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Neuromagnetic Mismatch Negativity in Individuals at Clinical High Risk State for Psychosis

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Abstract

Advances in electroencephalography (EEG) and magnetoencephalography (MEG) have allowed the investigation into the neurophysiological basis of perceptual and cognitive disturbances across different stages of psychosis. The EEG/MEG recorded (neuromagnetic) mismatch negativity (MMN(m)) is a component of the event-related potential/field reflecting early pre-attentive auditory processing. Reduced MMN amplitude is a well-replicated finding in chronic schizophrenia patients and there is evidence for a smaller MMN impairment in first episode patients. Interestingly, studies have suggested that MMN deficits may be present even prior to the onset of psychosis in individuals at clinical high risk state for developing psychosis (CHR), suggesting that MMN amplitude could be a potential marker of psychosis risk. However, in contrast to the robust finding of an attenuated MMN amplitude in schizophrenia, results are more inconsistent at the earliest stages of illness. Moreover, to date most studies have used a conventional analysis for assessing MMN amplitudes in different stages of psychosis although brain connectivity measures, such as dynamic causal modelling (DCM) allow investigating effective connectivity in the brain network underlying the MMN generation. Also, two decades of research into characteristics of CHR individuals has revealed that they are functioning poorly regardless of subsequent transition to psychosis. However, while MMN amplitude has been studied as a potential marker for predicting psychosis among CHR individuals in several studies, its utility to predict other clinically relevant outcomes remains unknown.

In the current thesis, I sought to examine MEG-recorded MMNm peak amplitude in individuals at different stages of psychosis as well as its association with neuropsychological performance, attenuated psychotic symptoms and psychosocial functioning in CHR individuals (chapter 3). The aim was to assess the potential of MMNm amplitude as a marker for early stages of psychosis and to examine whether MMNm deficits are pronounced in CHR individuals with poor functioning and cognitive deficits. Secondly, I employed DCM to examine whether effective connectivity in the underlying network of duration change detection is altered in CHR individuals compared to controls (chapter 4). Lastly, I investigated whether baseline MMNm amplitude is able to predict the 12-month

outcome of CHR individuals in terms of transition to psychosis or sustained subthreshold psychotic symptoms and poor functioning (chapter 5). Given that the current study is the first large study that recruited CHR individuals predominantly from the community, clinical findings will also be reviewed and compared to previous studies with CHR individuals recruited from special early detection and intervention services.

The findings in chapter 3 show that compared to controls, MMNm peak amplitudes were intact in CHR individuals as well as in first episode patients. Chapter 3 also indicates a weak positive association between MMNm amplitudes and speed of information processing in CHR individuals. Chapter 4 results indicate that CHR individuals do not have abnormal duration deviant induced changes in frontotemporal connectivity network compared to controls. Collectively these findings suggest that neither the peak amplitude nor the measures of effective connectivity underlying the MMNm response are related to the CHR state. Lastly, chapter 5 indicates that baseline MMNm amplitude is not associated with progression to a first episode psychosis, although this finding needs to be considered limited due to the low transition rate to psychosis, or persistence of subthreshold psychotic symptoms and poor functioning in CHR individuals. Overall, the findings in the thesis do not support the utility of using MMNm as a marker for emerging psychosis. However, future longitudinal studies with several MEG recording time points are required to further determine the timing of MMN deficiency and whether it reflects emerging psychosis or illness progression. The clinical findings of the thesis demonstrate that CHR individuals recruited from the general population are characterised by several clinical concerns and despite the majority of them not developing psychosis and remitting symptomatically over 12 months, CHR individuals were characterised by persistent functional disability, highlighting the importance of evaluating and predicting more systematically psychosocial functioning in this clinically meaningful population.

Finally, I discuss the key neurophysiological and clinical findings of the three data chapters in chapter 6 in the context of previous findings as well as the limitations and strengths of the current thesis. I also discuss the possibility and key challenges of implementing electrophysiological measures as part of a

multivariate and sequential testing in clinical practice as well as proposals for moving beyond the current UHR paradigm.

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Abbreviations

(f)MRI	(Functional) Magnetic Resonance Imaging
ANOVA	Analysis of Variance
APS	Attenuated Psychotic Symptoms
BACS	Brief Assessment of Cognition in Schizophrenia
BLIPS	Brief Limited Intermittent Psychotic Symptoms
BMS	Bayesian Model Selection
BS	Basic Symptoms
CAARMS	Comprehensive Assessment of At Risk Mental States
CHR	Clinical High-Risk for Psychosis
CHR-NR	Clinical High-Risk individuals who did Not achieve full Remission
CHR-NT	Clinical High-Risk individuals with No Transition to psychosis
CHR-R	Clinical High-Risk individuals who achieved full Remission
CHR-T	Clinical High-Risk individuals with Transition to psychosis
COGDIS	Cognitive Disturbances Criterion
COPER	Cognitive-Perceptive Criterion
DCM	Dynamic Causal Modelling
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DUP	Duration of Untreated Psychosis
DurMMNm	Duration Mismatch Negativity
EEG	Electroencephalography
EPS	Early Prodromal State
ERP/ERF	Event-Related Potential/Field
ES	Effect Size
FEP	First Episode Psychosis
GABA	Gamma Aminobutyric Acid

GAF	Global Assessment of Functioning
GM	Grey Matter
GP	General Practitioners
GWAS	Genome-Wide Association Study
HC	Healthy Controls
HG	Heschl's Gyrus
ICD	International Classification of Diseases
IFG	Inferior Frontal Gyrus
ISI	Inter-Stimulus Interval
LCMV	Linearly Constrained Minimum Variance
LPS	Late Prodromal State
MEG	Magnetoencephalography
MMN(m)	(Neuromagnetic) Mismatch Negativity
MNI	Montreal Neurological Institute
MTG	Middle Temporal Gyrus
NMDAR	N-methyl-D-aspartate receptor
OmiMMNm	Omission Mismatch Negativity
PLE	Psychotic-Like Experiences
ROI	Regions of Interests
SCID	Structured Clinical Interview
SD	Standard Deviation
SIPS	Structured Interview for Prodromal Syndromes
SOA	Stimulus Onset Asynchrony
SOI	Sensors of Interest
SPI-A	Schizophrenia Proneness Instrument, Adult version
STG	Superior Temporal Gyrus
TOI	Time Interval of Interest
UHR	Ultra High Risk State for Psychosis

1 Introduction

1.1 Psychosis

1.1.1 Psychotic disorders

Schizophrenia Spectrum and Other Psychotic Disorders- category in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), (American Psychiatric Association, 2013) includes a group of mental disorders that affect the person's thinking, perception and reality testing. Symptoms of psychotic disorders are typically divided into positive and negative symptoms (Kay, Fiszbein, & Opler, 1987) and the five key symptoms that define psychotic disorders are 1) delusions (false belief), 2) hallucinations (false perception), 3) disorganized speech, 4) disorganized behaviour (including catatonia) and 5) negative symptoms (American Psychiatric Association, 2013). While psychotic symptoms are a defining characteristic of the schizophrenia spectrum disorders, psychotic symptoms can also occur in bipolar and depressive disorders (Arciniegas, 2015). The lifetime prevalence of all psychotic disorders has been estimated to be around 3-4 % and with the high associated personal, familial and societal costs, they are a major public health concern (Bogren, Mattisson, Isberg, & Nettelbladt, 2009; Perälä et al., 2007).

Schizophrenia is the most common psychotic disorder, affecting approximately 1 % of the population worldwide (American Psychiatric Association, 2013) with an incidence rate of 15.2 per 100,000 persons per year (McGrath et al., 2004) and a prevalence rate of 23.6 million worldwide in 2013 (Vos et al., 2017). It is the most severe disorder in terms of disability out of 220 mental and physical health disorders (Salomon et al., 2012) and has enormous societal costs (Gustavsson et al., 2011). The current DSM-5 diagnosis for schizophrenia requires the presence of two or more of the five aforementioned key symptoms for a significant portion of time during a one-month period and at least one of the symptoms needs to be delusions, hallucinations or disorganized speech. In addition, a functional impairment in work, self-care or interpersonal relations should have been present for a significant portion of time since the onset of symptoms. Overall, continuous signs of symptoms and functional impairment need to be present at least for 6 months.

1.1.2 **Aetiology of schizophrenia**

Despite decades of research, the exact causal factors and pathophysiology of schizophrenia remain unknown (Insel, 2010). One prominent and widely researched model, the neurodevelopmental model of schizophrenia, suggests that the neural basis of the disorder arise during abnormal brain development in the prenatal, perinatal and early adolescent periods due to an interaction of both genetic and environmental factors, resulting in the emergence of psychosis later in adulthood (McGrath, Féron, Burne, Mackay-Sim, & Eyles, 2003).

Twin and family studies of schizophrenia during the 20th century provided evidence for high heritability estimates around 80 % (T. D. Cannon, Kaprio, Lönnqvist, Huttunen, & Koskenvuo, 1998; Cardno et al., 1999) and having a first-degree relative with a diagnosis of schizophrenia is the greatest risk factor for developing the disorder (Laursen et al., 2005). While the exact genetic causes remain unknown, the rare-variant sequencing and genome-wide association studies (GWAS) have shown that the genetic architecture of schizophrenia is diverse and includes many common risk variants with low effect sizes and rare but penetrant genetic variants of larger effects (Henriksen, Nordgaard, & Jansson, 2017). An influential and ground-breaking large scale GWAS study with a sample size of 35,000 cases, testing for almost 10 million genetic variants, identified 108 independent schizophrenia-associated genomic loci that contribute to risk of schizophrenia (Ripke et al., 2014), highlighting the genetic complexity involving multiple risk factors. Furthermore, genetic changes may interact with each other as well as environmental risk factors, making it challenging to assess different factors separately and increasing the etiological complexity of the disorder (Van Os, Rutten, & Poulton, 2008).

Early environmental life factors that might injure the developing brain prior or immediately after birth include maternal malnutrition (Susser, 2011), obstetric complications (M. Cannon, Jones, & Murray, 2002; Verdoux et al., 1997), prenatal infections (Brown, 2006), season of birth (Torrey, Miller, Rawlings, & Yolken, 1997) and place of birth (Marcelis, Navarro-Mateu, Murray, Selten, & Van Os, 1998). Past research has linked increased risk of schizophrenia to several late environmental factors as well. Later environmental risk factors include childhood trauma and neglect (Read, Van Os, Morrison, & Ross, 2005), cannabis

use (Smit, Bolier, & Cuijpers, 2004), migration (Cantor-Graae & Selten, 2005), urbanicity (Pedersen & Mortensen, 2001; Vassos, Pedersen, Murray, Collier, & Lewis, 2012) and socio-economic disadvantage (Byrne, Agerbo, Eaton, & Mortensen, 2004). Interestingly, a recent umbrella review examined the strength of evidence for associations between numerous environmental factors and psychosis based on 54 previous meta-analyses. The authors found convincing evidence for the ultra-high risk state for psychosis and Black-Caribbean ethnicity in England and highly suggestive evidence for another six factors, suggesting that despite several environmental risk factors for psychosis, they are associated with different levels of evidence (Radua et al., 2018).

