome was each relevant endophenotype, and covariates included age, gender and study site. Considering the sample includes related individuals, robust standard errors were used in order to counteract effects of clustering within families.

Before investigating the associations between each pair of endophenotypes amongst the entire sample, the impact of group membership (patient, relative, control) on each interrelationship was investigated. Potential group differences were assessed by entering interaction terms between group and the predictor in the endophenotype pair.

For the relationships between pairs of endophenotypes which were not strongly impacted by group, the associations were investigated using linear regression in the whole sample, adjusting for between group differences along with age, gender and study site, and using robust standard errors.

For the pairs of endophenotypes that were impacted by group, the regressions with group specified in an interaction term have been reported, with the estimated difference in increase of association from controls in each group. As before, these regressions included the covariates age, gender and study site, and robust standard errors were used.

Although the tables report uncorrected p-values, the results discussed survived an adjustment for multiple testing. Because scores within measurement domains are expected to be highly correlated, I adjusted for three domains (EEG, MRI and cognition), and a total of 6 tests (group differences within each of the three

domains and their associations with each other). The significance threshold was thus set to p = 0.05/6 = 0.008. All analyses were conducted using STATA version 13.

4.3 Results

4.3.1 Sample characteristics

The sample characteristics are summarised in Table 4-1. Two-tailed t-tests showed that relatives were similar to controls on age (t = -1.07, p = 0.303), but patients were younger compared to both relatives (t = 27.67, p < 0.001), and to controls (t = 30.14, p < 0.001). Chi squared tests demonstrated that the patient group had a greater proportion of males to females when compared with controls (χ^2 = 234.32, p < 0.001) and relatives (χ^2 = 234.44, p < 0.001). Conversely, there were fewer males than females in the relatives group compared to controls (χ^2 = 19.04, p < 0.001). In order to account for effects of age and gender, these were entered as covariates into all analyses. A total of 6601 families were included in this sample, with 1 – 11 members per family; 37% of individuals had at least one relative participating (see Appendix C).

Table 4-1. Sample characteristics (N=8754).

	Patients w. psychosis	Unaffected relatives	Controls	Total sample
Sample size, N (%)	2212 (25.3%)	1487 (17.0%)	5055 (57.7%)	8754
Age, mean years (SD)†	33.6 (10.6)	46.0 (15.8)	45.5 (16.2)	42.6 (15.8)
Age range (years)	16 – 79	16 – 85	16 – 89	16 – 89
Gender (% female)†	32.10%	58.00%	51.50%	47.70%
Diagnoses; N (%)				
Schizophrenia	1396 (63.1%)	-	-	1396 (15.9%)
Bipolar I Disorder	135 (6.1%)	-	-	135 (1.5%)
Psychosis NOS	168 (7.6%)	-	-	168 (1.9%)
Schizophreniform Disorder	158 (7.1%)	-	-	158 (1.8%)
Schizoaffective Disorder	124 (5.6%)	-	-	124 (1.4%)
Brief Psychotic Disorder	56 (2.5%)	-	-	56 (0.6%)
Other psychotic illness	175 (7.9%)	-	-	175 (2.0%)
Depression		246 (16.5%)	232 (4.6%)	478 (5.5%)
Anxiety		47 (3.2%)	24 (0.5%)	71 (0.8%)
Other non-psychotic illness		62 (4.2%)	106 (2.1%)	168 (1.9%)
No psychiatric illness		1132 (76.1%)	4693 (92.8%)	5825 (66.5 %)
Endophenotypes; N, Mean (SD)*				
P300 amplitude (μV)	N=397 10.5 (6.1)	N=379 11.0 (6.7)	N=313 13.7 (7.0)	N=1089 11.6 (6.7)
P300 latency (ms)	N=401 382.6 (55.3)	N=386 390.8 (56.1)	N=315 356.9 (39.1)	N=1102 378.2 (53.3)
Lateral Ventricular Volume (cm3)	N=700 17.9 (9.9)	N=337 18.7 (11.2)	N=684 15.8 (8.8)	N=1721 17.1 (9.8)
Block Design (% of max. score)	N=850 49.9 (27.9)	N=895 47.4 (25.6)	N=3746 60.4 (21.2)	N=5491 56.6 (23.8)
Digit Span (% of max. score)	N=460 47.4 (15.9)	N=136 40.0 (4.5)	N=2531 51.5 (14.5)	N=3127 50.4 (14.9)
RAVLT immediate recall (No. of words recalled)	N=1232 7.6 (2.2)	N=934 8.4 (2.1)	N=1377 8.7 (2.0)	N=3543 8.2 (2.2)
RAVLT delayed recall (No. of words recalled)	N=1224 2.1 (1.0)	N=927 2.9 (1.0)	N=1358 2.9 (0.9)	N=3509 2.6 (1.0)

SD = Standard deviation; NOS = Not otherwise specified; RAVLT = Rey Auditory Verbal Learning Task; † Missing data for 717 ages and 6 gender; * Raw scores, unadjusted for covariates, are presented here.

Differences between the three groups (patients, relatives, and controls) on the different endophenotypes were in the anticipated directions, following the pattern controls > relatives > patients, or vice versa (presented in Table 4-2 and Figure 4-1).

Patients differed significantly from controls on all measures, and relatives differed significantly from controls on the P300 amplitude and latency, digit span, and block design. Lateral ventricular volume and RAVLT immediate and delayed recall showed no significant differences between relatives and controls.

Table 4-2. Group differences on endophenotype scores.

Endophenotype:	**Total Sample** Global p-value	**Patients – Controls** Mean difference (95% CI)	**Patients – Relatives** Mean difference (95% CI)	**Relatives – Controls** Mean difference (95% CI)
P300 amplitude	**< 0.001**	-0.53 (-0.70 to -0.36) **p < 0.001**	-0.18 (-0.33 to 0.04) p = 0.013	-0.35 (-0.52 to -0.17) **p < 0.001**
P300 latency	**< 0.001**	0.47 (0.33 to 0.61) **p < 0.001**	0.03 (-0.14 to 0.19) p = 0.749	0.44 (0.33 to 0.61) **p < 0.001**
Lateral Ventricular Volume	**= 0.006**	0.20 (0.08 to 0.32) **p = 0.001**	0.09 (-0.05 to 0.24) p = 0.210	0.11 (-0.04 to 0.25) p = 0.163
Digit Span	**< 0.001**	-0.72 (-0.88 to -0.55) **p < 0.001**	-0.14 (-0.32 to 0.05) p = 0.141	-0.58 (-0.77 to -0.39) **p < 0.001**
Block Design	**< 0.001**	-0.55 (-0.64 to -0.46) **p < 0.001**	-0.22 (-0.31 to -0.14) **p < 0.001**	-0.32 (-0.40 to -0.23) **p < 0.001**
RAVLT immediate recall	**< 0.001**	-0.75 (-0.83 to -0.67) **p < 0.001**	-0.65 (-0.74 to -0.56) **p < 0.001**	-0.1 (-0.18 to -0.01) p = 0.026
RAVLT delayed recall	**< 0.001**	-0.65 (-0.73 to -0.57) **p < 0.001**	-0.62 (-0.71 to -0.53) **p < 0.001**	-0.03 (-0.11 to 0.06) p = 0.545

Regression models adjusted for age, gender and study site, with robust standard errors, and using standardised scores. RAVLT = Rey Auditory Verbal Learning Task.

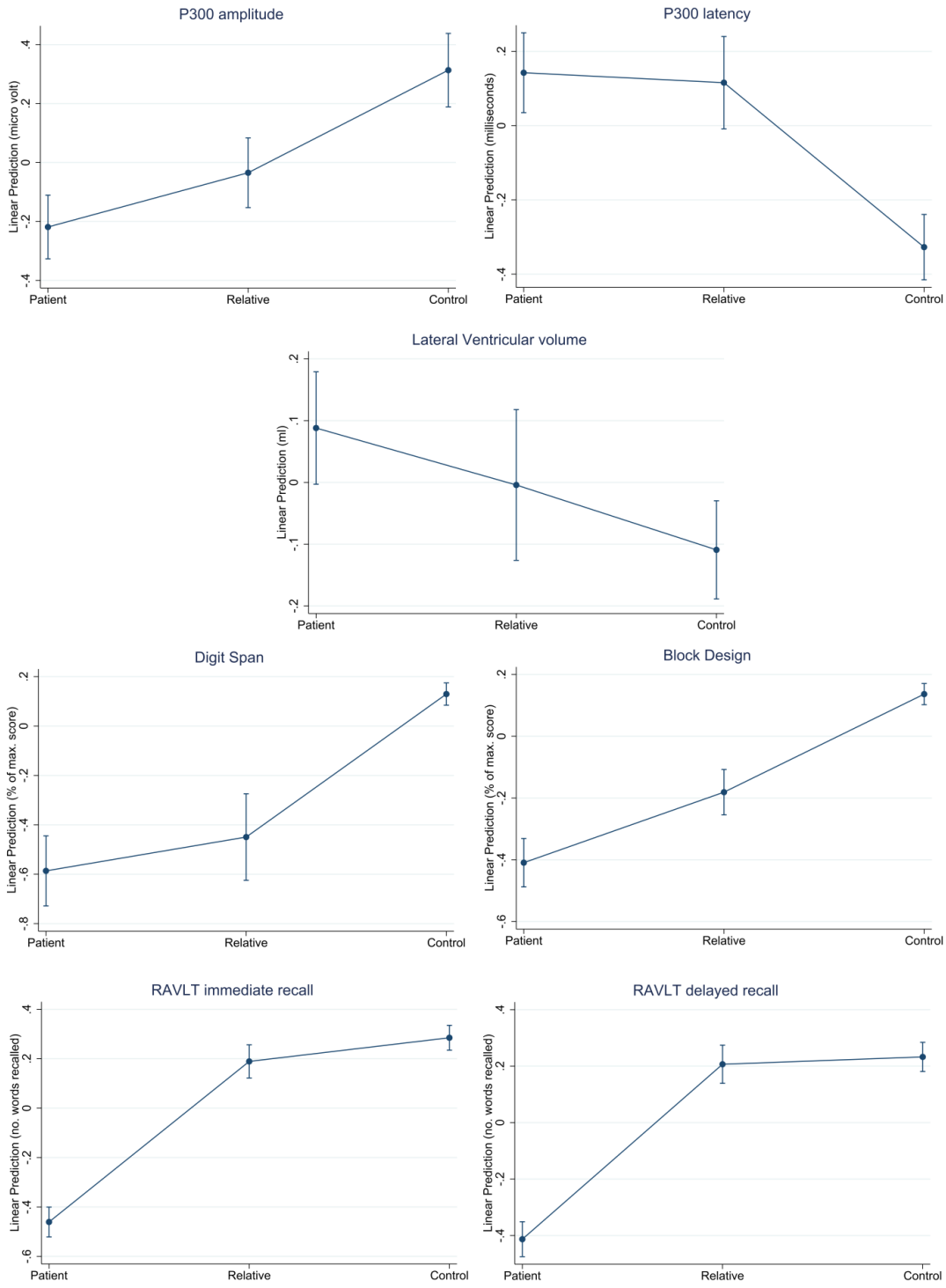

Figure 4-1. Endophenotype scores across groups.

Endophenotype (standardised) scores, estimated marginal means with 95% confidence intervals, across clinical groups (patients, relatives, and controls). Adjusted for age, gender, and study site. RAVLT = Rey Auditory Verbal Learning Task.

4.3.2 Associations between endophenotype pairs

Each relationship between pairs of endophenotypes was checked for interaction effects with group to determine if there are strong differences between patients, relative and controls in the relationships. This informed whether the relationship was examined in the whole sample combined, or by subgroup. For the majority of the associations, group did not have an interaction effect ($p>0.008$); these are reported in the next section. For two cognitive pairs, however, there were strong evidence of interactions with group, and these are reported in the subsequent section.

Associations between endophenotype pairs in the whole sample

Associations between different endophenotype pairs in the whole sample are reported in Table 4-3. The P300 amplitude and latency were not significantly associated with each other. The P300 amplitude was positively associated with digit span and block design performances (the former at a trend level), but not with either of the RAVLT measures. The P300 latency and lateral ventricular volumes were not significantly associated with any of the other measures. The strongest relationships were found between different cognitive measures, this was also reflected in the subgroup analysis reported below. All cognitive pairings were significantly positively associated across groups.

Table 4-3. Associations between endophenotypes in the whole sample.

	Outcome:					
Predictor:	**P300 amplitude**	**P300 latency**	**Digit Span**	**Block Design**	**RAVLT immediate recall**	**RAVLT Delayed recall**
P300 amplitude	-	-0.06 (-0.12 to 0.01) p = 0.060	0.15 (0.04 to 0.26) p = 0.009	0.19 (0.10 to 1.28) **p < 0.001**	0.11 (-0.02 to 0.25) p = 0.102	0.08 (-0.06 to 0.22) p = 0.281
P300 latency	-	-	-0.15 (-0.28 to -0.03) p = 0.017	-0.04 (-0.12 to 0.04) p = 0.333	0.03 (-0.09 to 0.15) p = 0.699	0.03 (-0.07 to 0.14) p = 0.501
Lateral Ventricular Volume	0.05 (-0.07 to 0.16) p = 0.393	0.02 (-0.10 to 0.14) p = 0.712	-0.02 (-0.04 to 0.08) p = 0.507	0.07 (-0.09 to 0.23) p = 0.380	-0.04 (-0.13 to 0.06) p = 0.479	-0.02 (-0.12 to 0.08) p = 0.738
Digit Span	-	-	-	-	0.39 (0.28 to 0.49) **p < 0.001**	0.31 (0.20 to 0.42) **p < 0.001**
RAVLT immediate recall	-	-	-	0.25 (0.21 to 0.30) **p < 0.001**	-	0.76 (0.74 to 0.78) **p < 0.001**

Regression models using standardised scores, adjusted for age, gender, study site and group using robust standard errors. Statistics reported are difference in mean estimate (95% confidence intervals) and p-values. RAVLT = Rey Auditory Verbal Learning Task.

Associations between endophenotype pairs by group

For two associations between pairs of cognitive endophenotypes, evidence of interactions with group was found. This indicates that the relationships between these endophenotype pairs differ between patients, relatives and controls, as reported in Table 4-4 and Figure 4-2. Importantly, these results show that the nature of the relationship between the pairs of cognitive endophenotypes were similar across all three groups; differing only in strength.

There were strong relationships between each of the cognitive measures in the control group. Both digit span and RAVLT delayed recall were positively associated with scores on the block design task, and patients showed the same pattern as

controls but to a significantly greater extent. Relatives did not differ significantly from controls in these associations.

Table 4-4. Group interactions on associations between endophenotypes.

Endophenotype relationship	Overall test of interaction effect	Controls Est. increase in association (95% CI)	Relatives Est. difference from controls (95% CI)	Patients Est. difference from controls (95% CI)
Digit Span x Block Design	**p < 0.001**	0.30 (0.27 to 0.34) **p < 0.001**	0.18 (0.02 to 0.35) p = 0.028	0.28 (0.19 to 0.38) **p < 0.001**
RAVLT del x Block Design	**p < 0.001**	0.21 (0.15 to 0.26) **p < 0.001**	-0.04 (-0.14 to 0.05) p = 0.390	0.19 (0.09 to 0.29) **p < 0.001**

Regressions on standardised scores including interactions terms between group (patient, relative, controls) and predictor, adjusted for covariates (age, gender and study site), using robust standard errors. RAVLT del = Rey Auditory Verbal Learning Task delayed recall; CI = Confidence Interval.

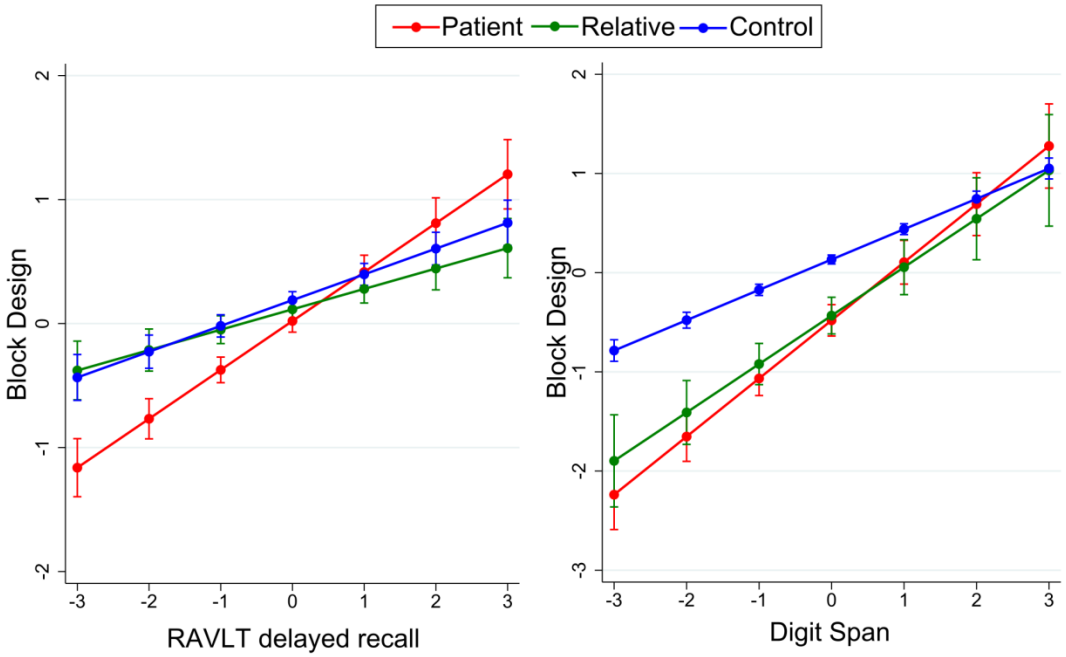

Figure 4-2. Interactions between endophenotype scores and group.

Interactions between group (patient, relative and control) and endophenotype pairs (standardised scores). Graphs are adjusted for covariates (age, gender and study site), and include 95% confidence intervals. RAVLT = Rey Auditory Verbal Learning Task.

4.4 Discussion

In this study, the relationships between different endophenotypes for psychosis were examined in a large sample of patients, their unaffected first-degree relatives, and controls. In particular, by exploring markers across brain anatomy and brain functional domains my aim was to characterise the amplitude and latency of the P300 event related potential in the context of well-defined cognitive markers.

Results showed that (i) the P300 amplitude and latency are distinct features, and the former associated with some of the cognitive measures; (ii) lateral ventricular volume is not significantly associated with any of the cognitive or brain functional measures; (iii) the cognitive endophenotypes were associated with each other in the expected directions; and (iv) individuals with psychotic illnesses, their unaffected relatives, and healthy controls all showed similar patterns of associations between all pairs of endophenotypes. These findings are discussed in turn.

Both patients and relatives showed reduced amplitudes and prolonged latencies of the P300, compared to controls, replicating past findings in this large multi-centre study, and providing further evidence that these are endophenotypes for psychosis (Bestelmeyer *et al.*, 2009; Bramon *et al.*, 2005; Price *et al.*, 2006; Schulze *et al.*, 2008; Thaker, 2008; Turetsky *et al.*, 2000). Since the P300 is thought to be closely related to attentional mechanisms, it is not surprising that abnormalities of this event-related potential are not specific to psychosis, but also observed in other psychiatric illnesses associated with impaired attention (Duncan *et al.*, 2009). The P300 has been suggested as an endophenotype for substance use disorder, including use of both alcohol and cocaine, where patients and their unaffected relatives show reduced amplitudes (Euser *et al.*, 2012; Singh and Basu, 2009). Furthermore, patients with dementia generally show prolonged latencies (Gironell *et al.*, 2005; Polich and Corey-Bloom, 2005), and attention-deficit hyperactivity disorder is associated with reduced amplitudes of the P300 (Barry *et al.*, 2003).

The P300 amplitude and latency were not associated with each other, highlighting that this relationship is of very small predictive value, and suggests a considerable degree of independence between the P300 amplitude and latency, as argued by others (van Dinteren *et al.*, 2014).

The associations between the P300 amplitude and both digit span (at a trend level) and block design are supported in the literature (Dong *et al.*, 2015b; Fjell and Walhovd, 2001; Hermens *et al.*, 2010; Kaur *et al.*, 2011; Polich *et al.*, 1997; Souza *et al.*, 1995). According to the context-updating theory (Heslenfeld, 2003; Kujala and Naatanen, 2003), the P300 amplitude indexes an attention-driven, context-updating mechanism facilitated by working memory, which subsequently feeds into memory stores (Polich, 2007, 2011). Hence, one would expect the amplitude to be associated with cognitive tasks that utilise attention and working memory processes (Baddeley, 1992; Ford, 2014; Näätänen, 1990), and my results support this. The context-updating theory also provides a possible account of the specific mechanism driving the strong association between P300 amplitude and block design; this task requires a participant to constantly update their mental representation of the blocks in the context of the representation of the template stimulus, in order to physically 'update' the block pattern (Polich, 2007, 2011). The lack of associations between P300 amplitude and the RAVLT tests support the idea that the impairments patients show on verbal recall memory are part of a distinct mechanism from that which underlies the reduction in P300 amplitude. This is in line with the characterisation of the P300 amplitude emphasising that the process may be associated with recognition memory, rather than the recall memory assessed by the RAVLT (Polich, 2011).

Turning to the latency of the P300, this was not significantly associated with any of the measures investigated here. Previous studies investigating associations between cognition and the latency of the P300 are less consistent compared to studies of the P300 amplitude; some have found associates with attention and working memory tasks (Polich *et al.*, 1983) whereas others have not (Dong *et al.*, 2015b; Fjell and Walhovd, 2001; Walhovd and Fjell, 2003). The P300 latency has

been conceptualised as a measure of the classification speed (van Dinteren *et al.*, 2014; Polich, 2011). As such one would expect timed tasks such as digit span and block design to be associated with the P300 latency. However, no such associations were found in this sample. Investigating the relationship between behavioural reaction times (i.e. the speed of button press in the task) and the P300 latency, some have found associations (Bashore *et al.*, 2014) whereas other have not (Ramchurn *et al.*, 2014). However, there is substantial research showing that the P300 latency as well as reaction times increase with ageing in healthy participants (Chen *et al.*, 2013; Polich, 1996). It is possible, based on these findings, that the P300 latency is a specific measure of processing speed at a basic neuronal level. In contrast, digit span and block design – while influenced by processing speed – reflect wider cognition including memory and spatial abilities. The more complex elements to these tasks may therefore obscure effects of a simple processing speed, and hence explain the lack of effect with P300 latency.

In terms of lateral ventricular volume, there was no evidence of relationships with any other endophenotype investigated. This is consistent with some previous research (Bornstein *et al.*, 1992; Ortiz-Gil *et al.*, 2011), however Keilp et al (1988) found an association with verbal memory. Furthermore, several studies have found enlarged lateral ventricles associated with poorer motor speed (Antonova *et al.*, 2004; Dong *et al.*, 2015a; Hartberg *et al.*, 2011), which was not directly measured in this study. One must interpret these negative results bearing in mind the heterogeneity of the MRI methodology between study sites, a limitation of the present study that might have obscured any true effects. Furthermore, although patients showed enlarged ventricles compared to controls, which is a very well supported finding in the literature (Cahn *et al.*, 2009; Kempton *et al.*, 2010; Steen *et al.*, 2006; Wright *et al.*, 2000), no differences were observed between relatives and controls. This is consistent with the latest meta-analysis of brain structure in relatives of patients with schizophrenia (Boos *et al.*, 2007), and suggests that enlarged ventricles in patients are not related to genetic risk for psychosis. Instead, this might be due to illness progression, or to effects of antipsychotic medication, as

has been observed in animal models of antipsychotic exposure (Dorph-Petersen *et al.*, 2005; Konopaske *et al.*, 2007).

For all cognitive measures, there were clear group differences with patients consistently performing less well compared to controls, consistent with a wealth of research (Ayres *et al.*, 2007; Bora and Murray, 2014; Bora *et al.*, 2010, 2014; Fatouros-Bergman *et al.*, 2014; Fusar-Poli *et al.*, 2012b). For the digit span and block design, there were also significant differences between relatives and controls, indicating an effect of increased genetic risk for psychosis. However, this was not seen for the immediate or delayed recall of the RAVLT task, where controls and relatives did not differ significantly. Although many have found impairments in verbal memory in unaffected relatives (Massuda *et al.*, 2013; Sitskoorn *et al.*, 2004; Wittorf *et al.*, 2004), this has not always been seen (Kim *et al.*, 2015a; Üçok *et al.*, 2013). These findings suggest that working memory and spatial visualisation might be more promising endophenotypes for psychosis than verbal memory is.

That working memory is abnormal in both patients with psychosis and their unaffected relatives is a consistent finding in the literature (Bora *et al.*, 2009; Botero *et al.*; Egan *et al.*, 2001; Park and Gooding, 2014; Saperstein *et al.*, 2006), and replicated here in this very large sample. Furthermore, working memory abnormalities also meet the additional endophenotypic criteria, being both heritable and state independent (reviewed in Park and Gooding, 2014). Hence, working memory appears to be a robust endophenotype for psychosis. It is worth noting, however, that studies have found schizophrenia to be more strongly associated with working memory impairments compared to bipolar illness, suggesting this might be a more suitable endophenotype for the former (Burdick *et al.*, 2009; Park and Gooding, 2014). Working memory is generally defined as a limited-capacity system that temporarily maintains and stores information (Baddeley, 2003). Because working memory is crucial for all forms of learning, including language, abnormalities can have severe consequences, and are likely to influence all aspects of cognitive functions, including social interactions (Park and Gooding, 2014).

These findings are also consistent using other methodologies, such as functional magnetic resonance imaging (fMRI), where abnormalities in both patients with psychosis and their relatives during working memory tasks have been observed (Dutt *et al.*, 2015; MacDonald *et al.*, 2009; Pearlson and Calhoun, 2009; Thermenos *et al.*, 2004). Working memory tasks performance rely on activation of a network of brain regions, including the dorsolateral prefrontal cortex, and this network has been shown to perform less efficiently in psychosis (Pearlson and Calhoun, 2009; Scognamiglio and Houenou, 2014; Thermenos *et al.*, 2013; Waters-Metenier and Toulopoulou, 2010). This is consistent with the dysconnection hypothesis (Friston, 1998; Stephan *et al.*, 2009) and effective connectivity abnormalities in psychosis discussed in chapter 3 of this thesis.

Investigating the relationships between pairs of cognitive measures, this data provide strong evidence for associations in the expected directions, and past research is consistent with these findings (Dickinson *et al.*, 2002; Gladsjo *et al.*, 2004; Seidman *et al.*, 2015; Sheffield *et al.*, 2014; Sullivan *et al.*, 2003). It is interesting to note that for some cognitive measures, the relationships interacted with group, although the direction of the effect remained the same across patients, relatives and controls. This is likely to reflect artefacts of the group differences on the individual endophenotypic measures. If a participant performs well on one cognitive test they will perform well on another, and vice versa. However, within the patient sample there is a greater range of scores, and thus individuals who perform less well facilitate a greater within-group contrast and a steeper gradient than seen in the control sample. The interaction effects with group were found exclusively amongst the cognitive measures, and not in any of the other sets of relationships. This is possibly due to the greater sample sizes for these measures, with greater statistical power enabling the detection of interaction effects which tend to be subtle.

Both the lack of interaction effects for most associations investigated, and the gradient effects identified where there was an interaction, support the conclusions of previous research that there are similar cognitive structures common both to

people with psychotic illnesses and controls (Dickinson *et al.*, 2006). This is consistent with the idea that psychosis is part of a continuum with the healthy population (Allardyce *et al.*, 2007; DeRosse and Karlsgodt, 2015; Esterberg and Compton, 2009; Ian *et al.*, 2010; Johns and van Os, 2001; Wiles *et al.*, 2006).

The main limitation of this study was the heterogeneity of methods between study sites. Differences in cognitive test versions, variation on the EEG protocols, as well as the large range of MRI protocols (including the use of scanners with different field strengths) all introduce noise into the data. However, if imaging biomarkers are to be used in genetic research the only way forward is to combine data from multiple centres. No individual centre alone has as yet collected a sample large enough to conduct independent large genome wide association studies. The noise introduced by multiple scanners makes it less likely to identify an association; therefore it does not increase type 1 errors. The potential gain in sample size offsets the limitation of scanner-variability.

Indeed, the large sample size acquired from multiple sites is one of the biggest strengths of the current study, as studies of endophenotypes for psychosis often have been limited by small sample sizes. As the Psychiatric Genomics Consortium's work shows, large international collaborations are essential in certain fields such as genetic studies of common diseases and traits (Lee *et al.*, 2013; Ripke *et al.*, 2014; Sklar *et al.*, 2011; Smoller *et al.*, 2013). Methodologically, another strength of this study has been the use of regressions as opposed to the correlations frequently seen in the literature (Breteler *et al.*, 1994; Brewer *et al.*, 1970; Brillinger, 2001; Kim *et al.*, 2003; Polich *et al.*, 1983, 1997). Not only did this approach avoid vulnerability to spurious correlations, but it allowed inspection of interaction effects across groups.

Another limitation of this study was that behavioural performance, including number of correct responses and reaction times, during the P300 experiment was only available for a subset of participants. The P300 experiment is designed to be an easy task, aimed at capturing the brain response to oddball tones that are correctly identified as such, and here a standard version of the P300 task was used, that has

been used in many previous publications (Bramon *et al.*, 2005; Doege *et al.*, 2009; Hall *et al.*, 2006; Horovitz *et al.*, 2002; Pan *et al.*, 2000; Price *et al.*, 2006; Waters *et al.*, 2009; Weisbrod *et al.*, 1999). Hence, the vast majority of participants have very high accuracy, and furthermore, only trials with correct responses were included in the analysis. It is a limitation of this study that reaction times during the P300 task was not available for the whole sample. It would have been of interest to investigate associations between reaction times in this task and the cognitive measures and also between the EEG and behavioural parameters.

In summary, this study has investigated the relationship between endophenotypes for psychosis – including measures of cognition, electrophysiology, and brain structure – with the aim of, in particular, characterising the P300 event-related potential. I have provided support for the notion that the amplitude and latency of the P300 are independent markers; the amplitude an index of attention and working memory, while the latency might be conceptualised as a correlate of basic speed of processing. A further conclusion of this study is that individuals with psychotic illnesses, their unaffected relatives, and healthy controls all show similar patterns of associations between all pairs of endophenotypes, endorsing the theory of a continuum of psychosis across the population.

Chapter 5: A polygenic score analysis of psychosis endophenotypes

5.1 Introduction

Psychosis has a highly polygenic architecture, involving thousands of common single nucleotide polymorphisms (SNPs) of very small individual effects that account for an estimated 32% of the heritability in psychosis (Lee *et al.*, 2012a, 2012b; Purcell *et al.*, 2009; Ripke *et al.*, 2013, 2014; Sklar *et al.*, 2011). Furthermore, large-scale genome-wide association studies have identified more than 100 SNPs that are significantly associated with an increased risk of developing schizophrenia (Ripke *et al.*, 2014) and bipolar disorder (Sklar *et al.*, 2011).

As endophenotypes are thought to be related to the genetic factors underlying disorders, it is likely that a subset of psychosis associated SNPs also influence these markers (Lencz *et al.*, 2014). This relationship between the genetics of endophenotypes and psychosis can be investigated using polygenic scores, where the combined effect of a large number of SNPs, each with a very subtle individual effect, is calculated (Purcell *et al.*, 2009). Several studies have shown that such polygenic scores differ between patients and controls, thus providing a useful tool to measure genetic liability to psychosis in independent samples (Bramon *et al.*, 2014; Derks *et al.*, 2012; Purcell *et al.*, 2009). A number of studies have investigated the relationship between endophenotypes and polygenic scores for schizophrenia

and bipolar disorder (Van der Auwera *et al.*, 2015; Hall *et al.*, 2015; Lencz *et al.*, 2014; McIntosh *et al.*, 2013; Papiol *et al.*, 2014; Terwisscha van Scheltinga *et al.*, 2013a, 2013b; Whalley *et al.*, 2012, 2013, 2015). However, these studies have reported mixed outcomes, and vary in discovery sample sizes used to calculate polygenic scores, in sample sizes used to test for associations, and in the specific endophenotypes investigated.

The aim of this study is to test whether polygenic scores for schizophrenia and bipolar disorder influence psychosis endophenotypes, in a large sample of patients with psychosis, their unaffected first-degree relatives, and healthy controls. The polygenic scores were calculated using p-values and odds ratios from the latest international mega-analyses by the Psychiatric Genomics Consortium (Ripke *et al.*, 2014; Sklar *et al.*, 2011).

Following on from the previous chapter, endophenotypes of three domains were considered; i) the amplitude and latency of the P300 event related potential; ii) lateral ventricular volume; and iii) measures of working memory (digit span), spatial visualisation (block design) and verbal memory (the Rey Auditory Verbal Learning task, immediate and delayed recall).

5.2 Methods

5.2.1 Sample, clinical and endophenotypic assessment

This sample is a subset of that presented in chapter 4, and overlapping methods have not been repeated here.

The total sample for this study included 4242 participants: 1087 patients with psychotic illnesses (see Table 5-1 for breakdown of diagnoses), 822 unaffected first degree relatives of probands (with no personal history of a psychotic illness), and 2333 unaffected controls (with no personal or family history of a psychotic illness).

The endophenotypes included were the P300 amplitude (N=510) and latency (N=515), lateral ventricular volume (N=789), and measures of cognition; block design (N=3089), digit span (N=1437), and the Rey Auditory Verbal learning task (RAVLT) immediate (N=2406) and delayed (N=2384) recall.

5.2.2 Genotyping methods

DNA was obtained from blood for all participants, and sent to the Wellcome Trust Sanger Institute (Cambridge, United Kingdom) for genotyping using the Affymetrix 6.0 Genome-wide Human SNP Array (www.affymetrix.com). Standard quality control of the data was conducted. This included removing samples with Mendelian inheritance errors, SNP missing data rates >5%, departure from Hardy-Weinberg equilibrium ($p < 10^{-6}$) or minor allele frequency (MAF) < 0.02, samples with >2% missing data, and divergent genome-wide heterozygosity.

Full details of genotyping methods and quality control procedures are described in Appendix D and in Bramon et al (2014).

Phasing and imputation

Phasing was done using Shapit2 v2.r790 (Delaneau *et al.*, 2013), with default parameters except for the specification of the duoHMM flag, which allows for incorporation of known pedigree information. Imputation with reference data from the 1000 genomes panel was performed with IMPUTE2 version 2.3.0 (Howie *et al.*, 2011, 2012), using the October 2014 release, and based on sequence data from 2,504 samples. Phased chromosomes were split into ~4.5 Mb chunk sizes prior to imputation, which was run with standard parameters assuming an effective population size of 20,000. After imputation, SNPs with poor imputation quality (INFO < 0.8) and missingness of > 1% were excluded.

Population structure analysis

To investigate the genetic structure of the data, principal component analysis (PCA) of unrelated individuals was conducted using EIGENSOFT version 3.0 (Patterson *et*

al., 2006) on a thinned set of SNPs. The following SNP pruning filters were applied on 695,193 SNPs, which remained after quality control: A 10% minor allele frequency, 10^{-3} Hardy-Weinberg equilibrium deviation threshold, and all SNPs within a 1,500 SNP window had to have r^2 below 0.2 (window shift of 150 used). Thus, a subset of 71,677 SNPs was selected for PCA using EIGENSOFT version 3.0 (Patterson *et al.*, 2006).

The first three components were included as covariates in all analyses to control for the confounding effects of population structure. This approach was used in previous work (Bramon *et al.*, 2014), and see Appendix D for the projection of the study participants onto the first two principal components of genetic structure.

5.2.3 Polygenic score analysis

Following the method described in Purcell et al (2009), polygenic risk profile scores were calculated separately for schizophrenia and bipolar disorder. Summary data from the most recent Psychiatric Genomics Consortium genome-wide association studies for schizophrenia (Ripke *et al.*, 2014) and bipolar disorder (Sklar *et al.*, 2011) were used. In both cases, I used data from the Psychiatric Genomics Consortium that did not overlap with the sample used in the current study. For schizophrenia polygenic scores, the discovery sample included 31,658 cases and 42,022 controls, and for bipolar disorder, the discovery sample included 7,481 cases and 9,250 controls (Ripke *et al.*, 2014; Sklar *et al.*, 2011).

Polygenic scores for each individual were calculated using the *--score* option in PLINK (Purcell *et al.*, 2007), from the number of risk alleles carried for each selected SNP (i.e. 0, 1 or 2), weighted by the log(OR) provided by the Psychiatric Genomics Consortium, and averaged across all SNPs. SNPs were selected from the Psychiatric Genomics Consortium's panel using six different significance thresholds ($p_T < 5\times10^{-08}$, 0.001, 0.05, 0.1, 0.5, 1), hence including an increasing number of SNPs the more liberal the threshold (see Appendix D for the number of SNPs included at each threshold).

5.2.4 Statistical analyses

Linear regression analyses were performed to test whether schizophrenia and/or bipolar disorder polygenic scores influence endophenotypes for psychosis. These included the P300 event related potential (amplitude and latency), lateral ventricular volume, and measures of cognition (digit span, block design, and the Rey Auditory Verbal Learning Task (RAVLT) immediate and delayed recall).

Endophenotype measures were standardised for each site separately (using the overall means and standard deviations within each site) to control for differences between the centres. Covariates included in all analyses were clinical group (patient, relative, or control), study site, the first three population structure principal components, age and gender. Because the sample included related individuals, robust standard errors were used to account for effects of clustering within families. The change in R^2 between a model only including the covariates and a model including covariates plus the polygenic score is reported, which represents the proportion of the variance explained by the score.

Linear regression analyses were performed for each endophenotype using the entire sample – patients with psychosis (including schizophrenia, bipolar disorder and other psychotic illnesses; see Table 5-1), unaffected relatives of probands, and controls – examining the associations with polygenic score at the different significance thresholds of the Psychiatric Genomics Consortium's SNP list. This was done separately for both the schizophrenia and bipolar disorder polygenic scores.

Although the tables report uncorrected p-values, the results discussed survived an adjustment for multiple testing. Because the four cognitive measures were highly correlated, I corrected for four measures (cognition, P300 amplitude and latency, and lateral ventricular volume) and two polygenic scores (schizophrenia and bipolar disorder). Hence, the alpha threshold for significance was set to $p = 0.05/8 = 0.006$. Statistical analyses were conducted using STATA version 13.

5.3 Results

5.3.1 Sample characteristics

Demographic information and mean values of the different endophenotypes are presented in Table 5-1. The patient group was significantly younger compared to both relatives (mean diff. = -11.8, $p<0.001$) and controls (mean diff. = -12.3, $p<0.001$), whereas relatives and controls did not differ in mean age (mean diff. = -0.5, $p=0.4$). There were more males in the patient group compared to both the control ($\chi^2 = 114.4$, $p<0.001$) and relative groups ($\chi^2 = 144.4$, $p<0.001$). The group of relatives contained more female participants than the control group ($\chi^2 = 15.8$, $p<0.001$). Age and gender are included as covariates in all analyses.

Mean scores on the different endophenotypes followed the expected pattern of patients < relatives < controls, or vice versa. See Appendix D for statistics of group differences and distributions across groups, after correcting for covariates of age, gender, and study site. Also note that this is a subset of the sample analysed in chapter 4 where group differences were reported.

2558 (60.3%) of individuals in this sample did not have a family member participating. 670 (15.8%) were part of families with 2 members in the study, 564 (13.3%) were in three-person families, 384 (9.05%) were part of four-person families, 60 (1.4%) were in five-person families, and there was one family with 6 members participating (0.14%).

Table 5-1. Sample characteristics (N=4242).

	Total Sample	Controls	Unaffected Relatives	Patients with Psychosis
Sample size (N, %)	4242	2333 (55.0%)	822 (19.4%)	1087 (25.6%)
Age (mean years ± SD)	42.5 (±15.8)	45.7 (±16.3)	45.27 (±15.65)	33.48 (±10.39)
Age range (years)	16 – 85	16 – 84	16 – 85	16 – 79
Gender (% female)	48.5%	52.0%	60.0%	32.4%
Diagnoses (N)				
Schizophrenia	703	-	-	703
Bipolar I Disorder	105	-	-	105
Psychosis NOS	86	-	-	86
Schizophreniform Disorder	68	-	-	68
Schizoaffective Disorder	60	-	-	60
Brief Psychotic Disorder	40	-	-	40
Other psychotic illness	25	-	-	25
Depression	273	137	136	-
Anxiety Disorder	47	15	32	-
Other non-psychotic illness	41	20	21	-
No Psychiatric Illness	2794	2161	633	-
Endophenotypes; N, mean (±SD)[§]				
P300 amplitude (μV)	N=510 11.9 (±6.8)	N=139 13.4 (±6.8)	N=160 12.1 (±7.5)	N=211 10.8 (±6.1)
P300 latency (ms)	N=515 377.2 (±51.6)	N=139 358.2 (±37.8)	N=164 386.5 (±55.5)	N=212 382.3 (±53.1)
Lateral Ventricular Volume (ml)	N=798 17.1 (±10.3)	N=299 16.1 (±9.5)	N=166 18.5 (±11.6)	N=333 17.2 (±10.2)
Block Design (% of max.)	N=3089 57.4 (±23.8)	N=1997 60.0 (±21.6)	N=603 51.8 (±25.7)	N=489 54.0 (±28.0)
Digit Span (% of max.)	N=1437 50.4 (±14.7)	N=1115 51.5 (±14.5)	N=59 41.5 (±13.3)	N=263 47.5 (±14.2)
RAVLT immediate recall (No. words recalled)	N=2406 8.2 (±2.2)	N=962 8.7 (±2.0)	N=633 8.4 (±2.1)	N=811 7.5 (±2.2)
RAVLT delayed recall (No. words recalled)	N=2384 2.6 (±1.0)	N=948 2.9 (±0.9)	N=629 2.8 (±1.0)	N=807 2.1 (±1.0)

SD = Standard deviation; NOS = Not otherwise specified; RAVLT = Rey Auditory Verbal Learning Task;
[§] Raw scores presented here, for mean differences adjusted for covariates of age, gender and study site see Appendix D.