Longitudinal epidemiological and clinical studies have also provided evidence for the neurodevelopmental hypothesis by showing that individuals who later develop schizophrenia frequently have premorbid deficits in cognitive and motor performance in childhood and adolescence (Dickson, Laurens, Cullen, & Hodgins, 2012). Furthermore, obstetric complications have been shown to interact with later motor developmental delays in an additive manner resulting in increased risk of schizophrenia (Clarke et al., 2011). Moreover, a number of neuroimaging studies have revealed structural brain abnormalities to be present before the onset of illness, especially reduced grey matter and enlargement of ventricles (T. D. Cannon et al., 2015; Dietsche, Kircher, & Falkenberg, 2017).

1.1.3 **Pathophysiology of schizophrenia**

There is a large body of research focused on elucidating the pathophysiology of schizophrenia, namely the disordered physiological processes associated with the disorder, which has revealed a number of aberrant neurotransmitter signalling systems in schizophrenia patients.

1.1.3.1 **The dopamine hypothesis**

The classical dopamine hypothesis of schizophrenia proposed by Van Rossum in 1966 states that symptoms, particularly positive symptoms, present in the disorder are due to a hyperactive dopamine receptor signalling. This theory is supported by post-mortem studies revealing increased D2r/D3r levels in schizophrenia patients (Kessler et al., 2009) and findings demonstrating that

dopamine-mimetic drugs, such as levopoda and amphetamine, induce hallucinations while first-generation antipsychotics that are D2 receptor antagonists show efficacy in the reduction of positive symptoms (Abi-Dargham & Grace, 2010). The original dopamine hypothesis was later revised to account for negative and cognitive symptoms as well, the revised version suggesting that hypoactive dopamine system in the prefrontal cortex mediates negative symptoms and cognitive deficits whereas hyperactive dopamine transmission in the subcortical mesolimbic areas is related to positive symptoms (Brisch et al., 2014; da Silva Alves, Figee, van Amelsvoort, Veltman, & de Haan, 2008; Walter, Kammerer, Frasch, Spitzer, & Abler, 2009). However, the findings showing that dopamine antagonists are not effective for all patients with schizophrenia indicate an involvement of other neurotransmitter systems in the pathophysiology of schizophrenia.

1.1.3.2 **Glutamate, GABA and serotonin**

There was a shift away from the dominating dopamine hypothesis in the 1980s when the main excitatory neurotransmitter in the central nervous system, glutamate, started to gain attention as it was found that antagonists of a major glutamate receptor subtype N-methyl-D-aspartate receptor (NMDAR), such as phencyclidine and ketamine, elicited and increased positive, negative and cognitive symptoms in controls and schizophrenia patients (Lahti, Holcomb, Medoff, & Tamminga, 1995; Malhotra et al., 1996, 1997; Reich & Silvay, 1989). Conversely, drugs that reduced glutamate release, for instance lamotrigine and topiramate, attenuated the psychotropic effects elicited by ketamine (Anand et al., 2003; Krystal et al., 2005) and improved symptoms in patients with schizophrenia (Patil et al., 2007; Tiihonen et al., 2005). In addition, a large GWAS has identified schizophrenia-associated genes belonging to the glutamatergic system (Ripke et al., 2014). Furthermore, proton magnetic resonance spectroscopy imaging studies have revealed increased glutamate levels in early stages of the disorder (Fuente-Sandoval et al., 2011; Hashimoto et al., 2005) whereas schizophrenia patients show decreased glutamate levels (Tayoshi et al., 2009; Wijtenburg et al., 2017) with a recent review providing evidence for a decline with disease duration (Schwerk, Alves, Pouwels, & Van Amelsvoort, 2014). Moreover, a review of multiple lines of evidence from post mortem, genetic, imaging and psychopharmacological studies concluded that

dysfunction of glutamatergic neurotransmission may indeed play a role in the pathophysiology of schizophrenia (Goff & Coyle, 2001). Subsequently it has been proposed that if the glutamatergic dysfunction is present already prior to the onset of a first episode psychosis, glutamatergic therapies could be useful in psychosis prevention (Egerton, Fusar-Poli, & Stone, 2012).

Another potential neurotransmitter playing a role in the pathophysiology of schizophrenia is gamma aminobutyric acid (GABA), the key inhibitory neurotransmitter in the brain. Evidence for GABA dysfunction comes mainly from post mortem studies which in combination with animal studies have shown that schizophrenia is associated with GABA dysfunction (Benes, Vincent, Marie, & Khan, 1996; Lewis, Volk, & Hashimoto, 2004; Sherman, Davidson, Baruah, Hegwood, & Waziri, 1991). On the other hand, a recent meta-analysis of 16 proton magnetic resonance spectroscopy studies of GABA concentrations showed no consistent alterations in schizophrenia (Egerton, Modinos, Ferrera, & McGuire, 2017). However, there was a substantial amount of heterogeneity across studies, which highlights the need for further GABA studies with more similar clinical and methodological variables. Also serotonin has been studied as a potential neurotransmitter playing a role in schizophrenia as second generation antipsychotics are, among other neurotransmitters, serotonin antagonists (for a review, Abi-Dargham, 2007). Collectively, it is likely that several abnormal neurotransmitter systems and their interactions contribute to the pathophysiology of schizophrenia.

1.1.4 **Treatment and prognosis of psychosis**

The typical first generation antipsychotics, which block dopamine D2 receptors, were discovered in the 1950s. These drugs, however, are ineffective in treating negative and cognitive deficits associated with psychosis and cause a range of side effects including tremors and rigidity (Kinon & Lieberman, 1996; Miyamoto, Duncan, Marx, & Lieberman, 2005). Second-generation atypical antipsychotics introduced after the 1970s not only reduce dopamine neurotransmission but also act on other receptors, especially serotonin, and were developed to reduce side effects of typical antipsychotic medications. However, although second generation antipsychotics elicit less extrapyramidal symptoms (drug induced movement disorders) (Leucht, Wahlbeck, Hamann, & Kissling, 2003), metabolic

side-effects are frequent. Moreover, evidence for their superior efficacy or tolerability is not robust, apart from clozapine (Chakos, Lieberman, Hoffman, Bradford, & Sheitman, 2001; Geddes, Freemantle, Harrison, & Bebbington, 2002). Although clozapine is the most effective medication for schizophrenia in terms of its efficacy and safety, it has a range of side effects, such as weight gain and cardiac problems (Newcomer et al., 2002; Üçok & Gaebel, 2008) that limit its use to treatment-resistant schizophrenia (Chakos et al., 2001; Daniel C Javitt, 2014; Wahlbeck, Cheine, Essali, & Adams, 1999). In terms of treating negative and cognitive symptoms, both antipsychotic types are rather ineffective and have shown little clinically meaningful improvement (Davidson et al., 2009; Swartz et al., 2007; Tandon, 2011). Moreover, schizophrenia is typically treated with antipsychotic medication and psychosocial therapy based on evidence showing supporting the combination of them to be more effective than medication alone to improve clinical and functional outcomes (Patterson & Leeuwenkamp, 2008).

The long-term prognosis of schizophrenia is very heterogeneous and is typically characterised by periods of remission and relapse. Reviews and meta-analyses have reported a good outcome in approximately 40 % of schizophrenia patients (Hegarty, Baldessarini, Tohen, Waternaux, & Oepen, 1994; Menezes, Arenovich, & Zipursky, 2006), evidence suggesting females to be more likely to have a favourable outcome than males (A. Riecher-Rössler & Hafner, 200AD). Moreover, schizophrenia is associated with a two to three-fold increased mortality risk compared to the general population (Masoudzadeh, Khalilian, & Hosseini, 2007), evidence showing that this gap has increased in recent decades (Saha, Chant, & McGrath, 2007). Schizophrenia patients have a life expectancy of 15-20 years shorter than the general population (Hennekens, Hennekens, Hollar, & Casey, 2005); they are more likely to die by suicide early in the course of the disorder (Palmer, Pankratz, & Bostwick, 2005) whereas older patients are more likely to die by cardiovascular diseases, the main cause of premature mortality in schizophrenia (Hennekens et al., 2005).

Taken together, despite decades of research on pharmacological and psychosocial interventions, more effective treatments for psychotic disorders remain to be developed (Insel, 2010). In addition, non-compliance with available antipsychotic medication is a challenge in treatment (Leucht & Heres, 2006) as it

is associated with an elevated risk of relapse, longer time to remission and higher rates of suicide attempts and rehospitalisation (Robinson et al., 1999). Poor adherence is not only limited to anti-psychotics but is also a problem with other treatment recommendations, such as exercise and diet.

1.1.5 Cognition in chronic schizophrenia and first episode psychosis

During the last two decades, a large body of work has examined the pattern and extent of deficits in higher cognitive processes, such as working memory, attention, language and executive functioning, in schizophrenia patients. Despite high methodological and clinical heterogeneity across studies, several meta-analyses and systematic reviews have consistently reported impairments in all domains in schizophrenia (e.g. Heinrichs & Zakzanis 1998). For instance, a recent meta-analysis of 247 papers on cognitive performance reported schizophrenia patients to have deficits with large effect sizes in various cognitive functions compared to controls; patients performed worse in memory functioning (ES of 1.22), global cognitive functioning (ES = 0.96), language (ES = 0.99), executive function (ES = 1.10) and attention (ES = 0.99) in contrast to controls (Fioravanti, Bianchi, & Cinti, 2012). In fact, cognitive deficits are currently considered to be a core feature of schizophrenia, although not a part of the diagnostic criteria, and they generally remain stable throughout the course of the illness and are largely independent from symptoms (Censits, Ragland, Gur, & Gur, 1997; Heaton et al., 2001). Moreover, changes in cognition have also consistently been found in first episode patients who show medium to large deficits in a range of neurocognitive measures compared to controls (Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009) and cognitive abnormalities are often observed in unaffected relatives as well (Agnew-Blais & Seidman, 2013; Bora et al., 2014).

Schizophrenia remains one of the most debilitating mental disorders in large part because of a decline in several cognitive functions and the fact that many anti-psychotic medications are effective in treating only positive symptoms but not cognitive deficits (Keefe et al., 2012). In addition, cognitive deficits contribute to intellectual (McGlashan & Fenton, 1993) and functional impairments (Bowie et al., 2008) and data from several original studies as well as systematic reviews

have linked cognition to functional outcomes in schizophrenia patients with small to medium effect sizes (Green, 1996; Fett et al., 2011), making them potentially useful treatment targets (Green, 2006). As a result, the past two decades have seen a rapid increase in clinical and research interest in cognitive training methods to improve cognition and functional recovery in schizophrenia. Converging evidence suggests that cognitive training is an effective method for enhancing cognitive performance in schizophrenia, two meta-analyses reporting moderate effect sizes of cognitive remediation on improving cognition and daily functioning and a small effect size on symptoms (McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). Still, the best functional outcome is reached when cognitive training is combined with other psychosocial rehabilitation (McGurk et al., 2007; Wykes et al., 2011) and despite the encouraging results for cognitive training in schizophrenia treatment, it is an expensive and time-consuming treatment limiting its accessibility.

1.2 Early psychosis detection and intervention paradigm and clinical staging model for psychosis

1.2.1 Ultra high risk state for psychosis approach

While aforementioned genetic and environmental risk factors for psychosis act in early life, it is not until later in adolescence and early adulthood that symptoms of psychosis typically begin to emerge, males having a slightly earlier psychosis onset than females (Aleman, Kahn, & Selten, 2003; Eranti, MacCabe, Bundy, & Murray, 2013). Moreover, retrospective studies of first episode patients have shown that the first episode of psychosis is preceded in about 75 % of all cases by an average prodromal phase of five to six years, characterised by non-specific symptoms (Häfner et al., 1998) which are often accompanied by psychosocial impairment (Jones et al., 1993). Given the individual and societal impact of psychosis and the association between longer duration of untreated psychosis (DUP), namely the time between symptom onset and treatment initiation, and a poorer outcome on treatment response and global functioning (Farooq, Large, Nielssen, & Waheed, 2009; Loebel et al., 1992), the importance of early detection of and intervention in psychosis started to be acknowledged in psychiatry in the 1980s. It is important to note, that the retrospective prodromal

concept implies inevitable progression to full blown psychosis, in line with the early views of Kraepelin (1919) and Bleuler (1950) emphasising the inevitable deterioration, and can be confirmed only after a formal diagnosis. As a result, Yung and McGorry (1996) introduced the At Risk Mental State term and the Ultra High Risk (UHR) state for psychosis paradigm and criteria to develop a prospective definition and identification of the prodromal stage in 1996 which subsequently initiated research into the high risk stages of psychosis.

The UHR criteria was developed to identify help-seeking individuals at increased risk for developing a first episode psychosis in the near future (6 to 12 months) and it includes symptoms that resemble frank psychotic symptoms but are lower in intensity, frequency and/or duration. An individual might, for example, have a persecutory belief of someone trying to hurt him but with less than delusional conviction, or a delusional idea with a full conviction might be very fleeting and last for less than hour although it occurs twice a week. To operationalise the UHR criteria, Yung and colleagues developed the Comprehensive Assessment at Risk Mental States (CAARMS) in Melbourne in 1998. In order to be considered at risk for developing psychosis according to the UHR criteria, individuals need to have experienced attenuated positive symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS) or to have a first degree relative with a psychotic disorder in a combination with recent functional decline (GRD) (for detailed inclusion and exclusion criteria and descriptions of the operationalised UHR criteria see Recruitment Process 3.2.2). Additionally, these experiences need to be new to differentiate them from schizotypal personality features that represent a trait rather than a state risk factor for developing psychosis.

1.2.2 **Basic symptoms approach**

In addition to the UHR approach, the basic symptom (BS) approach is often used as a complementary approach to the UHR criteria to identify individuals theorised to be at an earlier high risk stage than those identified using the UHR criteria (He & Hu, 2014; Frauke Schultze-Lutter, Ruhrmann, Berning, Maier, & Klosterkötter, 2010; Yung, Yuen, Phillips, Francey, & McGorry, 2003). The BS approach is based on longitudinal studies of schizophrenia patients in the 1960s when Huber and colleagues described subtle, subjective deficits in stress tolerance, affect, cognitive-perceptive processes, drive and vigilance that

occurred throughout various stages of the illness. Huber considered these deficits as the most fundamental and first psychopathological expressions of the organic processes underlying psychotic disorders and therefore termed them ‘basic symptoms’. Instead of defining symptoms behaviourally, BS are based on the patient’s descriptions of their subjective experiences (Koehler & Sauer, 1984) and thus the symptoms remain predominantly subjective although developed coping strategies, such as social isolation, may become observable to other people.

BS were operationalised as 178 items in five categories in the Bonn Scale for the Assessment of Basic Symptoms (BSABS) by Gross and colleagues in 1987 and their prognostic accuracy was examined prospectively in the Cologne Early Recognition Study (1987-1991). This first long-term prospective early detection study revealed that baseline BS indeed predicted development of schizophrenia within an average follow-up period of 9.6 years. As a result, two partially overlapping BS criteria were developed for defining the initial prodrome of psychosis, especially schizophrenia: 1) the Cognitive-Perceptive basic symptoms criterion (COPER) that showed a 65 % transition rate to schizophrenia and 2) the Cognitive Disturbances (COGDIS) criterion that had a transition rate of 79 % during the 10 year follow-up period (Klosterkötter, Hellmich, Steinmeyer, & Schultze-Lutter, 2001). The subset of 14 BS included in these two criteria include symptoms that were specific to the development of a first episode psychosis within 9.6 years, unlike some of the original BS described by Huber that were diagnostically unspecific (Frauke Schultze-Lutter et al., 2016). Subsequently a shorter version of the BSABS, called the Schizophrenia Proneness Instrument (SPI-A, Schultze-Lutter et al., 2007) was designed to assess both characteristic and uncharacteristic BS with the possibility to assess only psychosis-specific symptoms by utilizing the COGDIS and COPER criteria.

1.2.3 **Two-stage model of clinical risk for psychosis**

The German Research Network on Schizophrenia has proposed a two-stage theoretical model of the high risk stage for psychosis that differentiates an early prodromal state (EPS), defined by the presence of BS that are thought to be the earliest manifestation of psychosis risk, from a late prodromal state (LPS), defined by the presence of APS or BLIPS (Häfner et al., 2004). According to the

two-stage framework, these two different at risk groups differ in their distance to psychosis onset and indeed there is some suggestive evidence showing that BS might occur before APS supporting the proposed sequence of symptom development in the at risk phase (Frauke Schultze-Lutter et al., 2010). To date there have been only a few studies comparing characteristics of individuals at different stages of high risk for psychosis but evidence suggests BS samples to have intermediate neurocognitive performance between controls and UHR individuals (Frommann et al., 2011) and P300 amplitude deficits to be greater in the late than early high risk stage (Frommann et al., 2008), indicating potential differences in electrophysiology and neuropsychology between the two high risk subgroups.

1.2.4 **Combining UHR and BS approach**

Based on the two-stage model suggesting the early high risk stage to be characterised by the presence of BS and APS to emerge in the later stage (Klosterkötter et al., 2001), it is common to combine BS and UHR criteria to improve the detection of individuals at risk for developing psychosis (Figure 1.1). The notion of combining the two approaches is supported by a 48-month follow-up study that found individuals meeting both BS and UHR criteria to have a significantly higher transition risk (hazard rate = 0.66) and shorter time to transition to psychosis than individuals who met only BS (hr = 0.23) or UHR criteria alone (hr = 0.28) (Frauke Schultze-Lutter, Klosterkötter, & Ruhrmann, 2014). On the other hand, a meta-analysis of twenty-seven studies that used UHR or/and BS criteria to define individuals at risk for psychosis reported the predictive accuracy of combined sets of criteria to be lower (22.5 %) compared to the BS approach (48.5 %) or the UHR approach (27.7 %) alone (Paolo Fusar-Poli, Bonoldi, et al., 2012). However, a more recent meta-analysis concluded that individuals who met both UHR and BS criteria had higher psychosis risk than the UHR criteria only (Paolo Fusar-Poli, Cappucciati, et al., 2016). Accordingly, the present thesis combines the two approaches to identify individuals that meet the UHR and/or BS criteria and henceforth the term ‘individuals at clinical high risk (CHR) state for developing psychosis’ is used to describe these individuals in this thesis.

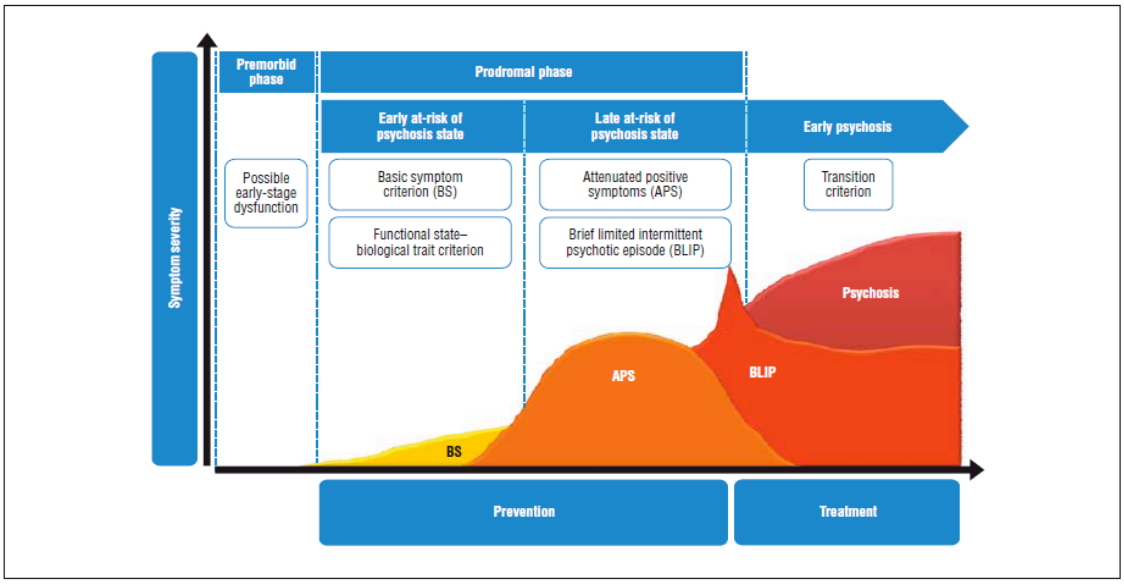


Figure 1.1 Model of psychosis onset from the clinical high-risk state based on the BS/UHR criteria (Paolo Fusar-Poli, Borgwardt, et al., 2013).

1.2.5 **Clinical staging model in psychiatry**

Unlike the use of clinical staging in general medicine, the application of clinical staging models to mental health disorders is less common (Cosci & Fava, 2013). The underlying idea of clinical staging is that intervening earlier will be more effective than in the later stages of the illness and can lead to better clinical and functional outcomes (Mcgorry, Hickie, Yung, Pantelis, & Jackson, 2006). However, the introduction of the UHR concept in 1996 resulted in an important paradigm shift towards a preventative approach in psychosis research and clinical practice and also facilitated the adoption of the clinical staging model in psychiatry, especially in the field of psychosis and more recently in non-psychotic disorders (Hartmann, Nelson, Ratheesh, Treen, & McGorry, 2019).