5.3.2 Schizophrenia polygenic score analysis

The schizophrenia polygenic score differed significantly between the three groups ($F(2,3184)=86.6$, $p=2.3\times10^{-37}$; controls vs. patients $p=1.6\times10^{-35}$, controls vs. relatives $p=3.6\times10^{-4}$, patients vs. relatives $p=1.1\times10^{-16}$), with patients having the highest scores, followed by relatives and lastly controls (see Figure 5-1, left panel).

The polygenic score for schizophrenia predicted scores on the block design task at the SNP p-value threshold of $p_T < 0.05$, with 0.2% of variance explained, at a trend level of significance ($p=0.009$). Higher polygenic score was nominally associated with poorer performance on the block design task. No other associations approached significance after correcting for multiple testing. These results are shown in Figure 5-2a (for full results see Appendix D).

5.3.3 Bipolar disorder polygenic score analysis

The bipolar disorder polygenic score differed significantly between the three groups ($F(2,3184)=21.8$, $p=4.0\times10^{-10}$; controls vs. patients $p=4.9\times10^{-11}$, controls vs. relatives $p=6.1\times10^{-4}$, patients vs. relatives $p=2.8\times10^{-3}$), with patients having the highest scores, followed by relatives and lastly controls (see Figure 5-1, right panel).

Proportions of variances explained by the bipolar disorder polygenic score were all < 0.2% (and mostly below 0.1%), and none of the associations were significant after correcting for multiple testing. These results are shown in Figure 5-2b (for full results see Appendix D).

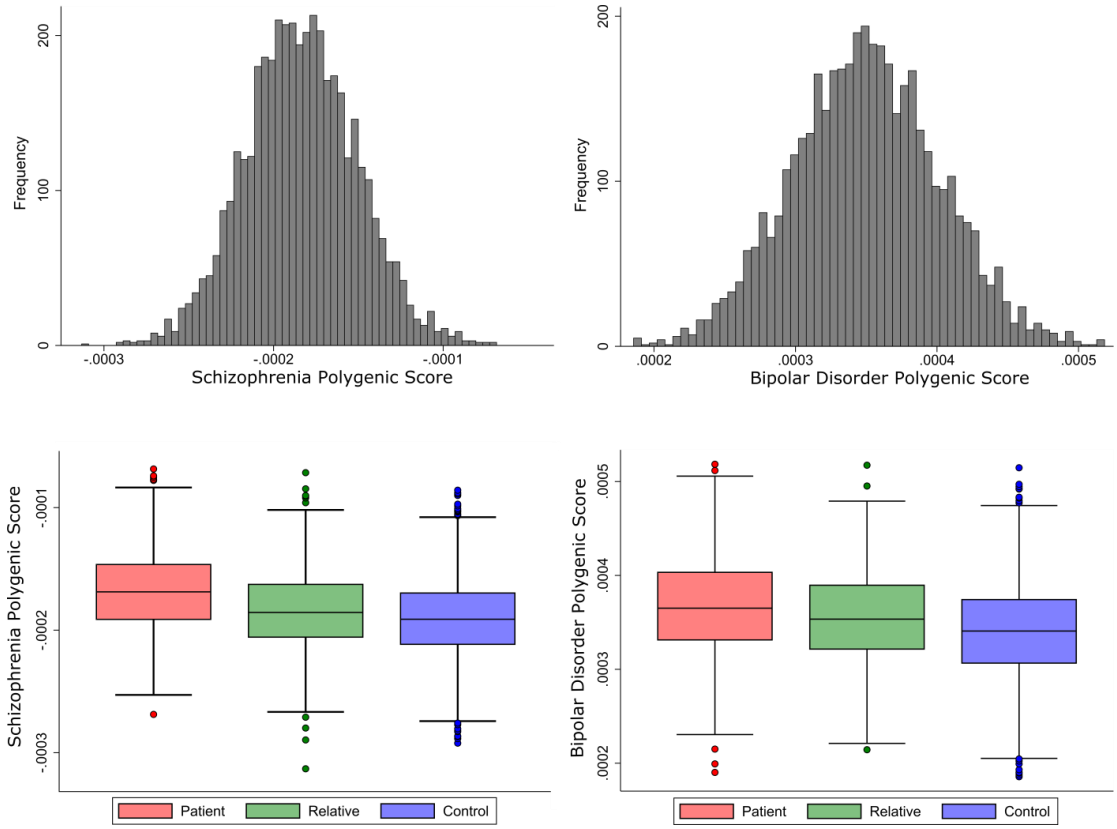

Figure 5-1. Distribution of polygenic scores

Distribution of schizophrenia (left panel) and bipolar disorder (right panel) polygenic scores at the most liberal SNP p-value threshold ($p_T < 1$), for the whole sample (upper panel) and across the three groups (lower panel).

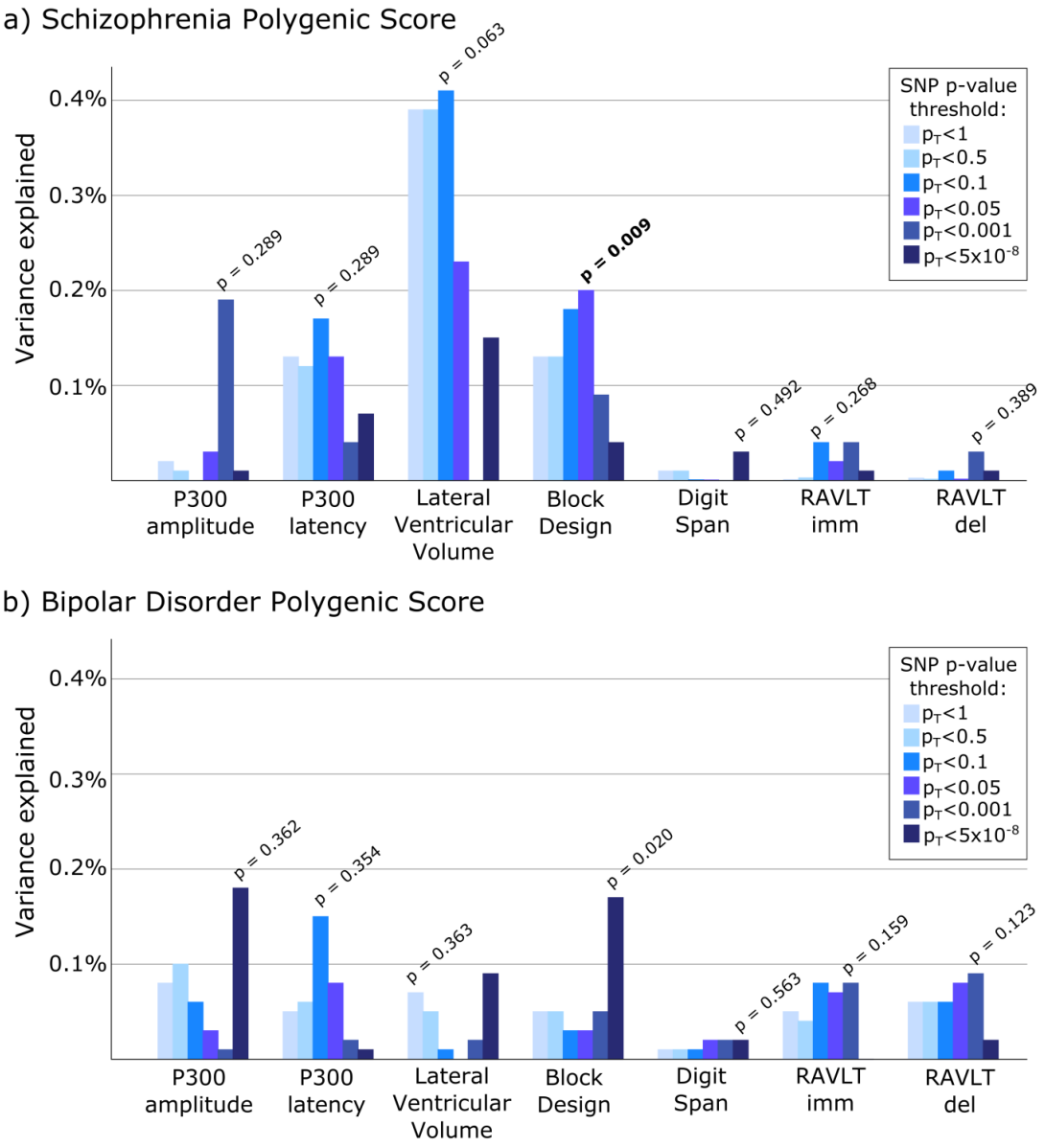

Figure 5-2. Polygenic score analyses results.

Variance explained (R^2) by schizophrenia (a) and bipolar disorder (b) polygenic scores across endophenotypes. Blue bars represent different single nucleotide polymorphism (SNP) p-value thresholds (p_T). The lowest p-value for each endophenotype is displayed above the corresponding bar; the p-value in bold shows a trend-level finding. RAVLT = Rey Auditory Verbal Learning Task; imm = immediate recall; del = delayed recall.

5.4 Discussion

The aim of this study was to test whether polygenic scores for schizophrenia and bipolar disorder – based on the latest mega-analysis from the Psychiatric Genomics

Consortium – influence a range of endophenotypes for psychosis. This included the P300 event related potential amplitude and latency, lateral ventricular volume, and measures of cognition (block design, digit span, and the Rey Auditory Verbal Learning Task). No association remained significant after correction for multiple testing. However, the schizophrenia polygenic score predicted poorer performance on the block design task at a trend-level, with 0.2% of variance in block design explained by the polygenic score.

Several studies have investigated the relationship between cognition and polygenic score for schizophrenia. Terwisscha van Scheltinga et al (2013b) failed to show an association with intelligence in a sample of 672 patients with schizophrenia and controls, but McIntosh et al (2013) found an association with cognitive change between the ages of 11 and 70 in 937 controls. Further, in a large sample of 4900 controls, Lencz et al (2014) saw an association between schizophrenia polygenic score and general cognitive ability. Lencz and colleagues (2014) also calculated polygenic score for cognition (i.e. including SNPs associated with cognitive performance) in healthy controls, and used this to significantly predict disease status in a sample of over 5000 patients with schizophrenia and 5800 controls, with ~0.5% of the variance in disease risk explained by the cognitive polygenic score.

Hence, research suggests that there is a genetic overlap between cognitive performance and schizophrenia (Lencz *et al.*, 2014; Toulopoulou *et al.*, 2010), and the trend-level finding for the block design task is in line with this. This provides some support for the notion that this measure of spatial visualisation is an endophenotype for schizophrenia, and that genetic risk variants are shared between the traits. However, there was no association between measures of working and verbal memory and this polygenic score, and furthermore, no associations were significant for bipolar disorder polygenic score. This could be due to a lack of power, as these genetic effects are likely to be subtle as discussed below.

Similarly to this study, Hall et al (2015) also investigated the association between polygenic score for schizophrenia and bipolar disorder and the P300 event related

potential. The total sample size was smaller than in this current study (including 392 patients with psychosis and controls, but no unaffected relatives), but polygenic scores were also calculated using the latest data from the Psychiatric Genomics Consortium. Similarly to my results, none of their associations remained significant after correction for multiple testing.

Research has suggested that the P300 has a significant genetic component. Abnormalities in unaffected first-degree relatives of patients have been identified (Schulze *et al.*, 2008; Thaker, 2008), its heritability is around 60% (van Beijsterveldt and van Baal, 2002; Hall *et al.*, 2006), and about 27% of variance in P300 amplitude can be accounted for by common genetic variation (Malone *et al.*, 2014b). Furthermore, a significant genetic overlap of about 34% between the P300 amplitude and bipolar disorder has been observed (Hall *et al.*, 2007). However, it is possible that the overlap in common variants involved in both psychosis and the P300 is small, suggesting subtle effect sizes requiring very large samples.

As for the influence of polygenic scores on measures of brain volumes, Terwisscha van Scheltinga et al (2013a) and Papiol et al (2014) both looked at total brain, white and grey matter volumes, and associations with schizophrenia polygenic score based on an early version of the Psychiatric Genomics Consortium data (including about 9400 cases of schizophrenia); the former found a significant association whereas the latter did not. Van der Auwera et al (2015) tried to replicate this using data from the latest Psychiatric Genomics Consortium analysis (including nearly 37,000 patients with schizophrenia), and a test sample of 1470 healthy controls. They failed to show an association between schizophrenia polygenic score and whole brain, grey or white matter volumes (Van der Auwera *et al.*, 2015). My results investigating lateral ventricular volume are in line with this.

Studies have suggested that ventricular volume has a genetic basis; heritability of up to 70% has been observed (Carmelli *et al.*, 2002; Kremen *et al.*, 2010, 2012; Peper *et al.*, 2009; Schmitt *et al.*, 2007) – although not in all studies (Baaré *et al.*, 2001; Wright *et al.*, 2002) – and McDonald et al (2002) found increased volumes in unaffected relatives of individuals with familial schizophrenia, but not in relatives of

individuals with a non-familial illness. However, in a meta-analysis of 1065 unaffected relatives of schizophrenia patients and 1100 healthy controls, Boos and colleagues (2007) did not find an overall effect in relatives. Importantly, group differences in lateral ventricular volume in this chapter were not significant, although when including the larger sample in chapter 4, patients had significantly enlarged ventricles compared to controls. However, relatives and controls did not differ significantly from each other. Taken together, this suggests that lateral ventricular volume might not be strongly associated with genetic risk for psychosis, and this may have contributed to my negative findings. Instead, as also discussed in the previous chapter, the enlarged ventricles in psychosis might be due to illness progression, or to effects of antipsychotic medication.

Overall, although research has shown that there is a genetic component contributing to variability in the biomarkers investigated here, these are all complex (multifactorial and heterogeneous) phenotypes, and environmental factors play important roles too. Abnormalities in patients might be influenced by, for example, illness duration, medications, and other environmental factors such as alcohol and drug use, diet, stress, or childhood trauma (e.g. Arseneault, 2004; McGrath *et al.*, 2004; Varese *et al.*, 2012; Vassos *et al.*, 2012). Furthermore, all complex traits are likely to have complex genetic influences, including a substantial polygenicity (Geschwind and Flint, 2015; de Geus, 2014; Munafò and Flint, 2014; Rees *et al.*, 2015), and only a subset of SNPs associated with psychosis will also be related to particular endophenotypes, and vice versa, suggesting that effect sizes for the associations of overlapping genetic factors might be small (Lencz *et al.*, 2014). This has indeed been found for the phenotypes investigated, with the amount of variance explained by polygenic scores mostly below 1% (Van der Auwera *et al.*, 2015; Hall *et al.*, 2015; Lencz *et al.*, 2014; McIntosh *et al.*, 2013; Papiol *et al.*, 2014; Terwisscha van Scheltinga *et al.*, 2013a, 2013b; Whalley *et al.*, 2012, 2013, 2015). Hence, it is possible that very large samples are needed to detect such subtle effects.

That only associations approaching significance were seen with the endophenotype with the largest sample size of the measures tested (the block design task) suggests that power might indeed be an issue. For the EEG and MRI measures, that are more laborious to obtain, sample sizes in this study ranged from just over 500 to about 800, which means that a variance explained of 1-1.5% or higher could be detected, suggesting power was limited for these phenotypes. For the cognitive endophenotypes, however, the sample sizes were larger and a variance explained of 0.25-0.55% or higher could be detected (see Appendix D for details of this power analysis).

A limitation of this study – as discussed in the previous chapter – was the heterogeneity of methods between study sites in terms of endophenotype collection, processing and analysis. This might have added noise to the data and thus obscured any true effects. However, an important strength of this study was that genotyping of all samples was done at the same laboratory using the same platform, and that all genetic analyses and quality control were completed in a unified way.

Although common variants are thought to explain up to 30% of heritability in psychosis, genome wide association studies to date have only *significantly* identified about 3% of this (Fernandes *et al.*, 2013; Lee *et al.*, 2012a). More can be captured by calculating polygenic scores, although false positives will also be included (Iyegbe *et al.*, 2014; Wray *et al.*, 2014). It is important to note that a larger discovery sample used to calculate polygenic scores is likely to include a higher proportion of true positive hits, and hence lead to a more reliable measure (Chatterjee *et al.*, 2013; Dudbridge, 2013; Plomin, 2013; Wray *et al.*, 2014). Compared to the discovery sample size used to calculate the schizophrenia polygenic score (including about 31,700 cases; Ripke *et al.*, 2014) the discovery sample for the bipolar disorder score was more than four times smaller – including only about 7,500 cases (Sklar *et al.*, 2011) – and this could thus explain the lack of findings with the bipolar disorder polygenic score.

Importantly, there are highly significant differences in polygenic scores between the clinical groups, both in this sample and in previous studies (Bramon *et al.*, 2014; Derks *et al.*, 2012; Purcell *et al.*, 2009; Ripke *et al.*, 2014), indicating that this measure does capture genetic variants that differ between patients, unaffected relatives, and healthy controls. However, their predictive power at the individual level remains too low, and polygenic scores are not currently able to predict illness status reliably enough to be used clinically, for example as a screening tool. This would require very large discovery data sets, a large catalogue of genetic risk variants (potentially including both common and rare markers), and most likely the inclusion of a combination of genetic and non-genetic risk factors such as cognition, brain imaging, or family history, as well as age and gender (Chatterjee *et al.*, 2013; Dima and Breen, 2015; Dudbridge, 2013; Iyegbe *et al.*, 2014; McCarroll and Hyman, 2013; Wray *et al.*, 2010).

In order for the polygenic score to be used clinically for diagnosis, its ability to correctly identify both patients (i.e. its sensitivity) and healthy individuals (i.e. its specificity) would need to be high. To evaluate the sensitivity and specificity of potential diagnostic tests, analysis of the Receiver Operating Curve (ROC) and the area under the curve (AUC) – the latter as a measure of accuracy, or the probability that a randomly chosen individual with the disorder is rated as more likely to be diseased than a randomly chosen unaffected individual – is often used (Hajian-Tilaki, 2013; Kumar and Indrayan, 2011). An AUC of 1 indicates a perfect test, whereas a test with an AUC of 0.5 performs at a chance-level. It is generally assumed that a good diagnostic test should have an AUC of 0.8 or above (Ebell, 2016; Tape, 2016). The polygenic score does not currently perform at this level. I am involved in a study where we are investigating the potential of the score to distinguish between patients and controls (in the same sample that I have used for my thesis), and the AUC for the schizophrenia and bipolar disorder polygenic scores are 0.66 and 0.58, respectively. Therefore, even though both schizophrenia and bipolar disorder risk scores can discriminate individuals with psychosis from controls very well and group differences are highly significant, the accuracy of this prediction does not support their use as either predictive or diagnostic tests.

Nevertheless, the polygenic scores do provide a standardised and relatively straightforward method to capture the contribution of common genetic variation in these disorders and constitute a powerful research tool.

In future, as our understanding of the genetic architecture of psychosis improves, and as discovery samples become larger, the performance of the polygenic score is likely to be further enhanced. Polygenic scores could then be useful for testing hypotheses about the functional effects of risk variants, or to investigate the associations between disease risk and severity of illness, symptoms dimensions, and treatment or functional outcomes. This method could potentially be used to stratify populations into groups with shared genetic features, or to identify individuals at high-risk of developing an illness (Maier *et al.*, 2015; Wray *et al.*, 2014). Furthermore, using polygenic scores based on selected genetic risk variants clustering on specific functional pathways, rather than a broad selection of SNPs, could become beneficial in the investigation of the specific effects that genetic risk factors for psychosis have on brain function/structure and cognition.

In conclusion, results from this study indicate that the combined effect of common genetic risk variants for schizophrenia is nominally associated with performance on spatial visualisation (as measures by the block design task), providing some further evidence that this measure is an endophenotype for the disorder with shared genetic risk variants. However, no other associations between polygenic scores for psychosis and endophenotypes approached significance. This could be due to a lack of power, and larger samples might be needed to detect these small effects. Furthermore, as discovery samples get larger, and additional and better targeted genetic information is included, the performance of polygenic scores will be further enhanced. Larger association studies using these scores on deeply phenotyped samples may in future provide a promising approach to investigate the functional effects of genetic risk variants for psychosis.

Chapter 6: General discussion

This thesis has been investigating endophenotypes for psychosis in people diagnosed with psychotic illnesses, unaffected first degree relatives of probands, and controls. There were four specific aims of this thesis, corresponding to the four experimental chapters presented, and in short, I have shown that:

i) Resting state EEG activity does not appear to be a promising endophenotype for psychosis, since no abnormalities were observed in the risk groups. However, low frequency abnormalities in chronic patients with psychosis could provide biomarkers for the disease that could be useful in non-genetic research.

ii) Effective connectivity underlying the mismatch negativity event-related potential – specifically, the excitability of superficial pyramidal cells in prefrontal cortex – appears to be abnormal in psychosis as well as in unaffected relatives, indicating that this could be related to the genetic aetiology, and is a candidate endophenotype for the illness.

iii) The P300 event-related potential amplitude and latency, as well as working memory and spatial visualisation are reliable endophenotypes for psychosis. The P300 amplitude and latency appear to be distinct mechanisms, reflecting attention and working memory, and basic processing speed, respectively. Furthermore, individuals with psychotic illnesses, their unaffected relatives, and healthy controls all show similar patterns of associations between pairs of

endophenotypes, supporting the view of a continuum of psychosis across the population.

iv) The polygenic score (a combined measure of many common genetic risk variants) for schizophrenia predicts performance on a spatial visualisation task at a trend-level, suggesting shared genetic risk variants between these two traits. Larger samples are needed to yield further significant findings, and as discovery samples continue to grow the use of polygenic scores is promising.