Clinical staging to psychiatric disorders was first introduced by Fava and Kellner in 1993 when they developed staging methods for depression, panic disorder and schizophrenia ranging from the prodromal to chronic stage (Fava & Kellner, 1993). The staging for psychotic disorders was later elaborated by McGorry and colleagues in 2006 who developed a staging system for psychosis that uses the symptom severity to classify individuals into different illness stages accompanied by stage-specific treatments (Mcgorry et al., 2006). The model is based on the notion that psychosis emerges over time through successive stages marked by symptoms of increased clarity and intensity (Mcgorry & Van Os, 2013), ranging from stage 0 indicating a pre-symptomatic genetic risk to stage 1a with mild

non-specific symptoms followed by stage 1b characterised by more specific APS and ending with stages 2-4 that range from a first psychotic episode to chronicity. In the context of clinical staging, it has been suggested that the BS approach can be conceptualised as stage 1a and the UHR approach that identifies individuals at a later illness stage as 1b (Hartmann et al., 2019). The current thesis adopts the severity-based clinical staging for psychosis as a framework and focuses on the stages 1 (high risk) and 2 (first episode of psychosis), the stages 3 (persistent symptoms, relapses and remissions) and 4 (unremitting illness) not being relevant here.

1.3 Prevalence and characteristics of CHR individuals

1.3.1 Prevalence rates of PLEs and CHR states in the general population

Several studies using both self-report questionnaires and interviews have shown that psychotic-like experiences (PLE), namely subtle and subclinical hallucinations, are frequently reported by non-treatment-seeking general samples, especially by children and adolescents. A meta-analytical evidence shows a median prevalence rate of 5 % for subclinical psychotic symptoms in the general population (Van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009) while studies among children and adolescents have shown even higher prevalence rates, one meta-analysis reporting a median prevalence rate of 17 % among 9- to 12-year-olds and 7.5 % among 13- to 18-year-olds (Ian Kelleher, Connor, et al., 2012). The relatively high prevalence of PLEs among the general population has raised questions regarding the utility of the UHR paradigm and concerns about misclassifying people with fluctuating PLEs as being at risk for developing psychosis (Carpenter, 2014; Weiser, 2011).

One of the first community-based epidemiological studies using clinical interviews found that 0.9 % to 8 % of the general population aged 11 to 13 years old met the criteria for the at risk for developing psychosis, depending on the criteria applied (Ian Kelleher, Murtagh, et al., 2012). The prevalence rate seems to be lower among young adults as shown by study findings that only 0.3 % (with onset/worsening criterion) or 2.6 % (no onset/worsening criterion) of the 16- to 40-year old general population sample met the APS criteria according to the

Structured Interview for Prodromal Syndromes (SIPS; Schultze-Lutter, Michel, Ruhrmann, & Schimmelmann, 2014). This is in line with more recent epidemiological studies reporting prevalence rates of 1.3 % and 2.4 % of individuals meeting UHR criteria in the general population (Schimmelmann, Michel, Martz-Irngartinger, Linder, & Schultze-Lutter, 2015; Frauke Schultze-Lutter, Michel, Ruhrmann, & Schimmelmann, 2018). Collectively, these epidemiological studies demonstrate the effect of age on both PLEs and APS and the overall low prevalence of individuals meeting the high risk criteria for psychosis in the community.

1.3.2 Clinical significance of APS

Previous studies have examined the clinical significance of APS and found them to be associated with psychiatric comorbidity and lower functioning in both clinical and community-based CHR samples. Kelleher and colleagues, for instance, reported that a young (11-13 years) non-help-seeking CHR sample had a lower global functioning and a higher level of co-occurring psychopathology compared to controls (Ian Kelleher, Murtagh, et al., 2012). This is in accordance with findings from an older community CHR sample (16 to 40 years) that found APS to be associated with poorer functioning and higher levels of comorbid mental disorders (Frauke Schultze-Lutter, Michel, et al., 2014), mirroring findings in samples of help-seeking individuals who were engaged by specialised early-intervention services (Paolo Fusar-Poli, Nelson, Valmaggia, Yung, & McGuire, 2014).

1.3.3 Characteristics of CHR individuals

1.3.3.1 Functioning, suicidal ideation and comorbidity

Impaired daily functioning, such as maintaining employment, communication with others, independent living and functioning in the community, is evident in schizophrenia and is present already during the first episode of psychosis (Bellack, Morrison, Wixted, & Mueser, 1990; Marwaha & Johnson, 2004); Lee, Kim, Lee, & An, 2017). Impaired functioning is largely responsible for the burden not only for patients but also for their families, caregivers and the wider society (Jungbauer, Wittmund, Dietrich, & Angermeyer, 2004; Knapp, Mangalore, & Simon, 2004; Perlick et al., 2006). Furthermore, a substantial body of evidence

shows that while more severe in schizophrenia, functional deficits are present already in CHR individuals who report reduced subjective quality of life (Bechdolf et al., 2005) and impairments in global, (Paolo Fusar-Poli et al., 2015; Hui et al., 2013) social, (Addington, Penn, Woods, Addington, & Perkins, 2008), occupational and academic functioning compared to controls (S. J. Lee et al., 2017). In fact, the functional level of individuals in the at-risk stage has been shown to be closer to first episode patients than healthy controls (Paolo Fusar-Poli et al., 2015).

Besides functional impairments, the majority of schizophrenia patients have suicidal ideation with up to 80 % of patients reporting suicidal ideation at some point during their illness (Skodlar, Tomori, & Parnas, 2008). Moreover, a number of studies have found the CHR individuals to be characterised by high prevalence rates of suicidal ideation as well, with findings ranging from the prevalence rate of 43 % to 58 % (Gill et al., 2015; Hutton, Parker, Bowe, & Ford, 2012). An even higher 66 % prevalence rate of suicidal ideation among CHR individuals, similar to rates during the first episode of illness, was reported by a recent meta-analysis of 21 studies (Taylor, Hutton, & Wood, 2015).

Previous studies have found CHR samples to be characterised by a high level of comorbid non-psychotic diagnoses, especially mood and anxiety diagnoses. Specifically, a large study of 377 CHR individuals reported a prevalence of 69 % of one or more mood/anxiety diagnoses at baseline (Woods et al., 2009), similar to the 71 % prevalence rate of nonpsychotic diagnosis reported by another study (Salokangas et al., 2012). These findings were confirmed by a meta-analysis of 1683 CHR individuals that found that 41 % had a comorbid baseline depressive disorder and 15 % anxiety disorder (Paolo Fusar-Poli et al., 2014). Importantly, depressive and anxiety disorders are not only highly prevalent in the high risk for psychosis stage but they have also been shown to contribute to functional deficits (Paolo Fusar-Poli et al., 2014) and to be the most frequent reason to seek help among CHR individuals (Falkenberg et al., 2015). Taken together, converging evidence suggests that individuals at clinical high risk for developing psychosis are characterised by extensive clinical co-morbidity in addition to APS.

1.3.3.2 **Cognitive deficits**

Past studies have examined whether cognitive impairments observed in schizophrenia and first episode patients emerge prior to the onset of psychosis and have found that indeed deficits are present already in CHR individuals at the level that is intermediate between control and FEP samples (e.g. Keefe et al., 2006; Lencz et al., 2006), those CHR individuals who later developed psychosis being more impaired at baseline than those who did not (Seidman et al., 2010). These individual study findings were confirmed by meta-analyses that found evidence for small to moderate cognitive deficits in each domain (Bora et al., 2014), independent of recruitment strategies and inclusion criteria (Paolo Fusar-Poli, Deste, et al., 2012), indicating that cognitive deficits are present already in the high risk stage but less pronounced than in the later stages of the illness. Accordingly, cognitive performance has been suggested to be a potential marker of increased vulnerability to psychosis.

Previous studies examining cognitive performance as a potential predictor of functional outcome in CHR samples have suggested that the link between cognition and functioning exists already in the high risk stage of psychosis. For instance, Lin and colleagues (2011) found an association between functional outcome and specific baseline neurocognitive deficits, namely verbal learning and memory, processing speed and attention and verbal fluency, independent of transition to psychosis. Similarly another study reported baseline processing speed to predict 10 % and 7 % of social and role functioning independent of positive symptoms (Carrión et al., 2011) while Niendam and collagues (2007) found improved social and role functioning not to be predicted by baseline cognition but by improved processing speed and visual memory over the follow-up period.

1.4 **Outcomes of CHR individuals**

1.4.1 **The specificity of UHR criteria and transition rates**

One of the earliest studies to assess the predictive validity of clinical UHR criteria in relation to onset of psychosis reported a 40 % (8/20) transition rate at 6 months, (Yung et al., 1998) and with an expanded sample size at 12 months a 41 % (20/49) transition rate (Yung, Phillips, et al., 2003) and finally a 35 %

(36/104) transition rate with the final sample size at 12 months (Yung, Phillips, Yuen, & McGorry, 2004). In line with these transition rates, Miller and colleagues found a 54 % transition rate to a first episode psychosis at 12 months using a similar UHR criteria but a different instrument (Structured Interview for Prodromal Syndromes; SIPS) (Miller et al., 2002). However, in contrast to transition rates ranging from 30 % to 50 % reported by early CHR studies, there has been a higher variance in transition risks across more recent studies and lower transition rates ranging from 10 % to 20 % (Simon & Umbricht, 2010; Yung et al., 2008). Indeed, there is evidence for a decline in transition rates from 1995 to 2000 in the Personal Assessment and Crisis Evaluation clinic which was partially explained by the earlier detection of UHR individuals (Yung et al., 2007). Other factors contributing to declining rates suggested by later studies include effective treatment strategies, follow-up time, the level of clinic's specialization in early detection of psychosis, recruitment and sample characteristics (Ruhrmann, Schultze-Lutter, & Klosterkötter, 2010). However, even the lower transition rates reported by more recent CHR studies are still greater than the transition rate of 0.6 % in samples of non-help-seeking general population reported by a meta-analysis of six studies (Kaymaz et al., 2012).

Another key factor moderating the transition rates over the years is the recruitment method of CHR individuals. The first studies investigating the predictive utility of clinical CHR criteria relied systematically on samples recruited from special early detection and intervention services for psychosis whereas more recent studies have adopted wider recruitment strategies to reach the general public and as a result have included higher proportions of community recruited than clinically referred help-seeking individuals. A recent meta-analysis of 11 studies examined the relationship between recruitment strategies and transition risks reported a 15 % pre-test risk for psychosis at 38 months, namely the underlying risk of the population from which the individual is selected, in clinically referred samples compared to a 0.1 % risk in samples recruited from the general population (Paolo Fusar-Poli, Schultze-Lutter, et al., 2016).

In terms of specific DCM/ICD diagnostic outcomes of CHR individuals, an early meta-analytical investigation found that out of 27 % of CHR individuals who

developed psychosis over the mean follow-up time of 2.3 years, 73 % of them transitioned to schizophrenia spectrum disorders (schizophrenia, schizophreniform, schizoaffective) and 11 % were diagnosed with affective psychoses (psychotic depression, bipolar psychosis) (Paolo Fusar-Poli, Bechdolf, et al., 2013). Moreover, although high risk individuals are commonly characterised by comorbid disorders, the majority of them are present already at baseline (A. Lin et al., 2015) and the UHR criteria has shown specificity for the development of psychotic disorders, not for emerging non-psychotic disorders (Paolo Fusar-Poli, Rutigliano, et al., 2017; Webb et al., 2015), supporting the specificity of the CHR criteria to identify prodromal phases of psychotic rather than non-psychotic disorders.

1.4.2 Outcomes of CHR individuals who do not develop psychosis

Since the introduction of the UHR paradigm and the clinical staging model of psychosis, the majority of research has focused on the progression from the high risk stage (stage 1) to a first episode of psychosis (stage 2). However, as discussed above, only a minority of CHR individuals become psychotic within the follow-up period (Yung et al., 2007). While the low incidence rates of psychotic disorders observed in recent studies fit well with the view of the UHR concept that progression from the high risk stage to psychosis is not inevitable, low sample sizes result in insufficient statistical power to study potential predictors of psychosis. Moreover, the emphasis on psychosis as the only outcome of interest has been criticised as the accumulation of evidence over time has shown that many CHR individuals have poor outcomes and require clinical care regardless of whether they transition to psychosis (Carrión et al., 2013; Os & Guloksuz, 2017). As a result, more recent research has started to investigate trajectories and outcomes of CHR individuals who do not transition to psychosis (CHR-NT).

One of the first studies to investigate the outcomes of CHR-NT individuals made a distinction between individuals who sustained APS and those who remitted from their initial CHR status within the follow-up period (Addington et al., 2011). Thus the first outcome studies of CHR-NT individuals mainly focused on the incidence of remission from baseline APS, reporting somewhat different but

relatively high symptomatic remission rates: 49.1 %, (Ziermans et al., 2011), 59.2 % (Simon & Umbricht, 2010) and 36 % (Schlosser et al., 2012). The first meta-analysis of the prevalence of symptomatic remission in CHR-NT individuals based on eight original studies reported that 46 % of CHR individuals fully remitted from their baseline APS during a 2-year follow-up (Simon et al., 2013). Collectively evidence suggest that the majority of UHR individuals do not become psychotic and only about half of CHT-NTs still meet the CHR criteria in two years, suggesting a high number of CHR individuals to possibly exhibit transient APS. Interestingly though, one of the first studies to include a functional outcome in addition to a symptomatic remission found that despite CHR-NT individuals achieving symptomatic remission and showing improved social and role functioning, their functioning still remained impaired compared to controls at a 2.5 year follow-up (Addington et al., 2011), indicating persistent functional impairment in this population.

Regarding the course of more general psychopathology of CHR-NT individuals, a recent study reported that nonpsychotic disorders were frequently (90 %) present at baseline, in line with evidence on comorbid diagnoses in CHR individuals discussed above, and were likely to persist (52 %) over the follow-up period (A. Lin et al., 2015). Furthermore, a recent meta-analysis examining several outcomes of CHR-NT individuals found that although about 50 % to 70 % remitted from their CHR status, more than half met the axis 1 or 2 disorder and many continued to have psychosocial impairments in a long term, highlighting the importance of assessing more systematically other clinically relevant outcomes and not solely APS in CHR studies.

1.5 **Predictors of outcome in CHR individuals**

The major focus of the high risk and early psychosis field has been on identifying predictors for progression from the high risk stage to the first episode stage to allow an early targeted proactive treatment approach. As discussed above, although the CHR individuals have an elevated risk for developing a first episode psychosis, most of them do not become psychotic within a 2-3 year follow-up (Yung et al., 2007). Thus a substantial body of research has been dedicated to finding clinical and neuropsychological predictors that could improve psychosis

prediction compared to the accuracy achieved based solely on the clinical CHR criteria.

1.5.1 **Transition to psychosis**

Several single- and multi-site studies have compared baseline demographic, clinical and neuropsychological characteristics of CHR individuals who transitioned to psychosis (CHR-T) and who did not (CHR-NT) and have found group differences in symptoms, global, social and role functioning (Atkinson et al., 2017; T. D. Cannon et al., 2008; Cornblatt et al., 2007; Mason et al., 2004). Moreover, a body of evidence shows that CHR-T groups have greater neuropsychological impairments than CHR-NT groups (Brewer et al., 2004; Lencz et al., 2006; Seidman et al., 2010), suggesting these clinical and cognitive measures to have potential utility as predictors of transition to psychosis. Large multi-site longitudinal studies have also revealed a number of variables that increase the positive predictive power for psychosis compared to using the at-risk clinical criteria alone (T. D. Cannon et al., 2008; Ruhrmann, Schultze-Lutter, Salokangas, et al., 2010). For instance, one of the largest studies to date, a large North American multi-site study, found that combining demographic variables with symptoms had a higher predictive power for transition to psychosis (74 – 81 %) than SIPS criteria alone (35 %) (T. D. Cannon et al., 2008). However, results on predictive values of neuropsychological measures have been mixed and differences in group means do not always translate to improved prediction; while some studies have shown neuropsychological measures to increase clinical prediction beyond using only clinical variables (Anita Riecher-Rössler et al., 2009), others have found cognitive variables not to contribute uniquely to psychosis prediction beyond clinical variables (Seidman et al., 2010). Overall, a number of different combinations of clinical and neuropsychological measures have been found to increase the predictive power for developing psychosis compared to the CHR criteria alone but the results and most significant predictors vary greatly across studies and there is a need for models to be externally validated on independent samples.

1.5.2 Symptomatic and functional outcomes

Past studies investigating baseline clinical and cognitive differences between individuals who remitted from their initial CHR status and those who did not have reported conflicting results. While some studies did not find any group differences in baseline socio-demographic characteristics and clinical symptoms (de Wit et al., 2014; M. Kim, Lee, Yoon, Lee, & Kwon, 2018; M. Kim, Lee, Lee, Kim, & Kwon, 2015; T. Y. Lee, Shin, et al., 2014; Simon & Umbricht, 2010), others found that less severe baseline negative and mood/anxiety symptoms were associated with higher rates of both symptomatic and functional recovery (Schlosser et al., 2012). Moreover, Lee and colleagues (2014) found that non-remitters had higher positive attenuated symptoms and higher antipsychotic medication at baseline compared to remitters. Regarding group differences in baseline cognitive performance, the same study found no difference in any cognitive domain between remitters and non-remitters. On the contrary, the largest single-site study to date found that baseline cognitive impairments differentiated those who remitted from their UHR status from those who did not (Lam et al., 2018) and another study found poor specific neurocognitive impairments to be related with functional outcomes regardless of transition to psychosis (A. Lin et al., 2011).

1.6 The utility of functional neuroimaging methods in psychosis research

In addition to aiming to utilise clinical and neuropsychological measures to improve psychosis prediction in CHR individuals, there has been a large interest in finding objective neuroimaging markers of transition from the high risk stage of psychosis to the first episode stage. Indeed the wide availability of non-invasive neuroimaging techniques has resulted in an extensive use of them to search for potential imaging markers for psychosis prediction in addition to elucidating the neural correlates of perceptual and cognitive disruptions throughout various stages of psychosis. The second part of the introduction chapter focuses on what advanced non-invasive electrophysiological methods have revealed about early and late information processing across different stages of psychosis and the search for reliable and replicable EEG and MEG based markers for psychosis.

1.6.1 **MEG and EEG methods**

Magnetoencephalography (MEG) is a non-invasive functional neuroimaging technique for mapping brain activity which was pioneered by Cohen in 1968 who later conducted an MEG recording using a superconducting quantum interference device that was capable of measuring weak magnetic fields created by the human brain in a magnetically shielded room resulting in signals that were comparable to electroencephalography (EEG) signals (Cohen, 1968; Cohen, 1972). It is necessary to conduct MEG recordings in a magnetically shielded room designed to minimize magnetic interference because the magnetic fields created by the brain are very small, in the range of femto-Tesla (10-15 fT) to pico-Tesla (10-12 fT), compared to the Earth's magnetic field (10-5 T).

One main advantage of MEG compared to EEG is that magnetic fields are less distorted by the skull and scalp surrounding the brain compared to electric fields and thus localization of brain sources of the MEG signal is more accurate due to less complex forward models (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). Indeed MEG is frequently combined with magnetic resonance imaging (MRI) to map brain activity and estimate source location of the MEG signal. Besides the good spatial resolution, MEG has to an excellent temporal resolution and since the 1980s, whole-head MEG systems with 100 to 300 sensors have slowly been implemented in research and clinical settings in addition to more frequently employed EEG device.

1.6.2 **Origin/electrophysiological basis of MEG signal**

Event-related potentials (ERPs) and their magnetic equivalents, event-related fields (ERFs), are time-locked brain responses to internal or external stimuli, averaged across a large number of trials (Luck et al., 2014). The ERP/ERF component, one of the component waves of the entire waveform, is described in terms of its amplitude and latency, latency being defined as the time point where the amplitude reaches its maximal value (peak). Both EEG and MEG record neural activity from a large number of simultaneously active neurons of the cerebral cortex, approximately 50 000 pyramidal neurons needed to be active to record a MEG/EEG signal (Hämäläinen et al., 1993). While EEG measures electric currents generated by activated synchronous cells, MEG

records magnetic flux produced by this electrical activity. Thus folding of the cortex is relevant to the MEG signal as only neural currents or sources that are tangentially, not radially, oriented to skull generate magnetic fields around them that can be detected outside of head (Baillet, 2017).

1.6.3 **Electrophysiological techniques in psychiatric research**

As both MEG and EEG are high temporal-resolution electrophysiological techniques that can quantify changes in neuronal processing related to different states of activity in response to external or internal events over a few milliseconds, they provide a good non-invasive tool to assess perceptual and cognitive disturbances and their underlying neurophysiological mechanisms in psychiatric conditions such as schizophrenia. These advanced non-invasive neuroimaging techniques have not only enabled researchers to begin to elucidate the neurobiological basis of cognitive and perceptual deficits observed across different stages of psychosis but also resulted in search for reliable and replicable EEG and MEG based biomarkers for psychosis.

Biological parameter, namely a biomarker is defined as “a characteristic that is objectively measured and evaluated as an indicator or healthy biological processes, pathological processes or pharmacological responses to therapeutic intervention ” (Biomarkers Definitions Working Group et al., 2001). Biomarkers have several potential applications as a tool for diagnosis, staging, prognosis and monitoring responses to interventions in psychiatry. Given that the diagnosis of psychotic disorders relies solely on subjective clinical assessments based on behavioural symptoms, there is a large body of research dedicated for searching a biomarker for psychosis, especially for schizophrenia. However, despite great efforts for finding clinically meaningful biomarkers to inform diagnosis or treatment in the field of psychosis, biomarkers or clinical tests for psychosis are still to be identified (Prata, Mechelli, & Kapur, 2014). Indeed, the ultimate aim of the clinical staging model of psychosis is to develop a clinicopathological model by supplementing different stages associated with different symptom severity and treatments with potential biomarkers as well (Mcgorry et al., 2006). However, currently there are no reliable electrophysiological measures for identifying different stages of psychosis or predicting illness progression. Interestingly though, there are several electrophysiological measures that have

been found to be abnormal in chronic schizophrenia that might emerge in earlier stages of psychosis and even prior to the onset of psychosis, potentially having utility as a marker for psychosis.