This thesis has thus contributed to the field of mental health research by investigating electrophysiological, cognitive and imaging endophenotypes for psychosis and their genetic influences. Well defined and reliably measured endophenotypes are valuable in psychiatric research for several reasons. They can help elucidate the functional effect of identified genetic risk factors, and they can provide ways of identifying groups of people with similar abnormalities, both within and between current diagnostic categories. This could improve the understanding of disease aetiology, point towards novel treatment targets, identify individuals at risk of developing a disorder who will benefit from early intervention, predict treatment and prognostic/clinical outcomes, and hopefully in the longer-term provide improved diagnostic tools (Braff, 2015; Braff *et al.*, 2007; de Geus, 2010; Glahn *et al.*, 2014; Hall and Smoller, 2010; Meyer-Lindenberg and Weinberger, 2006; Munafò and Flint, 2014).

In this final chapter I will discuss the findings from this thesis, their implications and future work, as well as the strengths and limitations of this research.

6.1 Implications of findings and future work

6.1.1 Resting state EEG activity

The first experimental chapter investigated whether resting state EEG activity could act as a suitable endophenotype for psychosis. This is important because alterations in resting state activity could influence perceptual and cognitive processing

(Baldeweg and Boyd, 2008; Finnigan and Robertson, 2011; Kam *et al.*, 2013; Malone *et al.*, 2014a; Stam *et al.*, 2002). Studies have, for example, looked at resting EEG and ERPs in combination, and found that the amplitude and latency of ERP peaks are related to resting EEG characteristics of the individual (Anokhin *et al.*, 2001; Intriligator and Polich, 1994; Lee *et al.*, 2011; Vogel *et al.*, 1986). Hence, it is possible that abnormalities of resting EEG oscillations in patients with psychosis also influence their ERP responses, and in order to understand brain responses induced by cognitive processing, it is important to characterise endogenous differences that may influence task related responses (Phillips and Uhlhaas, 2015). Although patients with psychosis often show abnormalities in this measure (reviewed in Boutros *et al.*, 2008), studies including risk populations have shown inconsistent findings (Alfimova and Uvarova, 2003; Gschwandtner *et al.*, 2009; Hong *et al.*, 2012b; Narayanan *et al.*, 2014; Venables *et al.*, 2009; Winterer *et al.*, 2001; Wuebben and Winterer, 2001), and it was unclear whether resting EEG constitute an endophenotype for psychosis.

Results presented in this thesis found no abnormalities in first episode patients, individuals with an at-risk mental state, or unaffected relatives, and consequently, resting EEG activity in the frequency bands examined is unlikely to be related to genetic predisposition to psychosis. Rather than endophenotypes, the low frequency abnormalities observed in chronic patients are probably related to illness progression, symptom severity, or possibly to the longer term use of antipsychotic medication. It has been suggested that increased delta activity is associated with negative symptoms of psychosis (Lavoie *et al.*, 2012), and specifically with a lack of motivation and anhedonia (Knyazev, 2012). Furthermore, the use of antipsychotics has been associated with a slowing of the EEG signal (Hyun *et al.*, 2011; Knott *et al.*, 2001; Schuld *et al.*, 2000).

Unfortunately, data was not available for the whole of my current sample to investigate these factors with sufficient statistical power (discussed in limitations section below). This is however an important avenue for future work and

longitudinal studies starting with medication-naïve patients are needed to disentangle the medication effects from the effects of the illness progression itself.

Nevertheless, the increased low frequency resting state EEG activity in chronic patients could be a useful biomarker in non-genetic research, for example as a prognostic or medication-response predictor. Resting EEG has several advantages over other electrophysiological measures: It is easy to collect and can be performed in a wide range of settings, it is also well tolerated by most patients as it does not require the participant to follow instructions or concentrate on a task (Anokhin, 2014; Winterer *et al.*, 2001). This contributes to its suitability as a potential clinically useful biomarker.

6.1.2 Dynamic causal modelling of the mismatch negativity

The second experimental chapter investigated brain connectivity – with a focus on the gain or excitability of superficial pyramidal cells – underlying the mismatch negativity (MMN) evoked potential, using dynamic causal modelling (DCM). The MMN has been linked to NMDA receptor function (e.g. Näätänen *et al.*, 2012; Schmidt *et al.*, 2012a), and glutamatergic theories of psychosis propose that hypofunction of NMDA receptors causes a loss of synaptic gain control (Harrison *et al.*, 2011; Lisman *et al.*, 2008; Phillips and Silverstein, 2013; Stephan *et al.*, 2006).

This was the first study using DCM to investigate the MMN in patients with psychosis as well as their unaffected relatives, and results suggested that the excitability of superficial pyramidal cells in response to the MMN task could be a potential endophenotype for psychosis. There were both context-dependent (condition-specific) and context-independent abnormalities in patients as well as in those with a genetic risk for psychosis.

Analysing EEG data at the scalp level has provided a wealth of information about changes of brain function in psychosis; however, source-level analyses such as DCM are important complementary approaches that can capture additional information provided by EEG data (Anokhin, 2014; Michel and Murray, 2012). DCM can be used

as a tool to acquire detailed and specific measures of brain effective connectivity, including potential endophenotypic markers. This could in future provide clinically useful means of identifying individuals at risk of developing a disorder or to predict clinical and treatment outcomes. The use of DCM and effective connectivity is advantageous because it provides neurophysiologically plausible measures that can point towards causative processes, such as the excitability of certain neuronal populations. Such detailed measures of brain function could help elucidate the functional effects of identified genetic risk markers, provide new treatment targets and, eventually, novel clinically useful markers of disease (Adams *et al.*, 2015; Brodersen *et al.*, 2014; Montague *et al.*, 2012; Stephan and Mathys, 2014; Stephan *et al.*, 2006). This is in contrast to measures of functional brain connectivity, which refers to statistical correlations among regional activity that is not causal and provides only limited insight into disease mechanisms (Brodersen *et al.*, 2014; Friston, 2011).

To produce well-defined and reliable measures using DCM would, of course, require careful validation work and independent replications, as well as longitudinal studies to test clinical predictions (Stephan and Mathys, 2014). Since DCM is a complex analysis method, automated analysis protocol would need to be developed, enabling users without high levels of expertise in DCM to process large numbers of individuals rapidly. In future, it might be possible to obtain EEG data from an individual, process it using a validated and standardised protocol in DCM, and extract measures of effective connectivity that could be used clinically as biomarkers or endophenotypes.

Some of this work is underway. For example, using machine learning and DCM for fMRI during a working memory task, it has been shown that DCM measures of effective connectivity (within a network of visual, parietal, and prefrontal regions) can distinguish between patients and controls more accurately than measures of functional connectivity (i.e. the statistical correlation between activity of the sources) in the same network (Brodersen *et al.*, 2014). Furthermore, in the same study, Brodersen et al (2014) showed that patients could be subdivided into three

groups based on their DCM-derived measures of effective connectivity during the working memory task – that mapped onto three clinically distinct groups differing in negative symptom scores. Although this needs replication, it shows the great potential of DCM.

In addition, compared to DCM for fMRI, using DCM for EEG data – a direct measure of brain activity, with precise temporal resolution of millisecond accuracy – provides a more detailed and realistic neuronal mass model. This makes it possible to distinguish different types of neurons and synaptic connections when using EEG, whereas using fMRI one is currently limited to connectivity between large neuronal populations (Brodersen *et al.*, 2014; Friston, 2011; Stephan and Mathys, 2014). DCM for EEG can thus lead to more nuanced measures than is possible using fMRI data, to use as biomarkers or endophenotypes for psychosis and other psychiatric illnesses.

Most DCM studies to date investigate connectivity underlying various cognitive processes. However, it is of course also possible to utilise resting state data for this type of analysis (Kiebel *et al.*, 2009; Moran, 2015; Moran *et al.*, 2009). It has been suggested that an increase in low frequency resting EEG relative to higher frequencies – as seen in chronic patient with psychosis – could be related to changes in synaptic gain (Kilner *et al.*, 2005). This could be tested empirically using DCM.

6.1.3 Associations between endophenotypes

Moving away from the identification of new endophenotypes, the third experimental chapter of this thesis investigated the relationships between several known endophenotypes for psychosis. This included measures of cognition, electrophysiology, and brain structure – with the aim of, in particular, characterising the P300 event-related potential. This is important because to optimise the use of endophenotypes for future genetic studies, they need to be carefully characterised, for example by assessing the relationships between different multi-modal

endophenotypes. Furthermore, replication of group differences between patients, their relatives, and controls in large multi-centre studies is vital since this type of studies are needed to be able to acquire the large sample sizes required for genetic analyses.

Results supports the notion that the amplitude and latency of the P300 are independent markers; the amplitude an index of attention and working memory, while the latency might be conceptualised as a correlate of basic speed of processing (Ford, 2014; Näätänen, 1990; Polich, 2007, 2011). A further conclusion of this study is that individuals with psychotic illnesses, their unaffected relatives, and healthy controls all show similar patterns of associations between all pairs of endophenotypes, endorsing the theory of a continuum of psychosis across the population (Allardyce *et al.*, 2007; DeRosse and Karlsgodt, 2015; Esterberg and Compton, 2009).

Importantly, this study replicated previous findings supporting the endophenotypic status of several markers, including the P300 amplitude and latency, and cognitive measures (digit span and block design, measuring working memory and spatial visualisation, respectively). However, lateral ventricular volume and verbal memory were not significantly different between controls and unaffected relatives of patients, suggesting they might not be related to genetic risk for psychosis.

The nature of multi-centre studies inevitably leads to some heterogeneity between sites in the methods used to obtain and analyse the data (Costafreda, 2009; Shokouhi *et al.*, 2011; Suckling *et al.*, 2008, 2012). This is clearly a limitation by adding noise to the data, and work needs to be done to ensure methods are as uniform as possible. However, utilising data from different centres makes it possible to achieve the large sample sizes needed for genetic analyses. It is important to note the main findings seen in this study, indicating that it is indeed possible to merge data collected at different locations. That significant group differences were observed for the majority of measures in this large sample collected across several research centres in Europe and Australia support their robust nature as endophenotypes for psychosis.

6.1.4 Polygenic risk scores and their link to psychosis endophenotypes

In the fourth and last experimental chapter, polygenic risk scores – a measure of the combined effect of a large number of common genetic risk factors of small individual effects – were used to investigate the relationship between genetic risk for schizophrenia and bipolar disorder, and several endophenotypes for psychosis. This is a novel method to investigate polygenic risk, and its use has increased rapidly in the last few years. The study presented here was one of the first to investigate polygenic scores and a range of endophenotypes of different modalities in psychosis, including a large family based sample of over 4000 individuals. Although endophenotypes were collected across several sites, all genetic analyses were conducted at the same laboratory using a unified methodology.

Results showed that common genetic variants associated with schizophrenia predict performance on a spatial visualisation task at a trend-level of significance. This suggests some further evidence that this cognitive measure is an endophenotype for the disorder with shared genetic risk variants between the traits. Hence, it was shown that with a sufficiently large sample size, the use of polygenic scores have the potential to confirm hypotheses about endophenotypes, by showing that such traits do share genetic risk variants with the disorder as hypothesised. Furthermore, studies such as this can help us to understand the mechanisms through which common genetic variation leads to the onset of the disease. Finally, with larger discovery samples, which are being collected through large international collaborations such as the Psychiatric Genomics Consortium, the performance of polygenic scores is likely to improve in future (Chatterjee *et al.*, 2013; Dudbridge, 2013; Plomin, 2013; Wray *et al.*, 2014).

It is also important to acknowledge that many types of genetic risk factors have now been identified. The polygenic score currently only includes common variants of very small individual effects (odds ratios < 1.2, and present in more than 1% of the population (McCarthy *et al.*, 2008)). However, rare variants of larger effects, such as copy number variants, associated with psychosis have also been identified (Grozeva *et al.*, 2011; Stefansson *et al.*, 2008; Stone *et al.*, 2008; Walsh *et al.*, 2008; Xu *et al.*,

2008). These are only observed in less than 1% of the population (often in as little as 0.1% of individuals), but they carry significantly increased risk, with odds ratios from 3 and up to >50 (Kirov *et al.*, 2014, 2015; Mowry and Gratten, 2013; Stefansson *et al.*, 2014). Including such risk markers in the polygenic score might increase its predictive value.

In combination with other measures – such as demographic (e.g. age, gender, family history), clinical (e.g. age of onset, symptom scores), brain structure and function, performance of cognitive tests, and rare genetic risk factors (e.g. copy number variants) – the clinical usefulness of polygenic scores is likely to be enhanced further (Chatterjee *et al.*, 2013; Dima and Breen, 2015; Dudbridge, 2013; Iyegbe *et al.*, 2014; McCarroll and Hyman, 2013; Wray *et al.*, 2010). Polygenic scores could, for example, be used to identify individuals at high risk of developing psychosis that would most benefit from early assessments and interventions ranging from psycho-education to reduce environmental risks to early treatment with psychological therapies (Maier *et al.*, 2015; Wray *et al.*, 2014). Such uses of polygenic methods for stratification of individuals have come further in other fields, for example in cancer research (Chowdhury *et al.*, 2013; Hawken *et al.*, 2010; So *et al.*, 2011). For breast and prostate cancer, it has been shown that including polygenic risk scores in addition to age can reduce the number of individuals screened, whilst still detecting the majority of cases that were identified using a predictive model only including age (Pashayan *et al.*, 2011).

Of course, phenotypes such as those derived from DCM could be combined with polygenic risk score analyses to, for example, test whether measures of brain connectivity share genetic risk variants with psychosis, and to investigate the functional effect of identified genetic risk markers[2]. Eventually, suitable endophenotypes for psychosis could be incorporated along with polygenic scores in a clinical prediction model including both genetic and brain functional measures.

[2] It is worth noting here that although cortical excitability during the MMN task appears to be an endophenotype for psychosis (as shown in chapter 3), it was not possible at this stage to include this measure in the associations with polygenic scores, because the sample size (N=84) was not large enough for a genetic analysis.

In summary, while the schizophrenia and bipolar disorder polygenic scores can discriminate cases from controls very well, their modest sensitivity and specificity precludes their use as a diagnostic or prognostic tool at the individual level in routine clinical practice (as discussed in chapter 5). Nevertheless, there is growing interest in the potential of polygenic scores in public health strategies to help deliver risk reduction and early treatment campaigns to those parts of the population who need it most (Wray *et al.*, 2013, 2014). Furthermore, polygenic scores constitute a powerful research tool, which combined with large epidemiological studies of environmental risks is likely to bring advances in our understanding of the aetiology of psychotic disorders (Dudbridge, 2013; Maier *et al.*, 2015).

6.1.5 Future research goals

The ultimate goal of this research is to improve the lives of people living with mental health needs, specifically psychosis. The use of endophenotypes can do this by investigating the functional effect of genetic risk factors, in order to improve the understanding of the aetiology of disorders. This, in turn, can help research move towards several future goals, such as improving treatment options, devising clinical prediction tools and personalised medicine, as well as developing new biologically-based diagnostic systems.

Well defined and reliably measured endophenotypes could point towards potential treatment targets, both biological and psychological. This could include, for example, cortical excitability potentially mediated by NMDA receptors – as estimated using DCM – or working memory dysfunction measured both using ERPs like the P300, and through traditional cognitive tests. In terms of medications, developing new treatment options for psychosis is vital, since about 30% of patients do not respond well to current medications (Bertelsen *et al.*, 2009), and antipsychotics have significant and sometimes severe side-effects (Leucht *et al.*, 2012; Staring *et al.*, 2009).

Endophenotypes (as well as biomarkers not related to genetic aetiology) also have the potential of being used as clinical tools, maybe to identify people at high risk of developing an illness in order to provide early interventions, to predict who will benefit from a particular treatment from a range of options available, and what the course of the illness is likely to be (Fu and Costafreda, 2013; Fu *et al.*, 2013; Fuggetta *et al.*, 2014; Turetsky *et al.*, 2014).

EEG has great potential here, being non-invasive, cost-effective and easy to obtain in a wide range of settings. It has been shown that EEG measures have some predictive value, and that both resting state EEG activity and event related potentials are able to identify individuals at risk who will later develop psychosis (Bodatsch *et al.*, 2011; Gschwandtner *et al.*, 2009; Lavoie *et al.*, 2012; van Tricht *et al.*, 2014; Zimmermann *et al.*, 2010). In a meta-analysis of five studies and a total of 225 at-risk individuals, Bodatsch et al (2014) found that the amplitude of the mismatch negativity event-related potential was significantly reduced in those who later converted to psychosis compared to those who did not develop the illness. This is early evidence that EEG parameters could be useful tools for risk prediction, probably in combination with clinical or other factors.

In future, personalised medicine in psychiatry might be a possibility, with treatments targeted to the needs of the individual patient, based on genetic information as well as biomarkers/endophenotypes of, for example, physiology, cognition or neuroanatomy. This could involve using biomarkers towards disease stratification, that is uncovering illness subtypes to improve the way individuals are categorised and can then choose a treatment such as a drug from several licensed compounds (Insel and Cuthbert, 2015). Personalised medicine has come further in other fields of medicine, such as in oncology, where diagnoses can now sometimes be made based on molecular evidence, leading to truly individualised treatment plans and improved outcomes (Collins and Varmus, 2015; Fenstermacher *et al.*, 2011).

Machine learning methods are promising here, because such approaches can find patterns among large amounts of multivariate data to classify individuals into

groups with similar characteristics (Bone *et al.*, 2015; Fu and Costafreda, 2013; Klöppel *et al.*, 2012; Phillips, 2012). For example, Bedi and colleagues (2015) used language patterns during clinical assessments to predict who would develop psychosis in a clinical high-risk sample, and Costafreda et al (2009) used neuroanatomy to predict treatment response to antidepressant medication. Interestingly, Yang et al (2010) found that a combination of functional brain imaging (fMRI activity during an auditory oddball task) and genetic data (a set of selected SNPs) performed better that either measure alone in classifying patients with schizophrenia and controls.

A longer-term goal of this research is to develop improved diagnostic measures and nosology. Current diagnoses are based on clinical observations, relying on the patient's ability to communicate and the clinician's expertise, and they are not rooted in biology and do not reflect aetiology or prognostic factors (Brodersen *et al.*, 2014; Fu and Costafreda, 2013; Insel and Cuthbert, 2009; Jablensky, 2010). Hence, there is a pressing need to improve diagnoses, and biological markers and endophenotypes have great potential here. As the understanding of disease aetiology improves, diagnostic categories are likely to be refined. Recent genome wide association analyses have, for example, found that there is considerable genetic overlap between schizophrenia and bipolar disorder, as well as some overlap between these and major depressive disorder (Lee *et al.*, 2013), and some SNPs and CNVs have been found that confer risk to a range of disorders including schizophrenia, bipolar disorder, autism spectrum disorder, attention deficit-hyperactivity disorder, and major depressive disorder (Geschwind and Flint, 2015; Moreno-De-Luca *et al.*, 2010; Smoller *et al.*, 2013).

It has been argued that to be able to advance the understanding of disease mechanisms in psychiatry, research needs to move away from current disease classifications to reduce heterogeneity (Owen, 2014). The Research Domain Criteria (RDoC) is an approach introduced by the National Institute of Mental Health in the United States in 2009, and an attempt to develop novel ways of classifying psychiatric disorders (for research purposes initially), that are based on dimensions

of behaviours and neurobiology (NIMH, 2015). Endophenotypes at various level of analysis (e.g. molecular, neurophysiological, or behavioural) fit neatly with this approach to investigate abnormalities implicated in psychiatry that might cut across or subdivide current diagnoses (Glahn *et al.*, 2014; Insel and Cuthbert, 2009; Owen, 2014).

Because endophenotypes identified for psychosis are often not specific to this disorder (for example the P300 and working memory abnormalities, as discussed in chapter 4), the development of clinically useful tools will most likely require a combination of measures from different modalities (Borgwardt and Fusar-Poli, 2012; Prasad and Keshavan, 2008). Some studies have now shown that this approach has predictive power, although replications are needed (e.g. Schubert *et al.*, 2015; Shah *et al.*, 2012). Hence, a measure combining, for example, polygenic scores, neurophysiological markers such as ERPs or measures of effective connectivity, and cognitive performance – as well as family history and key clinical variables such as age and gender – might in future be able to classify individuals into risk groups or identify those most likely to benefit from a particular treatment. Such a model is currently used for cardiovascular disease risk prediction, including factors such as age, gender, ethnicity, smoking status, cholesterol levels, weight, and blood pressure (Boon *et al.*, 2014). The personalised medicine approach that is widely used in oncology and other fields of medicine is gradually starting to gain influence in mental health. As we develop a better understanding of the neurobiology of psychosis through imaging, genomics and other research, we are identifying suitable biomarkers. For psychosis, combined/composite markers could in future provide a tool for the identification of individuals at high risk of developing psychosis that would most benefit from early assessments and interventions ranging from psycho-education to reduce environmental risks to early treatment with psychological therapies, as discussed above.