1.6.4 Sensory processing deficits across different stages of psychosis

1.6.4.1 In schizophrenia, first episode patients and unaffected relatives

Besides examining cognitive impairments across different domains in schizophrenia, as discussed above, more recent research has focused on basic sensory functions and early information processing. Indeed a large body of evidence has revealed pronounced impairments in sensory processing, particularly in the auditory domain (for a review see (Daniel C. Javitt & Sweet, 2015)) but also in visual (D. Kim, Zemon, Saperstein, Butler, & Javitt, 2005; Revheim et al., 2006), olfactory (Moberg et al., 2014) and tactile domains (Teale, Pasko, Collins, Rojas, & Reite, 2013).

In the auditory modality, several electrophysiological measures have been studied extensively using both EEG and more recently MEG to gain insights into early pre-attentive auditory processing and later information processing in schizophrenia (Van Der Stelt & Belger, 2007). Indeed, a growing body of evidence shows that there are disruptions in early sensory processes as indicated by aberrant ERP/ERF components in schizophrenia. For instance, P50, an early component thought to reflect a sensory gating mechanism or inhibiting redundant stimuli, is a well-known measure of early auditory processing (Adler, 1982). Typically the P50 amplitude decreases in response to repeated stimuli, but there are several studies showing that patients with schizophrenia fail to show this normal P50 suppression, indicating an early auditory processing deficit in the disorder (e.g. Brockhaus-Dumke et al., 2008). Moreover, a meta-analysis of 20 studies reported a significantly larger P50 ratio (amplitude to the second stimulus divided by the amplitude to the first stimulus) with a large pooled standardized effect size of 1.56 in schizophrenia patients compared to controls (Elvira Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004). In contrast to established schizophrenia, findings on P50 gating among first episode patients have been inconsistent (de Wilde, Bour, Dingemans, Koelman, & Linszen, 2007; Morales-Muñoz et al., 2016). Interestingly, a recent meta-analysis provided

evidence for P50 suppression changes in unaffected relatives of schizophrenia patients (Earls, Curran, & Mittal, 2016).

Besides impairments in shorter latency exogenous ERP components, electrophysiological indices of higher cognitive processes, such as the endogenous P300 amplitude that is associated with directed attention and working memory-related operations (see Linden, 2005 for a review), have been widely studied in schizophrenia patients. While previous studies have shown a reduced auditory P300 amplitude to be a consistent finding in schizophrenia patients, results are less consistent for the P300 latency; a meta-analysis of 46 studies reported a large effect size of 0.85 for the P300 amplitude and a medium effect size of 0.57 for the P300 latency in schizophrenia patients compared to healthy controls (Elvira Bramon et al., 2004). Moreover, P300 deficiency seems to be also present in first episode patients, a recent meta-analysis reporting a smaller P300 amplitude with an effect size of 0.83 and prolonged P300 latency with an effect size of 0.48 (Qiu, Tang, Chan, Sun, & He, 2014), as well as in unaffected relatives (Earls et al., 2016).

1.6.4.2 **In individuals at clinical high risk state for psychosis**

Several recent studies have investigated sensory gating, as indexed by P50 suppression, in CHR individuals but have revealed mixed results, some studies have found P50 suppression deficits in CHR individuals in comparison with controls (Brockhaus-Dumke et al., 2008; Myles-Worsley, Ord, Blailes, Ngiralmau, & Freedman, 2004), but others not (Cadenhead, Light, Shafer, & Braff, 2005; Hsieh et al., 2012; Van Tricht et al., 2015). Compared to P50 gating deficits, attenuated P300 abnormalities appear to be consistently reported in CHR individuals as a number of studies have found significant P300 amplitude reductions to be present in this population, suggesting it to be a potential marker for psychosis risk (del Re et al., 2015; Frommann et al., 2008; Özgürdal et al., 2008; Van Der Stelt, Lieberman, & Belger, 2005).

1.7 Mismatch negativity

1.7.1 Basic characteristics of MMN

Auditory mismatch negativity (MMN; Näätänen, Gaillard, & Mäntysalo, 1978) and its magnetic counterpart (MMNm; Hari et al., 1984), first described by Näätänen and colleagues in 1978, is a component of an auditory event-related brain potential/field that is elicited automatically by a violation of a previously established auditory regularity (Näätänen et al., 1978; Näätänen, Paavilainen, Rinne, & Alho, 2007) and can be recorded non-invasively with EEG and MEG. The MMN response is commonly studied by using a classic oddball paradigm in which a series of identical standard stimuli precede the elicitation of MMN by a low probability deviant stimulus that differs on one or more feature dimensions such as frequency, duration or intensity. However, MMN can also be evoked by more complex and abstract changes, for instance by violating regularity in roving paradigms (Baldeweg, Klugman, Gruzelier, & Hirsch, 2004) or rhythmic violations (Vuust et al., 2005). The elicited MMN is obtained by subtracting the ERP in response to standard stimuli from the ERP to deviant stimuli. The MMNm response is an early response that typically peaks at 150-250 ms post-stimulus and is most frequently quantified as a peak or mean amplitude across a time interval of interest and sometimes complemented by information about its latency (Bartha-Doering, Deuster, Giordano, Am Zehnhoff-Dinnesen, & Dobel, 2015). As the MMN is optimally generated in the absence of attention unlike the P300, it makes it an ideal electrophysiological measure for clinical studies where motivation and attention are potential confounding variables (Näätänen, 2000). In the current study, we employed a simple visual detection task in order to direct participants' attention away from the auditory stimulation.

1.7.2 MMN paradigms

The MMN response is evoked by any discriminable change in a repetitive auditory pattern but the standard stimulus needs to be repeated a few times at the beginning of a stimulus block so that a representation of a standard sound can be developed and a deviant sound can evoke an MMN response (Cowan, Winkler, Teder, & Näätänen, 1993). The amplitude of the MMN response increases with increasing number of standards which is believed to reflect the strength of the

underlying memory trace (e.g. Javitt, Grochowski, Shelley, & Ritter, 1998). The amplitude is also modulated by the inter stimulus interval (ISI) where shorter ISIs elicit larger MMN amplitude responses, the response vanishing when the ISI is more than 10 seconds (Sams, Hari, Rif, & Knuutila, 1993) potentially due to memory decay for the standard stimuli (Mäntysalo & Näätänen, 1987) .

Additional factor affecting the MMN response is the probability of the deviant stimulus. For example, Javitt and collegues (1998) found that both in healthy controls and schizophrenia patients the MMN amplitude increased as the deviant occurrence decreased from 15 % to 0.56 %, potentially due a stronger representation of the standard stimuli with a lower deviant probability. Similarly it has been found that as the difference between the standard and deviant stimulus becomes larger in frequency, intensity (Novitski, Tervaniemi, Huotilainen, & Näätänen, 2004), or duration (Joutsiniemi et al., 1998), the MMN amplitude becomes larger and latency becomes shorter.

1.7.3 **Cerebral generators of MMN**

The hemispheric laterality of MMN depends on the stimulus type, namely the MMN response is right lateralized for simple tone stimuli (Levänen, Ahonen, Hari, McEvoy, & Sams, 1996) and left lateralized for language stimuli (Näätänen et al., 1997). Regarding MMN sources, studies suggest that the MMN is generated primarily in the temporal lobes with some studies reporting sources in primarily the right frontal lobe. While some studies using fMRI have found both activation in the superior temporal gyri (STG) bilaterally and in the right inferior frontal gyrus (IFG) (Opitz, Rinne, Mecklinger, Von Cramon, & Schröger, 2002; Schonwiesner et al., 2007), other fMRI studies could not detect significant activation in the IFG (Cacciaglia et al., 2015).

Source reconstruction studies using EEG have also reported frontal sources in addition to temporal sources (Doeller et al., 2003; Fulham et al., 2014; Marco-Pallarés, Grau, & Ruffini, 2005; Waberski et al., 2001). However, it has turned out to be more difficult to find frontal sources using MEG (Recasens, Grimm, Wollbrink, Pantev, & Escera, 2014). For example, an early study using both EEG and MEG found frontal activation only with EEG but not with MEG (Rinne, Alho, Ilmoniemi, Virtanen, & Näätänen, 2000), hence it is possible that the frontal

MMN source is deeper in the brain or radially orientated to which MEG is blind (Hämäläinen et al., 1993).

1.7.4 **Neurobiology of MMN**

NMDAR is a glutamate receptor subtype that plays an important role in various functions such as long-term potentiation (Cotman & Monaghan, 1988), memory (D.C. Javitt, Steinschneider, Schroeder, & Arezzo, 1996; Malhotra et al., 1996), learning and synaptic plasticity (Paoletti, Bellone, & Zhou, 2013). NMDAR dysfunction has been shown to contribute to various brain disorders (Lakhan, Caro, & Hadzimichalis, 2013) and there is a large body of evidence implicating NMDA receptors in the pathophysiology of schizophrenia as well. Previous pharmacological studies have shown that NMDA antagonist drugs elicit positive, negative and cognitive symptoms in controls and triggers psychosis in patients (Lahti et al., 1995; Malhotra et al., 1996, 1997; Reich & Silvay, 1989) and GWAS have revealed schizophrenia-associated genes involved in the glutamatergic system (Ripke et al., 2014). In fact, the majority of evidence for the previously discussed abnormal glutamatergic transmission in schizophrenia has primarily implicated the hypofunction of NMDA subtype of the glutamate receptor (Rubio, Drummond, & Meador-Woodruff, 2012).

The aforementioned well-replicated MMN alterations in schizophrenia have been linked to NMDA receptor hypofunction. Since the first study that demonstrated MMN to depend on NMDAR function in monkeys in 1996 (D.C. Javitt et al., 1996), a number of pharmacological studies in humans have shown MMN to be sensitive to activity of glutamate N-methyl-D-aspartate receptor (NMDAR) by blocking NMDA receptors using NMDAR antagonists, such as ketamine and phencyclidine (D. Umbricht, Koller, Vollenweider, & Schmid, 2002). Moreover, a recent meta-analysis of eight ketamine studies on MMN generation in humans showed that ketamine decreased MMN amplitude and increased latencies, the effects not varying between different deviant types (Rosburg & Kreitschmann-Andermahr, 2016). In the light of evidence for MMN generation to critically depend on NMDAR, MMN is typically considered as a useful non-invasive marker of NMDA receptor glutamate function in schizophrenia.

Although it remains largely unknown how the hypofunction of NMDAR results in excessive glutamate release, it has been suggested that NMDAR hypofunction disrupts the functioning of parvalbumin-expressing γ-Aminobutyric acid (GABA)ergic interneurons and results in an elevated excitatory and inhibitory ratio due to a loss of inhibition (Lewis, Hashimoto, & Volk, 2005; Marín, 2012), which has been proposed to play a role in the pathophysiology of schizophrenia (Gonzalez-Burgos & Lewis, 2012; Murray et al., 2014).

1.7.5 **Underlying mechanisms of MMN**

There are several theories to explain the generation of the MMN response and the underlying mechanisms continue to be debated. The model adjustment theory suggests that the MMN results from a comparison between the stimulus input and the memory trace, whereby the MMN response reflects an update of the auditory environment. According to this theory, the functional role of the MMN is to update the information about the auditory regularities rather than deviance detection per se (Winkler & Czigler, 1998; Winkler, Karmos, & Näätänen, 1996).

Another relatively recent hypothesis of the MMN generation is the neural adaptation hypothesis that proposes that the repeated presentation of the standard stimulus results in attenuated responses of feature-selective neurons. The MMN is thus solely generated by the deviant stimulus activating different, less adapted populations of neurons in the auditory cortex resulting in a larger ERP response (May & Tiitinen, 2010). In this framework, the MMN is not related to a higher-level comparison process but simply an attenuated and delayed, i.e. a modulated, N1 response due to synaptic depression and lateral inhibition.

More recently, a predictive coding account, which combines the model adjustment and neural adaptation hypothesis, has been proposed (Friston, 2005; Rao & Ballard, 1999). According to this framework, the brain constantly predicts the causes of sensory input by comparing incoming sensory input with top-down predictions generated by an internal model containing regularities extracted from previous sensory experiences. In this model, feedforward connections convey a residual prediction error between the thalamic input and the prediction that is conveyed by cortical feedback connections. This prediction

error signal in granular layer 4 is transmitted by feedforward connections upward to supragranural layers 2/3 to update the internal model and predictions about sensory input (Baldeweg, 2007; Friston, 2005). Importantly, evidence suggests that the auditory MMN signal is a direct index of a prediction error, and reflects implicit learning of sensory regularities (Garrido, Kilner, Stephan, & Friston, 2009; C. Wacongne, Changeux, & Dehaene, 2012). Moreover, previous studies have indicated that even unexpected sound omissions are capable of eliciting MMN (Salisbury, 2012; Catherine Wacongne et al., 2011; Yabe et al., 1998), providing evidence for the predictive coding account of MMN suggesting it to emerge by a violation of an internal predictive model of upcoming events based on previously established auditory regularities. In the current thesis, we recorded MMNm responses to both duration deviants and sound omissions.

1.8 MMN across different stages of psychosis

1.8.1 MMN amplitude deficits in chronic schizophrenia and first episode patients

Early auditory processing disruption as indexed by reduced MMN amplitude has consistently been shown to be present in schizophrenia patients since the first report in 1991 (Shelley et al., 1991), both in acute and chronic as well as in medicated and unmedicated patients (Catts et al., 1995). Indeed, it is now well established from more than 200 studies and confirmed by two meta-analyses that schizophrenia patients exhibit a large MMN deficit (ES = 0.95 – 0.99) (Erickson, Ruffle, & Gold, 2016; D. Umbricht & Krljesb, 2005), which has been linked to grey matter loss (Rasser et al., 2011; Salisbury, Kasai, McCarley, Kuroki, & Shenton, 2007) and NMDAR hypofunction (D.C. Javitt et al., 1996; Rosburg & Kreitschmann-Andermahr, 2016). Schizophrenia patients appear to be sensitive to the same aforementioned parameters as healthy controls, such as the probability of the deviant stimulus and the difference between the standard and deviant stimulus (Michie, Malmierca, Harms, & Todd, 2016). However, in line with a previous study suggesting MMN to complex regularities to be intact in schizophrenia (Todd et al., 2014), a recent meta-analysis comparing MMN amplitudes elicited by simple (frequency, intensity and duration) and complex (abstract) deviants in schizophrenia found that MMN deficits were larger to simple deviants compared to complex deviants (Avissar et al 2018).

Interestingly, evidence suggests that MMN deficits are present already in the earlier stages of psychosis before the chronic stage of the illness. Several studies have reported MMN amplitude to be attenuated already in first episode patients (e.g. R. Atkinson, Michie, & Schall, 2012; Higuchi et al., 2013; Kaur et al., 2011). On the other hand, some studies have failed to replicate this findings (Magno et al., 2008; Mondragón-Maya et al., 2013; D. Umbricht, Bates, Lieberman, Kane, & Javitt, 2006). However, a recent meta-analysis reported a medium MMN amplitude impairment (ES = 0.42) in first episode patients (Erickson, Ruffle, & Gold, 2016), which in comparison to a larger effect size of 0.99 in chronic schizophrenia could indicate MMN to have a progressive nature over the course of the illness as previously proposed by other studies (e.g. Salisbury, Shenton, Griggs, Bonner-Jackson, & McCarley, 2003). In summary, original studies of MMN amplitude in first episode patients have revealed inconsistent findings, which could be due to a number of confounds, but at a meta-analytical level it has been reported that MMN deficits are present in first episode patients.

1.8.2 MMN amplitude in individuals at clinical high risk state for psychosis

Past studies have investigated MMN amplitudes also in CHR individuals to examine whether the well-replicated large MMN deficit in schizophrenia and the smaller MMN deficit in first episode patients is present already before the first episode of psychosis. Interestingly, several studies have found impaired MMN responses to at least one type of deviant in CHR individuals compared to controls (Atkinson et al., 2012; Hsieh et al., 2012; Jahshan et al., 2012; Daniel C. Javitt & Sweet, 2015; Koshiyama et al., 2017; Lavoie et al., 2018; Nagai, Tada, Kirihara, Yahata, et al., 2013; Perez et al., 2014; Shaikh et al., 2012; Shin et al., 2009; Solís-Vivanco et al., 2014), suggesting that MMN is compromised prior to psychosis onset and could represent a marker of risk for psychosis development. However, not all studies have found MMN deficits in CHR individuals (Atkinson et al., 2017; Bodatsch et al., 2011; Brockhaus-Dumke et al., 2005; Higuchi et al., 2013; Hirt, Schubring, Schalinski, & Rockstroh, 2019; Koshiyama et al., 2017; Lepock et al., 2019; Mondragón-Maya et al., 2013). As some studies have reported reduced MMN to duration but not frequency deviants in CHR individuals (e.g. Nagai et al., 2013; Todd et al., 2008), it has been suggested that only duration MMN amplitude may be attenuated in the earlier stages of psychosis

and frequency MMN in the chronic stage of the illness. However, this notion is challenged by studies that found equally reduced duration and frequency MMN amplitudes in CHR individuals (Perez et al., 2014) and recent onset schizophrenia patients (Hay et al., 2015). Collectively, previous findings of reduced MMN amplitude in first episode patients and CHR individuals has led to the suggestion that MMN amplitude reduction has utility as a potential marker for early stages of psychosis.

1.9 Associations of MMN with cognition, symptoms and functioning

1.9.1 Schizophrenia

Besides past studies demonstrating robust impairments in early auditory processing, cognition and functioning in schizophrenia, (D. Umbricht & Krljesb, 2005), several studies have investigated basic auditory processing, as indexed by MMN, in relation to higher cognition, clinical symptoms and daily functioning. Interestingly, a number of studies have found that the degree of MMN impairment is linked to the degree of cognitive impairment (Baldeweg et al., 2004; Kawakubo & Kasai, 2006; S. H. Lee, Sung, Lee, Moon, & Kim, 2014; Miyanishi, Seo, Higuchi, Suzuki, & Sumiyoshi, 2013; Toyomaki et al., 2007), suggesting that MMN may provide insights into the origin of cognitive deficits in schizophrenia. However, this result has not always been replicated and not all studies have found evidence for the association between MMN and neuropsychological deficits in schizophrenia (Brockhaus-Dumke et al., 2005; Y. T. Lin et al., 2012).

Early auditory processing deficits have also been linked to functional impairments, including social cognition (Wynn, Sugar, Horan, Kern, & Green, 2010) and everyday functioning, such as GAF, living in a highly structured setting and socio-occupational functioning, in schizophrenia patients (Fulham et al., 2014; Hermens et al., 2010; M. Kim et al., 2014; S. H. Lee et al., 2014; Light & Braff, 2005; Rasser et al., 2011). This line of evidence supports the cascade model of information processing in which early auditory processing has a flow-on impact on cognition and functioning (Daniel C. Javitt, 2009). With regard to symptoms, while some studies have linked MMN to negative symptoms (e.g.

Javitt, Shelley, & Ritter, 2000; Kasai et al., 2002), and hallucinations (e.g. Youn, Park, Kim, Kim, & Kwon, 2003), two meta-analyses show that majority of studies could not find an association between MMN and symptoms in schizophrenia (Umbricht & Krljesb, 2005; Erickson et al., 2017).

Interestingly, a recent large study of 1415 schizophrenia patients aimed to further disentangle the relationships between MMN, cognitive deficits and functioning. They reported that auditory information processing deficits, as measured by MMN, P3 and reorienting negativity, contributed to functional outcomes through a direct effect on both cognition and negative symptoms, providing evidence for the notion that low level auditory processing impacts higher level cognitive performance and functional outcome. Moreover, this also suggests low level auditory processing to be a potential treatment target to enhance cognition and functional outcome (Thomas et al., 2017).

1.9.2 **Clinical high risk state for psychosis**

Currently very little is known about the association between MMN and cognitive performance in individuals in the high risk stage of psychosis and the existing studies have revealed mixed results. While one study found an association between MMN amplitude and verbal fluency (Higuchi et al., 2013), two other studies did not find any links between MMN and different neuropsychological domains in CHR individuals (Brockhaus-Dumke et al., 2005; Koshiyama, Kirihara, Tada, Nagai, Fujioka, Koike, et al., 2018). Likewise, studies are rare and findings conflicting on the functional significance of MMN in CHR individuals. There is some evidence for a link between early auditory processing and social and role functioning (Daniel C. Javitt & Sweet, 2015) as well as global functioning (Koshiyama, Kirihara, Tada, Nagai, Fujioka, Koike, et al., 2018), however, majority of previous studies have found no correlation between MMN and global functioning in CHR individuals (Jahshan et al., 2012; Shin et al., 2009; Solís-Vivanco et al., 2014). Comparable to findings in schizophrenia patients, majority of studies have failed to find correlations between symptoms and MMN in CHR individuals (Atkinson et al., 2012; Perez et al., 2014; Solís-Vivanco et al., 2014), apart from one study that reported CAARMS positive symptom and total severity scores to be moderately associated with MMN (Shin, Kim, et al., 2012), though the direction was different than hypothesised.