It is important here to briefly mention the many environmental risk factors for psychosis that have been identified and replicated. Both genetic and environmental factors are crucial to the development of psychiatric illnesses, and there is growing

interest in investigations on how they interact and influence each other (Kelly and Murray, 2000; van Os *et al.*, 2010; Stilo *et al.*, 2011). Some of the most well replicated environmental risk factors for psychosis include pregnancy and perinatal factors (Hultman *et al.*, 1999; Suvisaari *et al.*, 2013), growing up in an urban environment (Kelly *et al.*, 2010; Krabbendam and van Os, 2005; March *et al.*, 2008; McGrath *et al.*, 2004; Vassos *et al.*, 2012), migration and ethnic minority position (Bourque *et al.*, 2010; Cantor-Graae and Selten, 2005; Fearon *et al.*, 2006). Cannabis use, especially when occurring at an early age, is a well characterised risk factor for the development of schizophrenia (D'Souza *et al.*, 2005; Di Forti *et al.*, 2015; Minozzi *et al.*, 2010; van Os *et al.*, 2002), and is the focus of research investigating the interactions between environmental and genetic or other biological risks (Caspi *et al.*, 2003; Howes and Murray, 2014; Iyegbe *et al.*, 2014).

Related to this is the question of resilience; how come some people with an increased risk for psychosis – including those with an increased genetic risk such as first-degree relatives of patients – do not develop the illness? One key issue to keep in mind here this is that genetics are not deterministic and although an individual might inherit an increased genetic risk for psychosis, this does not mean that they will develop this disorder. As per recent genome wide association studies (Geschwind and Flint, 2015; Harrison, 2015; Ripke *et al.*, 2014) more than one hundred genetic variants have been identified reliably. These are common and present individually in 5% or more of the population and indeed many people are carriers of some of these risk variants. However, the odds ratios for these common variants are very small (in the region of only 1.1-1.2), thus increasing the risk only by 10-20% individually. As per work from our group (Calafato, personal communication 2016), even individuals with very high polygenic risk scores for schizophrenia or bipolar disorder might never develop the disease. Similarly, even the strongest known genetic risk factor for schizophrenia, namely 22q.11 deletions where the odds ratio is as high as 35, are in the majority of cases not affected with psychosis (Jonas *et al.*, 2014; Schneider *et al.*, 2014). Unlike rare Mendelian diseases, the genetics of common and complex diseases such as psychosis are far from deterministic and the idea of protective factors that can offer resilience is worth

emphasizing. Indeed, psychosis is not 100% heritable, and genetic factors are not the only ones involved in whether an individual develops the disorder or not. Environmental factors, as discussed above, are equally important. Hence, if an individual inherits an increased genetic risk, but grows up in a supportive family environment and gain adaptive coping mechanisms for dealing with stress, this might protect them against the genetic risk and they might not develop the disorder (Breitborde *et al.*, 2007; O'Brien *et al.*, 2006). Furthermore, although an individual might inherit genetic risk factors for psychosis, they might also inherit genetic factors that are protective against the illness (Maziade and Paccalet, 2013). There is more research aiming to identify risk factors compared to protective factors for psychosis, whereas identifying the latter is equally important and more research should in future focus on this. Identifying what protects individuals has the potential of leading to more efficient prevention in individuals at risk (Kelly *et al.*, 2010).

6.2 Strengths and limitations

There are limitations to this thesis, and although most have been stated in the discussions for the respective experimental chapters, some are relevant to the thesis as a whole and will be discussed briefly here. The strengths of this thesis will also be acknowledged.

The sample studied in this thesis included a broadly defined patient group, including individuals diagnosed with a range of psychotic illnesses – although mostly schizophrenia and bipolar I disorder. All patients studied here have experienced psychosis as part of their illness. Although there is clear evidence for overlapping aetiology and risk factors (Bramon and Sham, 2001; Lee *et al.*, 2013; Murray *et al.*, 2004; Smoller *et al.*, 2013), there are also factors that are distinct between different psychotic illnesses, and the inclusion of a broadly defined patient group could thus add noise to the phenotype definition (compared to a more homogenous sample). Nevertheless, some analyses in this thesis were repeated to examine a more narrow definition of schizophrenia, which did not change the overall conclusions.

Furthermore, as mentioned above, since current diagnostic categories are solely based on clinical observation and not on any biological tests, it is highly likely that the true aetiology will not map neatly onto current diagnoses (Insel and Cuthbert, 2009; Jablensky, 2010). Therefore, it is important to study this broadly defined group of patients, that all share some abnormalities or aspects of their illnesses (Weiser *et al.*, 2005), and this can be seen as a strength of this thesis. In addition, studying a broader phenotype has the added advantage of larger sample sizes and thus greater statistical power. Hence, both studying a narrowly and a broadly defined group of patients are important and valid for the advancement of psychiatric research, and should be seen as complementary approaches.

Another potential limitation of this thesis is the confounding effects of antipsychotic medications. The majority of patients included here were taking antipsychotics that are known to affect brain structure and function (e.g. Fusar-Poli *et al.*, 2013; Goozée *et al.*, 2014; Vita *et al.*, 2012). In macaque monkeys, for example, it has been shown that administration of antipsychotics over 2 years lead to significant overall reductions of both white and grey matter volumes (Dorph-Petersen *et al.*, 2005; Konopaske *et al.*, 2007). Furthermore, studies into the effects of antipsychotics on EEG activity in humans have shown that this can lead to, for example, a slowing of the EEG signal (Hyun *et al.*, 2011; Knott *et al.*, 2001; Schuld *et al.*, 2000).

However, EEG abnormalities have been reported in unmedicated patients (e.g. Brockhaus-Dumke *et al.*, 2008; Gallinat *et al.*, 2004), and it has been argued that treatment with antipsychotics might partially normalise some EEG changes associated with psychosis, such as the reduced amplitudes of the MMN and P300 event related potentials (Su *et al.*, 2012; Zhou *et al.*, 2013). Nevertheless, it is difficult to disentangle true illness effects from the effects of medications, and antipsychotic drugs might contribute to abnormalities found in patients with psychosis. This is one reason why studying unaffected relatives of patients is very advantageous, and a great strength of this thesis. Unaffected relatives carry an increased genetic risk for the illness, but do not have a diagnosis of a psychotic illness and are not taking antipsychotic medications. This group is thus ideal to

study effects related to genetic risk for an illness, without the confounding effects of the disease itself, including medication.

It needs to be acknowledged, however, that relatives do not only share some of their genetic makeup, but often also have some environmental factors in common. This shared environment could potentially influence the phenotypes investigated, including measures of brain function such as EEG (Rasetti and Weinberger, 2011). There are ways of investigating this, however, including the use of adoption and twin designs. Adoption studies can be used to confirm a genetic basis for the family resemblance by comparing adoptees with their biological and adoptive parents. However, these studies are difficult to conduct and prenatal and early life environmental factors could still be shared (Cannon, 2005). Another way of disentangle shared environmental factors from genetic influences is using twin studies, comparing monozygotic twins sharing 100% of their DNA and dizygotic twins sharing 50% of their genetic makeup. Research using such designs has confirmed some EEG measures as promising endophenotypes for psychosis, including the P300 event-related potential (Bestelmeyer *et al.*, 2009; Hall *et al.*, 2009).

An additional limitation to this thesis was that demographic and clinical information were not always available for all participants, because data were collected across several sites and during a long time-period. For example, when investigating resting state EEG data (chapter 2), it would have been of interest to assess associations with clinical or cognitive variables, but this was only available for a subset of individuals leading to a lack of statistical power for such analyses. Nevertheless, this approach led to large sample sizes for most analyses, adding value to the main analyses of interest here.

Lastly, this thesis has been utilising EEG data throughout, and this technique has great advantages. It is a non-invasive and safe method that is easily assessed and well-tolerated by participants. It is also a direct measure of brain function with excellent temporal resolution, and it is inexpensive (Baldeweg and Boyd, 2008; Cohen, 2014; Light and Makeig, 2015; Luck, 2005; McLoughlin *et al.*, 2014). All this

makes EEG suitable both for the large-scale studies needed for genetic research, and as clinically useful markers for psychosis.

6.3 Summary and Conclusions

In summary, I have investigated endophenotypes for psychosis, and findings from this thesis have contributed to psychiatric research by providing further evidence that (i) resting EEG activity is not a promising endophenotype for psychosis, but that (ii) effective connectivity underlying an auditory perceptual task could be. Furthermore, it has been shown that (iii) a range of endophenotypes for psychosis are available encompassing cognitive and neurophysiological domains. Although some are highly correlated, multi-modal approaches are needed to investigate psychosis and its genetic basis. Lastly, (iv) the use of polygenic scores has promise for future research and as sample sizes continue to grow the polygenic score should become more accurate and a more powerful predictor of disease susceptibility.

Well defined and reliably measured endophenotypes are valuable in mental health research by clarifying the functional effects of identified genetic risk factors, and by providing ways of identifying groups of people with similar abnormalities, both within and between current diagnostic categories. Findings from this thesis will contribute towards knowledge that can hopefully in future lead to improvements to the lives of people affected by psychosis.

Appendices

Appendix A: Additional material Chapter 2

Here I report additional analyses to the data presented in chapter 2 of this thesis.

Correlations between outcome variables

EEG amplitude (log transformed µV) in the four frequency bands and the three scalp sites were all significantly correlated ($p<0.001$), with correlation coefficients ranging between 0.29 and 0.99. Within each frequency band, correlations tended to be stronger between neighbouring electrodes (FZ-CZ or CZ-PZ) and weaker when FZ was compared to PZ. At the same location, delta and theta as well as alpha and beta tended to show the strongest correlations.

Table A1. Pearson's correlations between EEG amplitude (µV) in the four frequency bands and the three scalp sites.

		Delta			Theta				Alpha				Beta			
		CZ	PZ	m	FZ	CZ	PZ	m	FZ	CZ	PZ	m	FZ	CZ	PZ	m
Delta	FZ	0.89	0.74	0.93	0.71	0.68	0.60	0.68	0.40	0.41	0.35	0.40	0.30	0.29	0.28	0.29
	CZ		0.88	0.98	0.73	0.77	0.72	0.76	0.39	0.45	0.41	0.43	0.33	0.37	0.37	0.36
	PZ			0.92	0.71	0.76	0.83	0.78	0.42	0.49	0.53	0.50	0.38	0.42	0.47	0.43
	m				0.76	0.78	0.76	0.79	0.43	0.48	0.46	0.48	0.35	0.38	0.39	0.38
Theta	FZ					0.97	0.88	0.97	0.49	0.48	0.43	0.48	0.43	0.42	0.41	0.43
	CZ						0.93	0.99	0.48	0.50	0.45	0.49	0.44	0.47	0.45	0.46
	PZ							0.96	0.51	0.54	0.55	0.56	0.46	0.49	0.53	0.51
	m								0.51	0.52	0.49	0.52	0.45	0.47	0.47	0.48
Alpha	FZ									0.96	0.84	0.96	0.58	0.54	0.59	0.58
	CZ										0.89	0.98	0.56	0.57	0.62	0.60
	PZ											0.95	0.48	0.50	0.63	0.55
	m												0.55	0.55	0.64	0.59
Beta	FZ													0.96	0.90	0.97
	CZ														0.94	0.99
	PZ															0.97

All correlations significant, all $p < 0.001$. *m* = mean amplitudes across FZ, CZ, PZ.

Full Statistical Results

Delta frequency band: Amplitude was significantly higher in FZ compared to CZ ($p=0.003$) and PZ ($p<0.001$) in the control group. Furthermore, in the control group, there were significant effects of age ($p<0.001$), with amplitude decreasing with age,

and gender ($p<0.001$), with females showing higher amplitudes than males. There was no significant effect of EEG lab.

Theta frequency band: Regional effects showed that, in the control group, the amplitude reduced significantly from FZ to CZ ($p=0.008$) and from FZ to PZ ($p<0.001$). Further, there were significant effects of age ($p=0.003$), with theta amplitude reducing with age, and gender ($p=0.041$), with females showing higher amplitudes than males. There was no significant effect of lab.

Alpha frequency band: In the control group, there were significant regional effects, with the amplitude increasing from FZ to CZ ($p<0.001$) as well as from FZ to PZ ($p<0.001$). Further, females in the control group showed significantly higher resting alpha amplitudes compared to males ($p=0.005$). There were no significant effects of age or lab in the alpha frequency band.

Beta frequency band: Regional effects showed that, in the control group, the amplitude increased significantly from FZ to CZ ($p<0.001$) and from FZ to PZ ($p=0.035$). Females showed significantly greater amplitudes than males in the control group ($p<0.001$). There were no significant age or lab effects.

Table A2. Full mixed model linear regression results for the four frequency bands.

Delta frequency band					**Theta frequency band**				
	Coef.	p	95% CI			Coef.	p	95% CI	
Controls vs.					Controls vs.				
Relatives	0.01	0.746	-0.03	0.05	Relatives	0.01	0.637	-0.04	0.07
ARMS	-0.01	0.621	-0.05	0.03	ARMS	0.00	0.891	-0.06	0.06
First episodes	0.01	0.799	-0.03	0.04	First episodes	0.01	0.679	-0.04	0.07
Chronics	0.08	**<0.001**	0.05	0.12	Chronics	0.14	**<0.001**	0.08	0.2
FZ vs.					FZ vs.				
CZ	-0.01	0.003	-0.02	-0.01	CZ	-0.01	0.008	-0.02	-0.01
PZ	-0.06	<0.001	-0.06	-0.05	PZ	-0.06	<0.001	-0.07	-0.06
Covariates					Covariates				
Age	-0.01	<0.001	-0.01	-0.01	Age	-0.01	0.003	-0.01	-0.01
Gender	0.04	<0.001	0.02	0.06	Gender	0.03	0.041	0.01	0.07
Lab	0.02	0.272	-0.02	0.06	Lab	0.01	0.945	-0.06	0.06
Constant	0.98	<0.001	0.90	1.05	Constant	1.06	<0.001	0.95	1.17
Alpha frequency band					**Beta frequency band**				
	Coef.	p	95% CI			Coef.	p	95% CI	
Controls vs.					Controls vs.				
Relatives	-0.03	0.486	-0.10	0.05	Relatives	0.03	0.232	-0.02	0.09
ARMS	-0.05	0.254	-0.12	0.03	ARMS	-0.02	0.457	-0.08	0.04
First episodes	0.01	0.829	-0.06	0.08	First episodes	-0.01	0.644	-0.07	0.04
Chronics	0.04	0.319	-0.03	0.10	Chronics	0.06	0.018	0.01	0.11
FZ vs.					FZ vs.				
CZ	0.02	<0.001	0.009	0.027	CZ	0.01	<0.001	0.01	0.02
PZ	0.06	<0.001	0.051	0.069	PZ	0.01	0.035	0.01	0.01
Covariates					Covariates				
Age	-0.01	0.132	-0.01	0.01	Age	0.01	0.155	-0.01	0.01
Gender	0.06	0.005	0.02	0.10	Gender	0.07	<0.001	0.04	0.10
Lab	0.03	0.411	-0.04	0.10	Lab	0.05	0.102	-0.01	0.10
Constant	0.90	<0.001	0.76	1.04	Constant	0.90	<0.001	0.80	1.01

ARMS = At risk mental state; CI = confidence interval; Lab = EEG laboratory

Additional post-hoc analysis: Chronic patients vs. other groups

In the delta frequency band, the chronic patient group showed significantly increased resting EEG activity compared to all other groups (all p≤0.001). All such comparisons remained significant after correction for multiple testing. In the theta frequency band, again, the chronic patient group showed significantly increased activity compared to the other groups, surviving multiple testing (all p≤0.001).

No group differed significantly from the chronic patient group in alpha activity. Lastly, in the beta frequency band, the chronic patients showed increased resting

EEG activity compared to healthy controls and first episode patients. The former comparison did not survive correction for multiple testing for 4 tests (p=0.018), but the difference between chronic and first episode patients remained significant (p=0.012).

Table A3. Regression results with chronic patients as reference group.

Delta frequency band					**Theta frequency band**				
	Coef.	p-value	95% CI			Coef.	p-value	95% CI	
Chronic patients vs.					*Chronic patients vs.*				
Controls	-0.08	**<0.001**	-0.12	-0.05	Controls	-0.14	**<0.001**	-0.19	-0.08
Relatives	-0.08	**<0.001**	-0.11	-0.04	Relatives	-0.12	**<0.001**	-0.17	-0.07
ARMS	-0.09	**0.001**	-0.15	-0.03	ARMS	-0.13	**0.001**	-0.21	-0.05
First episodes	-0.08	**<0.001**	-0.12	-0.03	First episodes	-0.12	**<0.001**	-0.18	-0.06
Alpha frequency band					**Beta frequency band**				
	Coef.	p-value	95% CI			Coef.	p-value	95% CI	
Chronic patients vs.					*Chronic patients vs*.				
Controls	-0.03	0.319	-0.10	0.03	Controls	-0.06	0.018	-0.11	-0.01
Relatives	-0.06	0.047	-0.12	-0.01	Relatives	-0.027	0.231	-0.07	0.02
ARMS	-0.08	0.129	-0.18	0.02	ARMS	-0.08	0.032	-0.16	-0.01
First episodes	-0.03	0.494	-0.10	0.05	First episodes	-0.07	**0.012**	-0.13	-0.02

Mixed effects linear regression models on log transformed amplitudes with group (patient, relative, controls) and scalp site (FZ, CZ, PZ) as fixed effects, and family and subject as random effects. Covariates of age, gender and EEG laboratory included.

Publication: Impaired prefrontal synaptic gain in people with psychosis and their relatives during the mismatch negativity.

r Human Brain Mapping 00:00–00 (2015) r

Impaired Prefrontal Synaptic Gain in People with Psychosis and Their Relatives during the Mismatch Negativity

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Abstract: The mismatch negativity (MMN) evoked potential, a preattentive brain response to a discriminable change in auditory stimulation, is signif cantly reduced in psychosis. Glutamatergic theories of psychosis propose that hypofunction of NMDA receptors (on pyramidal cells and inhibitory interneurons) causes a loss of synaptic gain control. We measured changes in neuronal effective connectivity underlying the MMN using dynamic causal modeling (DCM), where the gain (excitability) of superf cial pyramidal cells is explicitly parameterised. EEG data were obtained during a MMN task—for 24 patients with psychosis, 25 of their f rst-degree unaffected relatives, and 35 controls—and DCM was used to estimate the excitability (modeled as self-inhibition) of (source-specif c) superf cial pyramidal populations. The MMN sources, based on previous research, included primary and secondary auditory cortices, and the right inferior frontal gyrus. Both patients with psychosis and unaffected relatives (to a lesser degree) showed increased excitability in right inferior

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Additional Supporting Information may be found in the online version of this article.

Contract grant sponsor: National Institute for Health Research, UK; Contract grant number: PDA/02/06/016

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Received for publication 1 July 2015; Revised 30 September 2015; Accepted 13 October 2015.

DOI: 10.1002/hbm.23035

Published online 00 Month 2015 in Wiley Online Library (wileyonlinelibrary.com).

frontal gyrus across task conditions, compared to controls. Furthermore, in the same region, both patients and their relatives showed a reversal of the normal response to deviant stimuli; that is, a decrease in excitability in comparison to standard conditions. Our results suggest that psychosis and genetic risk for the illness are associated with both context-dependent (condition-specif c) and context-independent abnormalities of the excitability of superf cial pyramidal cell populations in the MMN paradigm. These abnormalities could relate to NMDA receptor hypofunction on both pyramidal cells and inhibitory interneurons, and appear to be linked to the genetic aetiology of the illness, thereby constituting potential endophenotypes for psychosis. Hum Brain Mapp 00:000–000, 2015.

Key words: psychosis; schizophrenia; unaffected relatives; genetic risk; effective connectivity; dynamic causal modeling; DCM; cortical excitability; cortical gain; NMDA receptor

INTRODUCTION

Psychotic disorders are among the most severe and enduring mental illnesses, characterised by a distorted sense of reality; an inability to distinguish subjective experiences from the objective world. Disorders where psychosis is commonly experienced include, amongst others, schizophrenia, bipolar disorder, and schizoaffective disorder [NICE, 2014; WHO, 2008].

The mismatch negativity (MMN) event related potential is a pre-attentive brain response to a discriminable change in auditory stimulation [Duncan et al., 2009; Näätänen, 1992; Todd et al., 2013; Umbricht et al., 2005]. Reduced MMN amplitude is one of the most reliable f ndings in schizophrenia research, and since the f rst publication by Shelley et al [1991] over 100 papers have commented on this reduced amplitude [e.g., Baldeweg and Hirsch, 2015; Shaikh et al., 2012; Todd et al., 2013], with a mean effect size of 0.99 [Umbricht et al., 2005]. The MMN is abnormal in clinical risk groups as well as in patients, and is a promising biomarker for psychosis prediction [Bodatsch et al., 2014; Nagai et al., 2013]. Furthermore, the MMN has been proposed as a potential endophenotype or a biological marker of genetic risk for psychosis, because it is heritable [Hall et al., 2006, 2009; Hong et al., 2012], and abnormal in f rst degree relatives of patients, who have an increased genetic risk for psychosis [Jessen et al., 2001; Michie et al., 2002]. However, not all studies in unaffected relatives have found MMN abnormalities [Bramon et al., 2004; Hong et al., 2012; Kim et al., 2014].

Most previous studies of the MMN use classical electroencephalogram (EEG) analysis methods that investigate the observed amplitude of the event related potential at the sensor level. However, abnormal functional integration among brain regions or "dysconnection," has been proposed as a core pathology of psychosis [Friston, 1998; Stephan et al., 2006]. Motivated by this hypothesis, we investigated the MMN in terms of the underlying neuronal connectivity. We used dynamic causal modeling (DCM), which explains EEG data using a hierarchical network of dynamically coupled sources, and estimates effective connectivity—the inf uence that one neuronal system exerts over another—using Bayesian model comparison and inversion [David et al., 2006; Friston et al., 2003]. Several previous DCM studies have found abnormal effective connectivity in psychosis, both using EEG/MEG [Dima et al., 2010, 2012; Fogelson et al., 2014; Roiser et al., 2013] and fMRI methods [Crossley et al., 2009; Deserno et al., 2012; Dima et al., 2009; Mechelli et al., 2007; Schmidt et al., 2014]. However, this is the f rst DCM study investigating the MMN paradigm in patients as well their unaffected relatives, with a view to examining whether abnormal effective connectivity (and its modulation) could act as an endophenotype for psychosis.

Our hypothesis is based on current theories of psychosis that implicate the neuromodulation of postsynaptic excitability or cortical gain control [Harrison et al., 2011; Lisman et al., 2008; Phillips and Silverstein, 2013; Stephan et al., 2006]. The most ubiquitous neurotransmitter receptor involved in gain modulation is the glutamatergic N-methyl-D-aspartate receptor (NMDA-R), which is expressed more densely in superf cial cortical layers [Friston, 1998; Gonzalez-Burgos and Lewis, 2012; Lakhan et al., 2013]. NMDA-R hypofunction is known to be associated with psychosis; it is for example well established that NMDA-R antagonists such as ketamine or phencyclidine produce psychotomimetic symptoms in healthy individuals and worsen symptoms in patients with schizophrenia [Gilmour et al., 2012; Javitt and Zukin, 1991; Kantrowitz and Javitt, 2010; Krystal et al., 1994; Lahti et al., 1995; Malhotra et al., 1996; Pilowsky et al., 2006]. Recent genetic association studies also implicate the NMDA-R and its postsynaptic signaling cascade in the disorder [Purcell et al., 2014; Ripke et al., 2014]. Furthermore, the hypofunctioning of NMDA-Rs on inhibitory GABAergic interneurons is also thought to contribute to a loss of balance between excitation and inhibition, which has been implicated in the neuropathology of psychosis [Gonzalez-Burgos and Lewis, 2012]. Lastly, reduced MMN amplitudes have been observed in healthy volunteers after NMDA-R blockade, for example by administration of ketamine [Javitt et al., 1996; Näätänen et al., 2012; Schmidt et al., 2012a; Umbricht et al., 2000]. From a theoretical perspective, this loss of gain control or excitation-inhibition balance f ts comfortably with hierarchical predictive coding models of psychosis and false inference–that rest on the abnormal encoding of uncertainty or

TABLE 1. Sample demographics (N 5 84)

	Patients with psychosis N 5 24	Unaffected relatives N 5 25	Controls N 5 35
Mean age (years, SD)	34.6 (6 9.3)	43.7 (6 14.5)	41.8 (6 14.5)
Age range (years)	23–54	16–62	19–69
Gender (N male/female, % female)	18/6 (25%)	12/13 (52%)	17/18 (51%)
Education (mean years, SD)	13.6 (6 2.8)	14.0 (6 3.1)	14.4 (6 3.7)
Diagnosis (N, %)			
Schizophrenia	18 (75%)	–	–
Schizoaffective disorder	3 (13%)	–	–
Psychosis NOS	1 (4%)	–	–
Bipolar I disorder (w. psychosis)	2 (8%)	–	–
Major Depression	–	3 (12%)	1 (3%)
No psychiatric illness	–	22 (88%)	34 (97%)
Illness duration (mean years, SD)	12.1 (8.4)	NA	NA
Psychotropic medication (N, %)	23 (95.8%)	NA	NA
CPZ equivalent (mean, min-max)*	549.4 (30-1100)	NA	NA
Years medicated (mean, SD)	10.6 (6 8.6)	NA	NA
First medicated (mean years, SD)	24.4 (6 7.2)	NA	NA
PANSS (mean, SD)**			
Positive	12.5 (6 4.6)	7.2 (6 0.6)	7.0 (6 0.0)
Negative	14.9 (6 5.5)	7.2 (6 0.6)	7.0 (6 0.0)
General	24.3 (6 4.9)	17.5 (6 2.0)	16.1 (6 0.4)
Relationship to proband (N, %)			
Mother	NA	4 (16.0%)	NA
Father	NA	9 (36.0%)	NA
Sister	NA	8 (32.0%)	NA
Brother	NA	3 (12.0%)	NA
Daughter	NA	1 (4.0%)	NA

NA 5 not applicable; SD 5 standard deviation; NOS5 not otherwise specified; * CPZ equivalent 5 average chlorpromazine equivalent dosage (mg) for those taking antipsychotic medication (N 5 18); ** PANSS positive and negative scores range from 7 to 49, PANSS general scores range from 16 to 112

precision by the gain of (superficial pyramidal) cells reporting prediction errors [Adams et al., 2013].

Given the prominence of NMDA-Rs in superficial cortical layers, it is unsurprising that the gain of superficial pyramidal cell populations is strongly affected by NMDA-R function [Fox et al., 1990; Pinotsis et al., 2014]. In DCM, this gain is parameterized as the inhibitory self-connectivity (or "intrinsic connectivity") of superficial pyramidal cells within a cortical source [Friston, 2008]. Our aim in this study was to investigate group differences in MMN responses of patients with psychosis, their unaffected relatives, and healthy controls, and test whether these are best explained by modulations of synaptic gain at different levels of the cortical hierarchy. We hypothesised that, compared to controls, we would see abnormal cortical gain control in both individuals with psychosis and (to a lesser extent) in their first degree relatives.

MATERIALS AND METHODS

Sample and Clinical Assessment

The total sample of 84 participants included 24 patients with a psychotic illness (75% schizophrenia, no comorbid diagnoses; see breakdown in Table 1), 25 unaffected first degree relatives of psychosis sufferers (without any personal history of a psychotic illness), and 35 unrelated controls (without any personal or family history of psychotic illnesses).

A personal history of nonpsychotic psychiatric illnesses did not constitute an exclusion criterion for relatives or controls, provided they were well and not taking any psychotropic medication at the time of testing and for the preceding 12 months. This was to avoid recruiting biased control groups, unrepresentative of the general and local populations. Three relatives (12%) and one control (3%) had a history of major depressive disorder.

Patients with psychosis and relatives were recruited through voluntary organisations, advertisements in the local press and from clinical teams at the South London and Maudsley NHS Foundation Trust. Controls were recruited by advertisements in the local press and job centres. Participants were excluded if they had a diagnosis of alcohol or substance dependence in the last 12 months, neurological disorders or a previous head injury with loss of consciousness longer than a few minutes.

All participants were clinically interviewed to confirm or exclude a Diagnostic and Statistical Manual of Mental

Disorders, Fourth Edition [DSM-IV; APA, 1994] diagnosis. Instruments used included the Schedule for Affective Disorders and Schizophrenia—Lifetime version [SADS-L; Endicott and Spitzer, 1978] and the Positive and Negative Syndrome Scale [PANSS; Kay et al., 1987]. Information regarding psychiatric diagnoses of family members not directly assessed was collected from the most reliable informant(s) with the Family Interview for Genetic Studies [FIGS; Maxwell, 1992].

All participants gave informed written consent to participate, and the study was approved by the Institute of Psychiatry Research Ethics Committee, conforming to the standards set by the Declaration of Helsinki. This sample is part of the larger Maudsley Family Study of Psychosis [e.g., Dutt et al., 2012; Ranlund et al., 2014; Schulze et al., 2008; Shaikh et al., 2013].

EEG Data Acquisition

Electroencephalogram (EEG) was collected from 17 scalp sites according to the 10/20 International system (FP1, FP2, F7, F8, F3, F4, C3, C4, P3, P4, FZ, CZ, PZ, T3, T4, T5, T6), grounded at Fpz using silver/silver-chloride electrodes [Jasper, 1958]. Vertical, horizontal, and radial electrooculographs monitored eye movements, and the left ear lobe served as reference. Data were continuously digitised at 500 Hz with a 0.03–120 Hz band-pass filter (24 dB/octave roll-off). Impedances were kept below 5 kX [Bramon et al., 2004, 2005].

MMN paradigm

This was a duration-deviant auditory two tone paradigm. The stimuli were 1,200 tones (80 dB, 1,000 Hz, 5 ms rise/fall time), with a 300 ms inter-stimulus interval, presented in three blocks of 400 stimuli through bilateral intra-aural earphones. 85% of the tones were "standards" (25 ms duration), and 15% were "deviants" (50 ms duration) [Hall et al., 2009; Shaikh et al., 2012]. The total duration of the experiment was about 10 min.

Participants were sitting comfortably in an armchair, and were instructed to keep their eyes open, fixate on a point in front of them, and disregard the sounds presented.

The classical group comparisons of the MMN amplitude in this sample have been reported in a previous study [Bramon et al., 2004]. Here we undertake a new analysis of effective connectivity during the MMN task.

EEG Data Preprocessing

Signal processing was conducted using SPM 12b (http://www.fil.ion.ucl.ac.uk/spm/software/spm12) [Litvak et al., 2011] and FieldTrip (http://www.fieldtrip.nl) [Oostenveld et al., 2011] in MATLAB R2013b (www.mathworks.co.uk).

The raw EEG data were converted to SPM format, and re-referenced to the common average. A high-pass filter of 0.5 Hz was applied, followed by a low-pass 70 Hz filter. A stop-pass (49–50 Hz) filter was also applied, to remove line noise. The data were then downsampled to 200 Hz, and epoched with a peristimulus window of 2 100 to 300 ms. Baseline correction was performed using the 100 ms before stimulus onset.

Independent Component Analysis was used to correct for ocular artefacts in the data. The EEG activity was decomposed into 17 independent components, of which a maximum of two that clearly corresponded to eye blinks were removed from the data. Additional automatic artefact rejection was then conducted, removing any trials whose activity exceeded 6 70 l V across all channels. This resulted in an average of 45 trials (3.7%) being rejected per participant, which did not differ between the three groups ($F(2,81) = 1.1$, $P = 0.3$).

The EEG data were then averaged using robust averaging in SPM. This procedure produces the best estimate of the average by weighting data points as a function of their distance from the sample mean, so that outlier values have less influence on the overall mean [Wager et al., 2005]. This was followed by an additional low-pass filter of 70 Hz, as recommended with robust averaging [Litvak et al., 2011].

The grand average event related potential waveforms across subjects were computed for patients, relatives and controls separately. The use of grand average waveforms ensures cleaner (almost noiseless) data for each group and condition. Grand averages retain features that are conserved within groups, and suppress individual differences. These grand averages constitute six event related potentials—one for each group and stimulus condition (standard and deviant tones)—that were characterised in the subsequent DCM analysis [Fogelson et al., 2014].

Dynamic Causal Modeling

Dynamic causal modeling (DCM) explains measured data using a hierarchical network of dynamically interacting sources, and estimates effective connectivity (the influence that one neuronal system exerts over another), using Bayesian model inversion [Friston et al., 2007]. DCM was originally developed for fMRI [Friston et al., 2003] and was subsequently generalised to other modalities, including evoked responses measured by EEG [David et al., 2006].

DCM permits source reconstruction whilst incorporating biological constraints on neuronal dynamics and coupling [David et al., 2005; Kiebel et al., 2009; Pinotsis et al., 2012]. The neuronal model makes predictions about the dynamics of each source based on the underlying anatomy and biology. We used the canonical microcircuit neural mass model [Bastos et al., 2012], in which each neural source comprises four cell populations: Superficial and deep

pyramidal cells, spiny stellate cells and inhibitory interneurons. Each source is connected to other sources via extrinsic excitatory connections, and cell populations within sources are connected to each other via intrinsic connections [Pinotsis et al., 2013]. In this study, we focused on the self-inhibition of superf cial pyramidal cell populations (see Supporting Information Fig. S1), because the strength of this connection ref ects the gain (or excitability) of this population, which is linked to NMDA-R function.

Each source (i.e., each node in the network) was modeled with a single equivalent current dipole under bilateral symmetry assumptions [Kiebel et al., 2006]. We used a boundary elements head model [Fuchs et al., 2001] to approximate the brain, cerebrospinal f uid, skull and scalp surfaces. A canonical MRI head model was used, and coregistration of electrode positions and head model was performed for each subject to map the Montreal Neurological Institute coordinates to points on the head.

Following standard practice, the EEG data were projected onto eight spatial modes to ensure more robust model inversion and dynamical stability. These are the eight principal components or modes of the prior predictive covariance in sensor space [Fastenrath et al., 2009]. We modeled responses from 0 to 250 ms post stimulus onset, to ensure selective modeling of the MMN response per se, rather than later components [Garrido et al., 2008].

DCM specification

In DCM, Bayesian inference is used to optimise neural source dipoles based on a priori information about their locations. This information is available from studies investigating the sources underlying the MMN—using fMRI [Molholm et al., 2005; Rinne et al., 2005; Schönwiesner et al., 2007], PET [Dittmann-Balçar et al., 2001; Müller et al., 2002], EEG/MEG [Deouell et al., 1998; Fulham et al., 2014; Jemel et al., 2002; Rinne et al., 2000; Tiitinen et al., 2006], and DCM [Garrido et al., 2007, 2008, 2009a]—showing that the MMN is generated by temporal and frontal sources. Using DCM, the model with the most evidence consists of a three-level hierarchy comprising bilateral primary auditory cortices (Heschl's gyrus, A1), bilateral superior temporal gyri (STG), and the right inferior frontal gyrus (rIFG). The frontal source is lateralised to the right hemisphere for auditory paradigms [Garrido et al., 2009a; Levanen et al., 1996].

Following Garrido et al. [2008], we included the following f ve sources, with prior source locations in our DCM analysis (in Montreal Neurological Institute coordinates): Left A1 (2 42, 2 22, 7), right A1 (46, 2 14, 8), left STG (2 61, 2 32, 8), right STG (59, 2 25, 8), and right IFG (46, 20, 8), illustrated in Figure 1A. DCM incorporates source reconstruction, and the inversion algorithm provides eff cient Bayesian estimates of dipole sources that optimise these [David et al., 2005; Kiebel et al., 2009].

Our DCM assumes the existence of extrinsic (forward and backward) connections between, and intrinsic (interlaminar and intralaminar) connections within the specif ed sources. This has been supported by previous MMN research [Dietz et al., 2014; Garrido et al., 2007, 2008, 2009a]. We also included lateral connections linking left and right A1 and STG [Schmidt et al., 2012b]. Auditory stimuli were modeled as direct input, entering bilateral A1. This model is shown in Figure 1B.

Experimental effects

We used condition-specif c grand averaged data over all subjects within each group, allowing us to test for the effect of group directly, as well as the effect of condition by group interactions [e.g., Fogelson et al., 2014; Kiebel et al., 2007]. In other words, the grand averages were treated as the six cells of a 2 3 3 factorial design, with two levels of "condition" (standard and deviant tones) and three levels of "group" (controls, relatives and patients with psychosis).

Group effects were def ned as (i) having a genetic risk for psychosis (controls versus relatives and patients combined) and (ii) having a diagnosis of a psychotic illness, irrespective of genetic risk (relatives versus patients). We tested for a main effect of diagnosis and genetic risk on effective connectivity, and the interactions with the effect of condition (standard versus deviant tones). The interactions ref ect a diagnosis or risk effect on deviant-related changes in effective connectivity or postsynaptic sensitivity.

Bayesian model selection was used to f nd the model with the largest (free energy approximation to the) log model evidence, among the models tested, where models are penalised for increased complexity [Penny et al., 2004]. A difference in log evidence of three or more is considered strong evidence in favour of a model, corresponding to an odds ratio of about 20:1 [Friston and Penny, 2011].

Before testing for the effects of genetic risk and diagnosis, we established the best model to explain the effect of the deviant stimulus across all three groups. We considered eight candidate models with modulations of forward, backward and/or intrinsic connections. The model that allowed for modulations of intrinsic connections (self-inhibition of superf cial pyramidal populations) only had the highest evidence, and was used in all subsequent analyses (see Supporting Information Figs. S2 and S3).

To study the effects of genetic risk and diagnosis we used Bayesian model selection to establish where in the hierarchy synaptic gain—intrinsic (self-inhibitory) connectivity—was modulated. Our model space consisted of models with modulations of intrinsic connections at each of the hierarchical levels (A1, STG, rIFG), and all combinations of these. A total of 8 models were thus compared, shown in Figure 2.

Having established the model with the greatest evidence, we examined the posterior estimates of the effective connectivity under this model [Friston and Penny, 2011]. We focused on changes in intrinsic connectivity induced by the mismatch negativity, to identify any differences

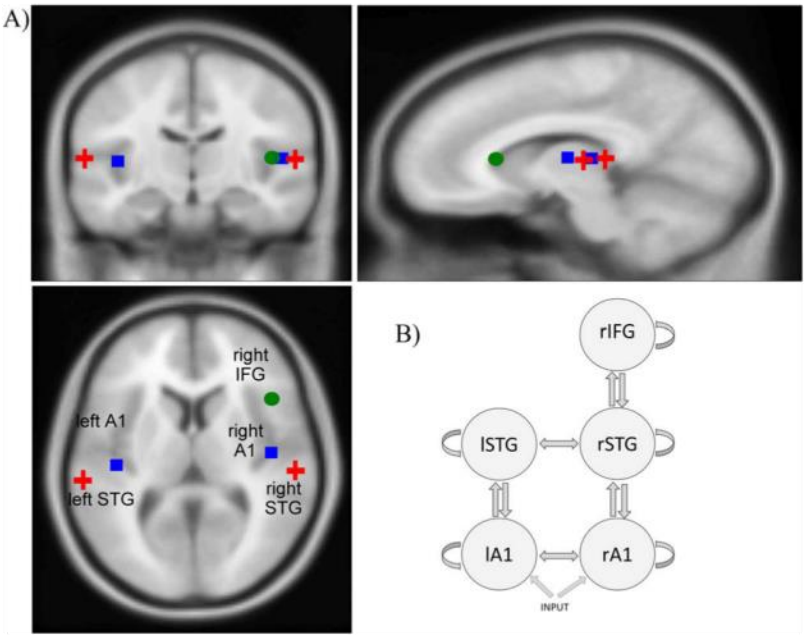

Figure 1.

Image showing (A) the prior source locations (overlaid on an MRI image of a standard brain) and (B) the structural model used for dynamic causal modeling. The sources are linked by extrinsic (forward, backward, and lateral) connections, and each source has intrinsic inhibitory self-connections. A1 5 primary auditory cortex; STG 5 superior temporal gyrus; IFG 5 inferior frontal gyrus; l 5 left hemisphere; r 5 right hemisphere. [Color f gure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

between patients with psychosis, unaffected relatives, and controls.

RESULTS

Sample Demographics

The demographic and clinical characteristics of the sample are detailed in Table 1. All participants were of European Caucasian ethnicity. Patients were signif cantly younger than controls (t 5 2.14, P 5 0.04) and relatives (t 5 2.60, P 5 0.01), and this group also contained more males compared to controls (v^2 5 4.1, P 5 0.04) and relatives (v^2 5 3.8, P 5 0.05). Controls and relatives did not differ signif cantly in age (t 5 0.51, P 5 0.61) or gender (v^2 5 0.002, P 5 0.97) distributions. Importantly, patients and relatives together (i.e., the genetic risk group) did not differ from controls in age (t 5 2 0.83, P 5 0.41) or gender (v^2 5 1.33, P 5 0.27) distributions. Years in education did not differ between groups (F 5 0.40, P 5 0.67).

The sample comprised 63 families, each including between 1 and 4 individuals. 49 participants (58.3%) were singletons, 18 (21.4%) were part of families with two members in the study, 9 (10.7%) were in three-person families, and 8 (9.5%) were part of families with four members participating. All unaffected relatives had a f rst-degree relative with a psychotic illness, although 8 (32%) did not have a proband participating in this study.

Mismatch Negativity Group Differences

The grand averaged event related potential waves for patients, relatives, and controls are shown in Figure 3. Group differences in the amplitude of the MMN wave of this sample have been reported in a previous paper [Bramon et al., 2004]: Patients with psychosis had signif cantly reduced MMN amplitude compared to both relatives and controls. The relatives did not differ signif cantly in MMN amplitude compared to the controls.

Dynamic Causal Modeling Results

The Bayesian model selection results are presented in Figure 4A, showing model evidences relative to the null model (with

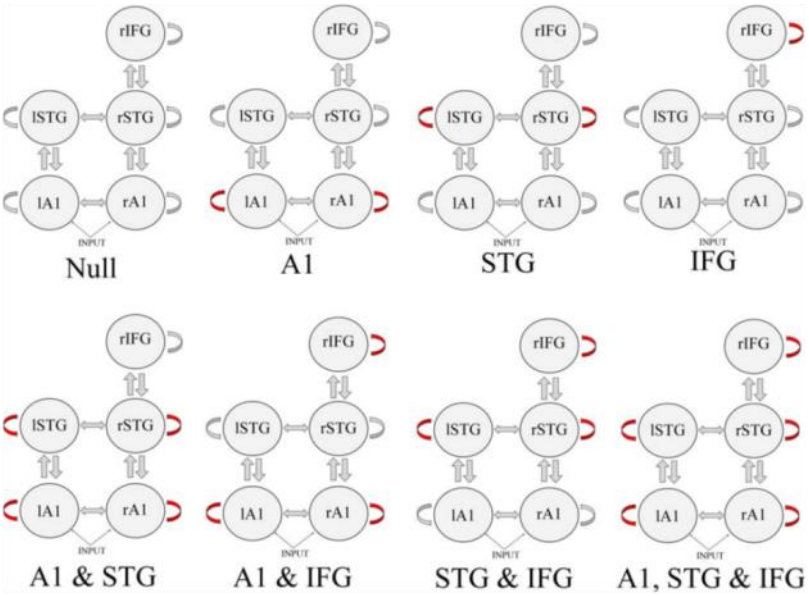

Figure 2.
Dynamic causal modeling model space; identifying group differences in intrinsic (self-inhibitory) connectivity. Red arrows indicate a modulated connection. A1 5 primary auditory cortex; STG 5 superior temporal gyrus; IFG 5 inferior frontal gyrus; l 5 left hemisphere; r 5 right hemisphere. [Color f gure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

no intrinsic modulations). The model that best explained the differences between groups allowed modulations of intrinsic connectivity in bilateral A1 and rIFG. The difference in model evidence between the winning model and the runner-up was 80. This is signif cant seeing as a difference of 3 (corresponding to an odds ratio of 20:1) is considered strong evidence in favour of the winning model [Friston and Penny, 2011].

Figure 4B shows the posterior estimates of the modulations of intrinsic connectivity in the winning model for each group (controls, relatives, and patients) and condition (standard and deviant trials). Note that because the intrinsic self-connectivity is inhibitory, increased values correspond to reduced neural excitability, and vice versa. Posterior estimates of the modulations are also shown in Figure 5, for each source and experimental effect.

The largest effects are observed at the high-level frontal source (rIFG), where there are striking group differences. First, both relatives and patients show reduced self-inhibition (increased excitability) across task conditions compared to controls (i.e., a main effect of having a genetic risk for psychosis). Second, patients with psychosis show an additional reduction in self-inhibition compared to relatives, across task conditions (i.e., a main effect of diagnosis).

Third, there is a clear interaction between having a genetic risk for psychosis and task condition in rIFG; both relatives and patients show the opposite pattern of responses to the task compared to controls. While controls demonstrate reduced inhibition (i.e., increased excitability)

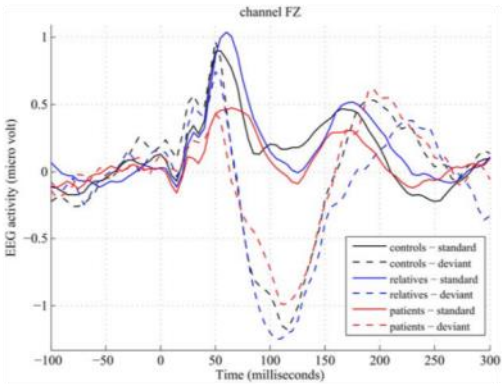

Figure 3.
EEG activity to standard and deviant tones for each group (grand averages across subjects), at channel FZ. [Color f gure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

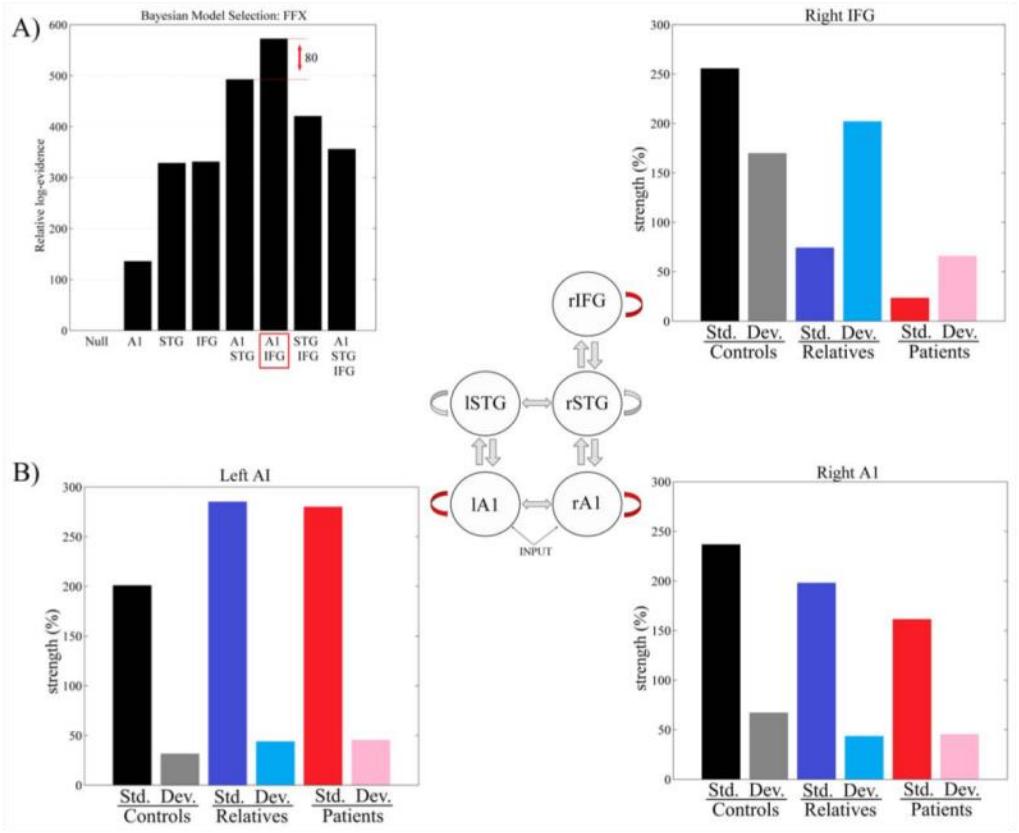

Figure 4.

(A) Bayesian model selection results investigating intrinsic (inhibitory) modulations at different levels of the hierarchy. Log model evidences relative to the null model are shown. The winning model has modulations at A1 and IFG, and the difference in log evidence between this and the runner-up is 80. (B) Changes in intrinsic connectivity strengths under the winning model, at each source, for patients, relatives and controls, and for standard (std.) and deviant (dev.) trials. A1 5 primary auditory cortex; STG 5 superior temporal gyrus; IFG 5 inferior frontal gyrus; l 5 left hemisphere; r 5 right hemisphere. [Color f gure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

in response to deviants compared to standard tones, the two groups with a genetic risk showed decreased excitability in response to changes in stimulus regularities.

At the sensory level (left and right primary auditory cortices, A1), all three groups show similar responses to the MMN task conditions: Increased excitability in response to deviant compared to standard tones.

DISCUSSION

The aim of this study was to investigate whether, compared to controls, patients with psychosis and/or their unaffected relatives show altered cortical gain control (intrinsic connectivity) within cortical sources using the mismatch negativity (MMN) paradigm. We used DCM, where intrinsic connectivity is a parameterisation of the (to some extent NMDA-R mediated) excitability of superf cial pyramidal cells, which is thought to be abnormal in psychosis [Stephan et al., 2006].

Our main f ndings were that; (i) the largest differences in cortical responses between controls and the other groups were expressed at the top of the cortical hierarchy in the right inferior frontal gyrus (rIFG), rather than in primary sensory areas (A1); (ii) in rIFG, both groups with an increased genetic risk for psychosis (patients and their

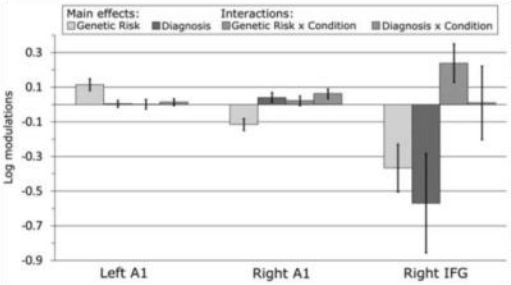

Figure 5.
Posterior estimates of the (log scaling of) intrinsic connection parameters and their 95% confidence intervals, for each source and experimental effects investigated. A1 5 primary auditory cortex; IFG 5 inferior frontal gyrus.

relatives) demonstrated an increase in cortical excitability across task conditions (with an additional increase in patients compared to relatives); and (iii) the two groups with a genetic risk for psychosis also showed a reversal of the normal pattern of increased excitability to deviant tones in rIFG.

Our finding of reduced self-inhibition within rIFG across task conditions in those with a genetic risk for psychosis—as well as an additional reduction in patients with psychosis compared to relatives—is in line with theories of NMDA-R hypofunction in psychosis [Abi-Saab et al., 1998; Corlett et al., 2011; Goff and Coyle, 2001; Olney et al., 1999; Stephan et al., 2006]. Specifically, NMDA-R hypofunction on parvalbumin positive inhibitory interneurons results in decreased inhibitory g-aminobutyric acid (GABA) input to (and therefore disinhibition of) pyramidal cells and hence a loss of balance between excitation and inhibition in prefrontal cortex [Lewis et al., 2012; Murray et al., 2014; Pinotsis et al., 2014]. These abnormalities may be linked to neurophysiological disorganisation [Diez et al., 2014], cognitive dysfunction and the development of symptoms of psychosis [Ahn et al., 2011; Lewis et al., 2008; Spencer et al., 2004].

Crucially, patients with psychosis and relatives show the opposite pattern of rIFG responses to deviant and standard tones, compared to controls. Controls show reduced self-inhibition (increased excitability) in response to deviants, whereas both patients and relatives show a reduction in excitability in this condition. This indicates that those with an increased genetic risk for psychosis (including both relatives and patients) fail to adjust or optimise the excitability of superficial pyramidal cells in response to changes of stimulus regularities.

In a visual target detection task, in which subjects had to respond to target appearances that were either predictable or unpredictable, Fogelson et al. [2014] also investigated differences in intrinsic connectivity in patients with schizophrenia and healthy controls using EEG and DCM. They found that changes in intrinsic self-inhibition in response to predictable stimuli were significantly attenuated in patients; this is further evidence that patients with schizophrenia fail to adjust neuronal connectivity in response to the context of incoming stimuli.

Our results can be interpreted in the context of predictive coding theories of brain function, in which the brain infers the causes of its sensory data using Bayesian inference by minimizing prediction errors throughout the cortical hierarchy [Friston, 2008; Rao and Ballard, 1999]. Predictive coding can be implemented neurobiologically by deep pyramidal cells sending top-down predictions about lower level representations, and superficial pyramidal cells sending bottom-up prediction errors (the difference between the actual and predicted activity) back up the hierarchy, in order to update the higher level representations [Friston, 2008]. These neurobiological details are important, because superficial pyramidal cells—that is, prediction error units—make the primary contribution to event related potentials [Garrido et al., 2009b; Lieder et al., 2013]. Crucially, the influence of ascending prediction errors on higher representations depends upon their precision, which is thought to be encoded by the gain or excitability of superficial pyramidal cells. In this setting, precision (inverse variance) corresponds to the confidence or reliability attributed to prediction errors at each level of the cortical hierarchy [Adams et al., 2013; Feldman and Friston, 2010].

In our MMN data, controls show increased synaptic gain (diminished intrinsic self-inhibition) in all cortical sources in the deviant condition—that is, their prediction error responses to deviant tones are processed as being unduly precise and are therefore less easily suppressed. This is also the case for all individuals with a genetic risk for psychosis at the primary sensory level, but in rIFG the opposite pattern is seen. This indicates an abnormal influence of context on prediction error responses in this group, as has been seen not only in perceptual paradigms like the MMN, but also in reward learning and causal inference paradigms [Corlett et al., 2007; Murray et al., 2008].

In computational modeling work, we have shown that a loss of precision at higher levels of a hierarchical model can explain a loss of influence of context [Adams et al., 2013]. Predictive coding simulations show that aberrant precision or gain control can reproduce classic findings in the schizophrenia literature, including a reduced MMN response [Adams et al., 2013]. NMDA-R hypofunction could confound precision or gain control in two ways, either by directly lowering synaptic gain in superficial pyramidal cell populations, or by reducing the excitability of GABAergic interneurons, thereby impairing sustained oscillatory firing of pyramidal cells and reducing their influence on lower areas [Adams et al., 2013]. Our current results lend more support to the latter mechanism, and it would be interesting to test this hypothesis directly by using DCM to assess the relative model evidences for

psychosis altering the excitability of superf cial pyramidal cell versus inhibitory interneuron populations.

Importantly, our results suggest that both patients and their f rst degree relatives have similar alterations in the excitability of superf cial pyramidal cell populations, compared to controls. This indicates that these changes are linked to genetic risk factors, and are not merely a consequence of the illness state or antipsychotic medication. This alteration in the gain of superf cial pyramidal cells could therefore be a potential endophenotype for psychosis [Gottesman and Gould, 2003]. The use of endophenotypes might help clarify the functional effects of genetic risk variants identif ed [Bramon et al., 2014; Hall and Smoller, 2010], and further research could investigate whether deviant-related changes in excitability can predict genotype; for example, looking at candidate genes linked to NMDA-R function. Other studies investigating effective connectivity in psychosis have also observed abnormalities in relatives of patients, including children of probands [Diwadkar et al., 2012, 2014; Winterer et al., 2003], and a previous study by Dima et al [2013] observed associations between fMRI derived measures of effective connectivity and risk genes linked to GABAergic interneuron function in patients with bipolar disorder.

Our results also suggest that patients show a further increase in excitability in rIFG across task conditions compared to unaffected relatives. This may indicate that—at least in prefrontal cortex—there are quantitative, rather than qualitative, differences between those with and without a diagnosis of a psychotic illness but at elevated genetic risk. Alternatively, this difference could be due to the effects of antipsychotic medication, which is known to inf uence brain function [e.g., Joutsiniemi et al., 2001; Knott et al., 2001]. The exact effects of psychotropic drugs on effective connectivity remain unclear; however, a study investigating effective connectivity in schizophrenia found abnormalities in an unmedicated at-risk group but not in f rst episode patients (prescribed antipsychotics), suggesting that medication might potentially normalise abnormalities [Schmidt et al., 2013]. Future longitudinal studies and research in unmedicated patient populations are needed to address this important issue.

A limitation of the current study is that our groups differed slightly in age and gender distributions. There is evidence for both age [Cooper et al., 2006; Cooray et al., 2014; Kiang et al., 2009; Näätänen et al., 2012] and gender [Brossi et al., 2007; Matsubayashi et al., 2008] effects on MMN responses, although a DCM study did not f nd signif cant effects of aging on intrinsic connectivity [Moran et al., 2014]. Importantly, however, we found the most signif cant effects when comparing those with a genetic risk for psychosis (i.e. both relatives and patients) with controls, and since these two groups did not differ in age or gender distributions, our main f ndings are unlikely to be inf uenced by such confounds.

Another potential limitation is the experimental procedure used to elicit the MMN response. Because the MMN is a preattentive response not depending on the person paying attention to the sounds, it has been suggested that using a distractor task (such as watching a silent video or reading a book) can be advantageous [Duncan et al., 2009; Lang et al., 1995]. In this study, no distractor task was administered, and participants were instructed to disregard the sounds presented to them. We can therefore not control whether participants were paying attention to the task or not. Nevertheless, this distractor-free design has been used previously and has been shown to generate clear MMN responses [Bramon et al., 2004; Haenschel et al., 2000; Javitt et al., 1998; Juckel et al., 2007]. Furthermore, attention has been found to modulate the MMN response suggesting this ERP might not actually be independent of attention [Auksztulewicz and Friston, 2015; Sussman et al., 2013; Woldorff et al., 1991].

Our Bayesian model selection result indicates that both bilateral A1 and rIFG are important in explaining group differences in modulations of intrinsic connectivity in response to deviant tones. However, modulations of self-inhibition in STG do not seem to be so important (and were not included in the winning model). Importantly, this does not mean that the STG makes no contribution to group differences in responses, but merely suggests that including modulations in this region did not increase the evidence for the model suff ciently to justify the increased complexity. Our results furthermore suggest that group differences are most pronounced in rIFG. This is in line with past research suggesting that psychosis is associated with abnormalities at high hierarchical levels, including the prefrontal cortex [reviewed in Adams et al., 2013; Harrison et al., 2011].

We chose to calculate condition-specif c grand average responses for each group, an approach that has been used previously [e.g., Fogelson et al., 2014]. While this produces cleaner data features by reducing noise and enhancing features that are conserved over subjects, it eliminates potentially interesting individual differences. Future work could obtain subject-specif c DCM estimates, allowing the investigation of individual differences within groups, and correlations between effective connectivity parameters and various clinical and cognitive measures, as well as with genotypes.

CONCLUSION

In summary, our main f nding is that patients with psychosis as well as their unaffected f rst-degree relatives show increased excitability in rIFG across task conditions, relative to controls, and crucially, a loss (reversal) of the normally increased excitability in deviant trials. Hence, our results suggest that psychosis is associated with abnormalities of the sensitivity (gain) control of superf cial pyramidal cell populations, which might be inf uenced by NMDA-R hypofunction in prefrontal cortex. These results are in line with theories about the neuropathology and pathophysiology of

psychosis. Importantly, abnormalities in unaffected relatives of patients suggest that these alterations are linked to the aetiology of psychosis and are potential endophenotypes (markers of genetic risk) for the illness.

ACKNOWLEDGMENTS

We would like to thank all the patients, relatives and controls who took part in this research, as well as the clinical staff who facilitated their involvement. Funding for this study was provided by the Medical Research Council (grant G0901310), the Wellcome Trust (grants 085475/B/08/Z, 085475/Z/08/Z, and 088130/Z/09/Z), and the European Commission Framework Programme for Research and Innovation (grant 330156/CODIP), and the National Institute of Health Research UK (PDA/02/06/016). We also thank the Psychiatry Research Trust, the Schizophrenia Research Fund, and the Brain and Behavior Research Foundation for financial support. All authors declare that they have no financial interests or potential conflicts of interest.

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Appendix C: Additional material Chapter 4

Here I present additional information to that presented in chapter 4 of this thesis.

Study centres

Table C1 shows the study centres included in the study, including the sample size for each centre and the endophenotypes collected.

Table C1. Study sites and sample sizes.

Affiliation	Country	Number of participants				Endophenotypes contributed
		Total	C	R	P	
The University of Western Australia	Australia	893	224	260	409	P300, LVV, RAVLT
Heidelberg University	Germany	78	23	19	36	P300, LVV
Ludwig-Maximilians, University of Munich	Germany	2185	2185	-	-	Block Design, Digit Span
GROUP consortium: University of Amsterdam, University of Groningen, Maastricht University, University of Utrecht	Holland	2993	1484	722	787	Block Design, RAVLT, LVV
Universidad de Cantabria, Pamplona	Spain	69	-	-	69	Digit Span, RAVLT
Universidad de Cantabria, Santander	Spain	630	359	-	271	LVV, Digit Span, RAVLT
University of Edinburgh	United Kingdom	160	87	-	73	LVV, Block Design, Digit Span
Institute of Psychiatry, King's College London	United Kingdom	1746	693	486	567	P300, LVV, Block Design, Digit Span, RAVLT

C = controls; R = relatives, P = patients; LVV = lateral ventricular volume; RAVLT = Rey Auditory Verbal Learning Task.

Table C2. Clinical diagnoses across study centres.

Affiliation	Number of patients	Diagnoses	N (%)
The University of Western Australia (Australia)	409	Schizophrenia Psychotic Disorder NOS Brief Psychotic Disorder Schizoaffective Disorder Schizotypal Personality Disorder Schizophreniform Disorder Bipolar Disorder Delusional Disorder Drug Induced Psychosis	N=343 (83.9%) N=20 (4.9%) N=11 (2.7%) N=10 (2.4%) N=10 (2.4%) N=7 (1.7%) N=3 (0.7%) N=3 (0.7%) N=2 (0.5%)
Heidelberg University (Germany)	36	Schizophrenia Schizoaffective Disorder Schizotypal Personality Disorder	N=29 (80.6%) N=5 (13.9%) N=2 (5.6%)
GROUP Consortium: University of Amsterdam, University of Groningen, Maastricht University, University of Utrecht (Holland)	787	Schizophrenia Psychotic Disorder NOS Bipolar Disorder Schizoaffective Disorder Brief Psychotic Disorder Schizophreniform Disorder Delusional Disorder Depression with Psychotic Features Drug Induced Psychosis	N=464 (59.0%) N=105 (13.3%) N=76 (9.7%) N=61 (7.8%) N=24 (3.0%) N=24 (3.0%) N=19 (2.4%) N=8 (1.0%) N=6 (0.8%)
Universidad de Cantabria, Pamplona (Spain)	69	Schizophrenia Schizoaffective Disorder	N=61 (88.4%) N=8 (11.6%)
Universidad de Cantabria, Santander (Spain)	271	Schizophrenia Schizophreniform Disorder Brief Psychotic Disorder Psychotic Disorder NOS Schizoaffective Disorder Delusional Disorder	N=161 (59.4%) N=65 (24.0%) N=21 (7.8%) N=17 (6.3%) N=5 (1.9%) N=2 (0.7%)
University of Edinburgh (United Kingdom)	73	Schizophrenia Bipolar Disorder	N=41 (56.2%) N=32 (43.8%)
Institute of Psychiatry, King's College London (United Kingdom)	567	Schizophrenia Bipolar Disorder Schizophreniform Disorder Schizoaffective Disorder Psychotic Disorder NOS Drug induced Psychosis	N=308 (54.3%) N=134 (23.6%) N=62 (10.9%) N=35 (6.2%) N=26 (4.6%) N=2 (0.4%)
NOS = Not Otherwise Specified			

Family sizes

The sample included in this study was of a family-design, and Table C2 shows the sizes of the families included.

Table C3. Family sizes.

Number of family members participating	Number of families	% of families	Number of individuals	% of total sample
1	5545	84.00%	5545	63.34%
2	456	6.91%	912	10.42%
3	306	4.64%	918	10.49%
4	214	3.24%	856	9.78%
5	49	0.74%	245	2.80%
6	17	0.26%	102	1.17%
7	10	0.15%	70	0.80%
8	2	0.03%	16	0.18%
9	1	0.02%	9	0.11%
11	1	0.02%	11	0.13%

Appendix D: Additional material Chapter 5

Here I present additional methods and results to that presented in chapter 5 of this thesis.

Genotyping details

This study includes a subset of data from a larger sample. Genotyping methods and quality control details are described in full in Bramon et al (2014) and below.

DNA Sample Preparation

Genomic DNA obtained from blood for all participants was sent to the Wellcome Trust Sanger Institute, Cambridge, United Kingdom. Samples were processed in 96-well plate format and each plate carried a positive and a negative control. DNA concentrations were quantified using a PicoGreen assay (Invitrogen, Life Technologies, Grand Island, New York) and an aliquot assayed by agarose gel electrophoresis. A sample passed quality control if the original DNA concentration was at least 50ng/mL and the DNA was not degraded.

Genotyping Methodology and Quality Control

To track sample identity, 30 single nucleotide polymorphisms (SNPs) including sex chromosome markers were typed on the Sequenom platform before entry to the whole genome genotyping pipeline. Of the initial 6935 samples, 347 failed quality control due to degraded or insufficient DNA or incorrect sex classification. The remaining samples were sent for genotyping with the Genome-wide Human SNP Array 6.0 at Affymetrix Services Lab (http://www.affymetrix.com).

Data Quality Control

Genotype calling was conducted using the CHIAMO algorithm (Burton *et al.*, 2007; Marchini *et al.*, 2007) modified for use with the Affymetrix 6.0 genotyping array. 11,610 SNPs with a study-wide missing data rate over 5% were excluded. 26,858

SNPs with four or more Mendelian inheritance errors identified with Pedstats were removed (Wigginton and Abecasis, 2005). Additional exclusion criteria were departure from Hardy-Weinberg equilibrium ($p < 10^{-6}$) or minor allele frequency (MAF) <0.02 with 2404 and 145,097 SNPs removed, respectively. A total of 38,895 SNPs from the X or Y chromosomes or mitochondrial DNA were also excluded from the analysis. Finally, 9499 poorly genotyped SNPs were removed following visual inspection of the genotyping intensity plots in the program Evoker (Morris *et al.*, 2010).

214 samples were excluded with more than 2% missing data across all SNPs. Another 70 samples were excluded due to divergent genome-wide heterozygosity (inbreeding coefficients were $F > 0.076$ or $F < -0.076$ as estimated with PLINK (Purcell *et al.*, 2007). Chromosomal sharing was inferred from a genome-wide subset of 71,677 SNPs and from each duplicate pair the sample with the most complete genotype data was kept. 70 duplicates and monozygotic twins were removed by excluding one of each pair of individuals showing identity by descent greater than 95%.

Initial analysis of the genotype data identified a high fraction of samples (approximately 30%), which showed poor signal-to-noise ratio in the genotyping assay. Because the experimental source of the problem was unclear and to ensure a robust set of genotype calls, these samples were removed from further analysis. The sample loss was randomly distributed across the three clinical groups (32% of patients, 30% of relatives, and 30% of controls; χ^2 (2 df) = 3.2; p = 0.20).

After quality control, 4835 individuals remained. The current study included a subset of this larger sample, comprising 4242 individuals with endophenotypic data available.

Principal Component Analysis

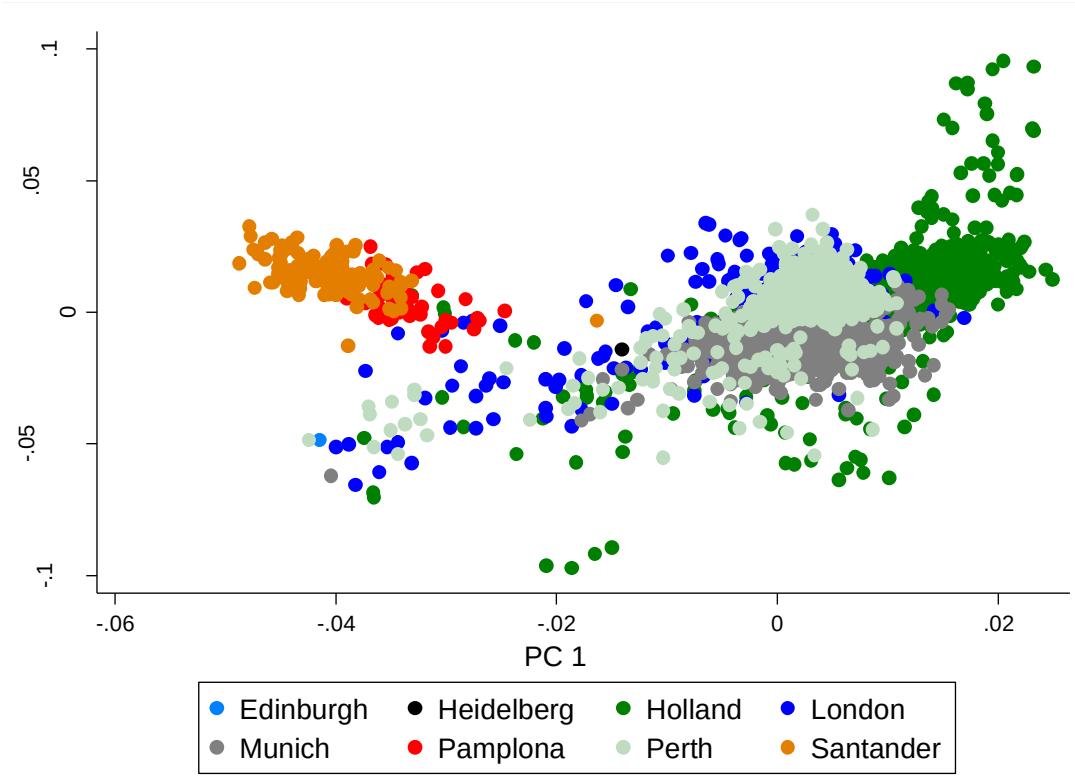

Figure D1. Principal component analysis.

Plotted is the projection of the individuals included in this study (N=4242) on to the first two principal components (PCs) of genetic structure. Individuals are coloured according to recruitment locations as given in legend.

Number of SNPs at each threshold

The number of single nucleotide polymorphisms (SNPs) from the Psychiatric genomics Consortium's panel included at each of the six p-value thresholds investigated in the study is shown in Table D1.

Table D1. Number of SNPs included at each p-value threshold.

SNP p-value threshold (p_T)	Number of SNPs	
	Schizophrenia Polygenic Score	Bipolar Disorder Polygenic Score
$p_T < 5x10^{-8}$	90	4
$p_T < 0.001$	3,073	733
$p_T < 0.05$	24,061	14,095
$p_T < 0.1$	35,410	23,988
$p_T < 0.5$	82,045	77,030
$p_T < 1$	103,860	108,353

SNP = Single nucleotide polymorphism

Endophenotype group differences

Patients differed significantly from controls on all measures investigated except the lateral ventricular volume. Relatives differed significantly from controls on the P300 latency, block design, digit span, and RAVLT immediate recall. These results are presented in Table D2 and Figure D2. Also note that this is a subset of the sample analysed in chapter 4 of this thesis, where group differences in that larger sample are presented.

Table D2. Endophenotype group differences.

Endophenotype	F statistics	**T statistics** (mean difference, p-value) Control vs patient	Control vs relative	Relative vs patient
P300 amplitude	F(2,504)=10.67 **p<0.001**	0.48, **p<0.001**	0.15, p=0.211	0.34; p=**0.002**
P300 latency	F(2,509)=6.73 **p=0.001**	-0.38, **p<0.001**	-0.30, **p=0.002**	-0.08, p=0.461
Lateral Ventricular Volume	F(2,789)=1.08 p=0.344	-0.12, p=0.142	-0.06, p=0.571	-0.06, p=0.524
Block Design	F(2,3083)=54.97 **p<0.001**	0.46, **p<0.001**	0.26, **p<0.001**	0.20, **p=0.001**
Digit Span	F(2,1431)=30.0 **p<0.001**	0.54, **p<0.001**	0.52, **p=0.003**	0.02, p=0.923
RAVLT imm. recall	F(2,2400)=118.3 **p<0.001**	0.74, **p<0.001**	0.14, **p=0.003**	0.60, **p<0.001**
RAVLT del. recall	F(2,2378)=92.5 **p<0.001**	0.65, **p<0.001**	0.07, p=0.172	0.59, **p<0.001**

Analyses conducted on standardised scores, with study sites, participant age and gender included as covariates. RAVLT = Rey Auditory Verbal Learning Task.

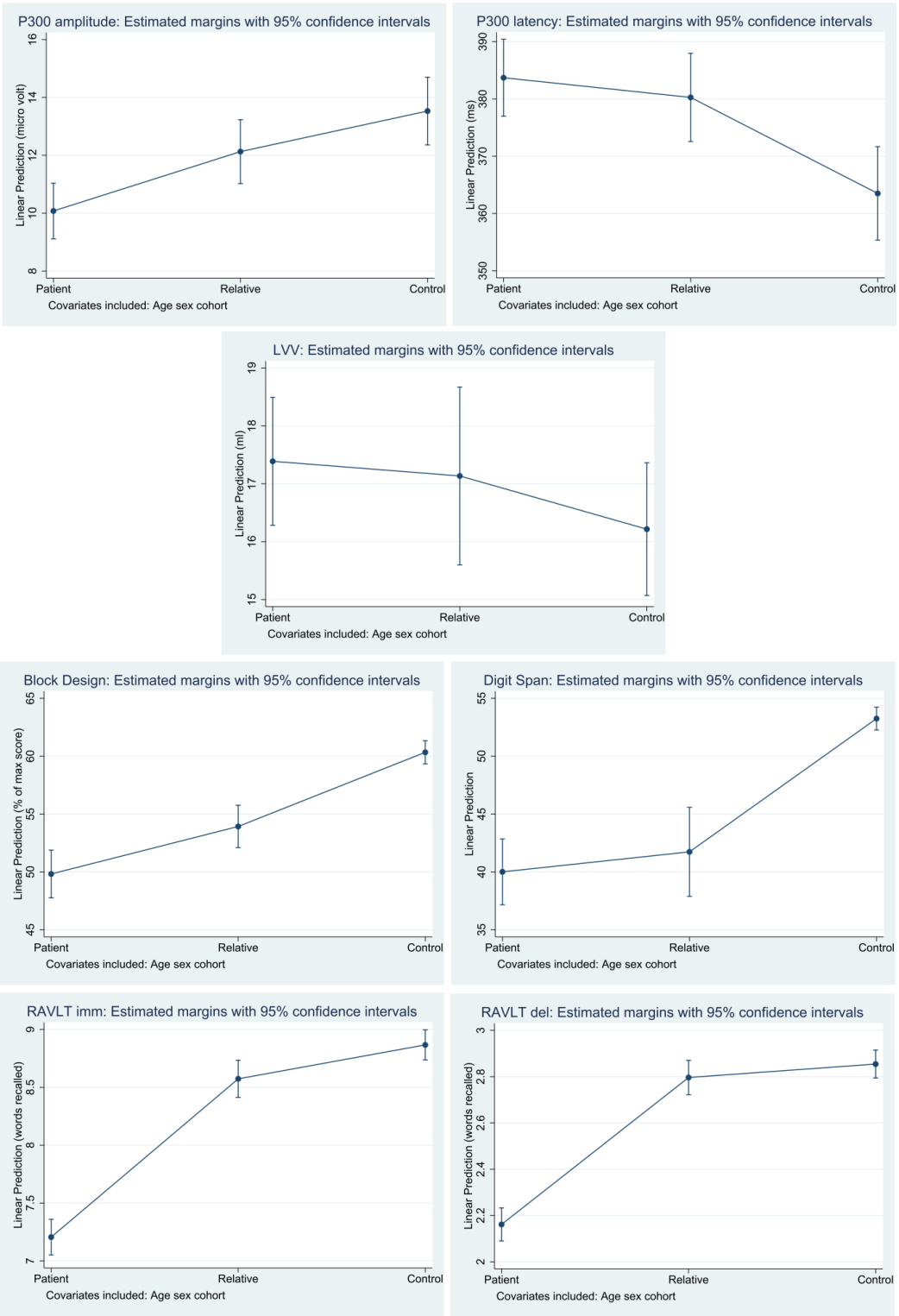

Figure D2. Endophenotype scores across groups.

Estimated mean values of the different endophenotypes across groups (patients, relatives, controls), with 95% confidence intervals, after controlling for covariates (age, sex and study site). LVV= Lateral Ventricular Volume; RAVLT = Rey Auditory Verbal Learning Task; imm. = immediate recall; del. = delayed recall.

Full regression results

Linear regressions investigating the associations between polygenic scores for schizophrenia and bipolar disorder, and endophenotypes. All analyses are adjusted for covariates of age, gender, study site, group (patient, relative, controls), and population structure, and include robust standard errors to account for correlations within families. The schizophrenia polygenic score (Table D3) was nominally associated with performance on the block design task. No other association approached significance after correcting for multiple testing, and for bipolar disorder polygenic score (Table D4), no association was significant.

Table D3. Schizophrenia polygenic scores full results.

P300 Amplitude (N=510)				**Digit Span (N=1437)**			
p_T	β	R^2	p-value	p_T	β	R^2	p-value
< 1	-402.65	0.02%	0.780	< 1	-333.5	0.01%	0.678
< 0.5	-276.1	0.01%	0.810	< 0.5	-232.14	0.01%	0.716
< 0.1	3.09	<0.001%	0.996	< 0.1	37.72	0.00%	0.910
< 0.05	-177.23	0.03%	0.697	< 0.05	-24.16	0.00%	0.925
< 0.001	-135.99	0.19%	0.289	< 0.001	-2.84	<0.001%	0.970
$< 5\times10^{-08}$	2.83	0.01%	0.857	$< 5\times10^{-08}$	-6.23	0.03%	0.492
P300 Latency (N=515)				**RAVLT immediate recall (N=2406)**			
p_T	β	R^2	p-value	p_T	β	R^2	p-value
< 1	1148.7	0.13%	0.382	< 1	-99.8	0.00%	0.866
< 0.5	912.47	0.12%	0.384	< 0.5	-137.84	0.00%	0.771
< 0.1	561.47	0.17%	0.289	< 0.1	-271.72	0.04%	0.268
< 0.05	384.9	0.13%	0.372	< 0.05	-147.37	0.02%	0.443
< 0.001	59.04	0.04%	0.644	< 0.001	-54.94	0.04%	0.323
$< 5\times10^{-08}$	9.64	0.07%	0.474	$< 5\times10^{-08}$	4.14	0.01%	0.548
Lateral Ventricular Volume (N=795)				**RAVLT delayed recall (N=2384)**			
p_T	β	R^2	p-value	p_T	β	R^2	p-value
< 1	1972.66	0.39%	0.068	< 1	163.2	0.00%	0.788
< 0.5	1576.21	0.39%	0.068	< 0.5	98.11	0.00%	0.839
< 0.1	849.52	0.41%	0.063	< 0.1	-116.66	0.01%	0.645
< 0.05	490.98	0.23%	0.172	< 0.05	-39.63	0.00%	0.839
< 0.001	-2.4	<0.001%	0.981	< 0.001	-48.84	0.03%	0.389
$< 5\times10^{-08}$	-13.3	0.15%	0.214	$< 5\times10^{-08}$	2.53	0.01%	0.706
Block Design (N=3089)							
p_T	β	R^2	p-value				
< 1	-1177.05	0.13%	0.035				
< 0.5	-953.24	0.13%	0.033				
< 0.1	-575.57	0.18%	0.013				
< 0.05	**-465.11**	**0.20%**	**0.009**				
< 0.001	-86.06	0.09%	0.091				
$< 5\times10^{-08}$	-6.37	0.04%	0.280				

pT = Single nucleotide polymorphism (SNP) p-value threshold; RAVLT = Rey Auditory Verbal Learning Task

Table D4. Bipolar Disorder polygenic score full results.

P300 Amplitude (N=510)				**Digit Span (N=1437)**			
p_T	β	R^2	p-value	p_T	β	R^2	p-value
< 1	-531.35	0.08%	0.514	< 1	211.3	0.01%	0.673
< 0.5	-443.863	0.10%	0.454	< 0.5	109.25	0.01%	0.764
< 0.1	-142.56	0.06%	0.588	< 0.1	55.96	0.01%	0.725
< 0.05	-77.52	0.03%	0.678	< 0.05	-62.18	0.02%	0.590
< 0.001	-3.413	0.01%	0.783	< 0.001	-11.91	0.02%	0.599
$< 5\times10^{-08}$	-1.824	0.18%	0.362	$< 5\times10^{-08}$	-0.63	0.02%	0.563
P300 Latency (N=515)				**RAVLT immediate recall (N=2406)**			
p_T	β	R^2	p-value	p_T	β	R^2	p-value
< 1	-425.696	0.05%	0.613	< 1	443.53	0.05%	0.288
< 0.5	-331.233	0.06%	0.581	< 0.5	304.44	0.04%	0.310
< 0.1	-231.561	0.15%	0.354	< 0.1	176.18	0.08%	0.170
< 0.05	-123.089	0.08%	0.502	< 0.05	120.78	0.07%	0.196
< 0.001	-13.565	0.02%	0.684	< 0.001	23.13	0.08%	0.159
$< 5\times10^{-08}$	-0.37	0.01%	0.851	$< 5\times10^{-08}$	-0.03	<0.001%	0.966
Lateral Ventricular Volume (N=795)				**RAVLT delayed recall (N=2384)**			
p_T	β	R^2	p-value	p_T	β	R^2	p-value
< 1	531.45	0.07%	0.363	< 1	514.36	0.06%	0.208
< 0.5	331.89	0.05%	0.433	< 0.5	359.35	0.06%	0.222
< 0.1	54.88	0.01%	0.771	< 0.1	162.09	0.06%	0.198
< 0.05	-1.70	<0.001%	0.990	< 0.05	133.91	0.08%	0.141
< 0.001	12.78	0.02%	0.642	< 0.001	25.63	0.09%	0.123
$< 5\times10^{-08}$	-1.24	0.09%	0.418	$< 5\times10^{-08}$	-0.63	0.02%	0.434
Block Design (N=3089)							
p_T	β	R^2	p-value				
< 1	-440.98	0.05%	0.226				
< 0.5	-344.74	0.05%	0.190				
< 0.1	-115.82	0.03%	0.309				
< 0.05	-74.87	0.03%	0.355				
< 0.001	19.49	0.05%	0.198				
$< 5\times10^{-08}$	1.69	0.17%	0.020				

pT = Single nucleotide polymorphism (SNP) p-value threshold; RAVLT = Rey Auditory Verbal Learning Task.

Post-hoc power calculation

Table D5. Post-hoc power calculation.

Endophenotype	N	Lowest R^2 detectable
P300 event related potential	515	1.52%
Lateral Ventricular Volume	789	1.00%
Digit Span	1437	0.55%
Rey Auditory Verbal Learning Task	2400	0.32%
Block Design	3089	0.25%

Alpha level 0.05, 80% power, 7 predictor in set one (covariates) and 1 predictor in set two (polygenic score). Reference: Soper (2015).

Table D5 shows a power calculation estimating the minimum effect size (i.e. variance explained, R^2) that could be detected with the sample size obtained for each endophenotype.

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