1.10 MMN amplitude as a potential marker for predicting psychosis and clinical outcomes in CHR individuals

Besides previous neurophysiological studies revealing the presence of early auditory processing deficits as indexed by MMN deficits in the high risk stage of psychosis using EEG and MEG, there has also been an interest in examining the utility of MMN deficiency for predicting psychosis in CHR individuals. Indeed, several previous studies have found a reduced baseline MMN amplitude in CHR-Ts compared to CHR-NTs (e.g. Higuchi et al., 2013; Shaikh et al., 2012). On the other hand, not all studies have found reduced MMN amplitude in CHR-Ts compared to CHR-NTs (Atkinson et al., 2017; Hsieh et al., 2012). Interestingly, while a recent meta-analysis of 17 studies reported a medium MMN impairment (ES = 0.40) in CHR individuals irrespective of transition to psychosis, they found a significant difference in effect size between CHR-Ts (0.79) and CHR-NTs (0.17) (Erickson et al., 2016). Furthermore, in addition to studies investigating group differences in MMN between CHR-Ts and CHR-NTs, previous studies have also reported that reduced duration MMN amplitude predicts the onset of psychosis in CHR individuals. For instance, Bodatsch and colleagues (2011) found that besides the baseline group differences in MMN between CHR-Ts and CHR-NTs, MMN was able to predict conversion and enabled stratification of two risk classes that differed regarding time to transition. Similarly, Perez and colleagues (2014) found that MMN to double deviants (frequency + duration) was able to predict time to psychosis onset in CHR individuals. Overall, this line of research suggests MMN deficiency to be a potential marker for predicting onset of psychosis in CHR individuals. However, majority of previous studies have been limited by insufficient power due to small sample sizes, potentially biasing the aforementioned meta-analysis results as well and thus more research is required before conclusions can be drawn.

Research on the utility of neurophysiological measures in predicting other important clinical outcomes in CHR individuals in addition to psychosis is important but currently scarce due to the focus on psychosis as the main interest of outcome. Interestingly, a recent study found that the P300 amplitude was able to predict symptom improvement over a 2-year follow up period, namely higher P300 amplitude was associated with greater negative and general symptom improvement, suggesting the amplitude of P300 to have predictive

validity for a short-term outcome in CHR individuals (M. Kim et al., 2015). Moreover, the same group recently reported that compared to controls and CHR individuals who remitted symptomatically and functionally, the MMN amplitude at baseline was reduced in non-remitters, suggesting MMN to have potential utility as a predictor for remission in addition to transition to psychosis. Finally, while it has been suggested that combining clinical variables with electrophysiological brain measures might improve psychosis prediction in CHR individuals, it remains unknown whether combining MMN with non-imaging markers enhances prediction of other clinically relevant outcomes in CHR individuals (McGuire & Dazzan, 2017; Paolo Fusar-Poli, Borgwardt, et al., 2013). This is an important question in terms of weighting the cost of obtaining an MMN measure compared to clinical and demographic variables that are financially more feasible and practically easier to obtain than electrophysiological measures.

1.11 **Thesis aims**

The main aim of chapter 3 was to investigate the characteristics of early auditory processing as indexed by MEG-based MMNm amplitude responses to both duration deviants and sound omissions in sensor and source space in a large sample of individuals at clinical high risk state for developing psychosis and in a smaller sample of first episode patients and healthy controls. Through this approach, the goal was to investigate whether the well-replicated MMN deficit in chronic schizophrenia (D. Umbricht & Krljesb, 2005) is present already in CHR individuals. The key question I sought to answer was whether MMNm amplitude is compromised prior to psychosis onset and could be a potential marker of risk for psychosis development. I also explored potential MMNm amplitude differences between CHR subgroups theorised to be in different high risk stages based on the two-stage model of clinical risk for psychosis (Frauke Schultze-Lutter et al., 2010). Furthermore, the associations between MMNm amplitudes and cognitive and clinical measures were assessed in the CHR sample to determine whether MMNm impairments are associated with poor functioning and cognitive deficits. The final objective of chapter 3 was to examine the clinical characteristics of community recruited CHR individuals to determine whether, similar to CHR samples identified through specialised early intervention services, this

population is characterised by psychosocial problems and comorbid disorders that require clinical attention.

In addition to the conventional analysis of MMNm peak amplitudes, the aim of chapter 4 was to use dynamic causal modelling (Friston, Harrison, & Penny, 2003) to examine effective connectivity underlying MMNm responses in CHR individuals and healthy controls. More specifically, based on the dysconnectivity hypothesis of psychosis (Friston, 1998) and previous DCM studies reporting disrupted effective connectivity in the MMN brain network in schizophrenia patients (D. Dima, Frangou, Burge, Braeutigam, & James, 2012; Ranlund et al., 2016), I sought to investigate whether altered connectivity is present prior to psychosis onset in the high risk stage of psychosis.

Chapter 5 presents the outcomes of the clinical follow-ups of CHR individuals at 12 months in terms of progression from the high risk stage to the first episode psychosis stage. In addition to transition to psychosis as an outcome of interest, I also examined the rates of both symptomatic and functional remission of CHR-NTs. The first aim of chapter 5 was to investigate whether MMNm amplitude is associated with progression to psychosis by comparing MMNm amplitudes of CHR-Ts and CHT-NTs. Moreover, we examined whether MMNm amplitude is able to discriminate those who achieved symptomatic and functional remission from those who did not. The final goal of chapter 5 was to determine whether MMNm amplitude has utility as a marker for predicting the severity of symptoms or functioning at 12 months in CHR individuals. Given that our study is the first study in a large sample of CHR individuals recruited predominantly from the community, follow-up clinical findings will also be reviewed and discussed to gain novel insights into trajectories of CHR individuals recruited from the community.

2 Methods

The recruitment, participants, study procedure as well as MEG stimuli, recording and data pre-processing covered in chapter 2 are applicable to all following three data chapters (chapter 3, 4 and 5). Chapter-specific statistical analyses are outlined separately in each chapter.

2.1 Recruitment

We recruited participants from different mental health services including the Community Mental Health Teams, the Child and Adolescent Mental Health Service, Early Intervention in Psychosis service and the Glasgow University counselling service. We also recruited participants from the general population through different recruitment strategies including the YouR-study website (https://www.your-study.org.uk/), email invitations to local university and college students in Glasgow and Edinburgh and advertisements on a free newspaper (Metro) and the Glasgow Subway. In addition, letters were sent to general practitioners (GP) and posters placed in the National Health Service clinics in Glasgow and Edinburgh. Finally, databases of GP practices were searched for potential participants who subsequently received an invitation letter that directed them to the YouR-study website. Recruitment pathways for HC, CHR and FEP groups are presented in Table 2.1.

Table 2.1 Recruitment pathways for HC, CHR and FEP groups.

	Recruitment Pathway								
Group	GP	CMHT	CAMHS	ESTEEM	Study Website	SPT Subway	UofG counselling	Third sector	Other
HC	0	0	0	0	0	0	0	0	49
CHR	1	2	3	2	4	1	2	2	88
FEP	0	1	0	1	1	0	0	0	9
Total	1	3	3	3	5	1	2	2	146

GP, General practitioner; CMHT, Community Mental Health Teams; CAMHS, the Child and Adolescent Mental Health Service; ESTEEM, First Episode of Psychosis Service, SPT, Strathclyde Partnership for Transport; HC, healthy control; CHR, clinical high risk; FEP, first episode psychosis.

2.2 Participants

The CHR group consisted of 106 participants that were between 16 to 35 years of age with normal to corrected vision. Participants fulfilled one of the clinical CHR

inclusion criteria based on the positive symptom subscales of the CAARMS (unusual thought content, non-bizarre ideas, perceptual abnormalities and disorganised speech) (Yung et al., 2005) or/and the SPI-A (Schultze-Lutter et al., 2007). Exclusion criteria for the CHR group included 1) existing neurological disorders, 2) metal implants in body, 3) pregnancy and 4) suicidal intent. The FEP group consisted of 17 participants and the inclusion criteria for the FEP group were similar to the CHR group but instead of fulfilling the CHR criteria, participants had experienced a first episode of psychosis based on the DSM-5 295.0. The exclusion criteria for FEP participants was identical to that of CHR participants.

We recruited 49 control participants from the University of Glasgow School of Psychology Subject Pool via email. Exclusion criteria for controls were identical to that of CHR and FEP participants with two additional criteria of not fulfilling the CHR criteria and not having a family history (1st degree relative) of schizophrenia. The Greater Glasgow and Clyde NHS Ethics board reviewed and approved the current study, and a written informed consent was obtained from all participants. All participants were compensated at the standard rate of six pounds per hour for their time.

2.3 Design and procedure

2.3.1 Online screening

Participants were directed to the study website (https://www.your-study.org.uk/) to complete an informed consent for the web screening and two questionnaires: 1) the 16-item version of the prodromal questionnaire (PQ-16) and 2) a 9-item perceptual and cognitive aberrations (PCA) scale that was developed to assess basic symptoms. The PQ-16 was developed from the 92-item prodromal questionnaire and designed for a screening of APS and to preselect participants for a subsequent screening interview. Previous study reported that among general help-seeking individuals a cut-off score of ≥ 6 items out of 16 on the PQ had a 87 % true positive rate and 87 % specificity for distinguishing CHR diagnosis from no CHR diagnosis (Ising et al., 2012). The nine items of the PCA were generated from existing patient descriptions of cognitive and perceptual experiences (Uhlhaas & Mishara, 2007) and from the SPI-A. Participants were

asked to provide ratings based on their experiences in the last 12 months. Participants who scored ≥ 6 items on the PQ and/or ≥ 3 on the PCA were invited through an email to participate in the second part of the study that involved a clinical assessment to determine their CHR status.

2.3.2 **Clinical screening**

All participants provided two informed consent forms, one for the participant and one for the study's records, before the screening assessment and were informed about their right to withdraw from the study at any point without their medical care being affected. Following informed consent, basic demographic information and patient history including family history of mental illness, medication, drug use and psychological treatments were obtained and the SPI-A and the positive symptoms subscales of the CAARMS instrument were administered by trained research assistant and MSc/PhD level researchers. The SPI-A instrument assesses a range of basic symptoms and their severity according to the maximum frequency of occurrence in the past three months. According to the SPI-A, there are two basic symptom criteria: 1) the Cognitive-Perceptive Basic Symptoms (COPER) and 2) the Cognitive Disturbances (COGDIS) criteria. COPER criteria requires the presence of at least 1 of 10 cognitive basic symptoms of at least moderate severity (SPI-A score of ≥ 3) during the last three months with first occurrence more than 12 months ago (Table 2.2). COGDIS symptom criteria requires the presence of at least 2 of 9 cognitive basic symptoms of at least moderate severity (SPI-A score ≥ 3) during the last three months (Table 2.3).

Table 2.2 Cognitive-perceptive basic symptoms criteria based on the SPI-A.

Presence of ≥ 1 of the following 10 basic symptoms with a SPI-A score of ≥ 3 within the last 3 months and first occurrence ≥1 year ago
1. Thought interference
2. Thought blockages
3. Disturbance of receptive speech
4. Thought pressure
5. Unstable ideas of reference
6. Thought perseveration
7. Decreased ability to discriminate between ideas and perception, fantasy and true memories
8. Derealization
9. Visual perception disturbances
10. Acoustic perception disturbances

Table 2.3 Cognitive disturbances criteria based on the SPI-A.

Presence of ≥ 2 of the following 9 basic symptoms with a SPI-A score of ≥ 3 within the last 3 months
1. Inability to divide attention
2. Disturbance of expressive speech
3. Disturbances of abstract thinking
4. Captivation of attention by details of the visual field
5. Thought interference
6. Thought blockages
7. Disturbance of receptive speech
8. Thought pressure
9. Unstable ideas of reference

SPI-A, Schizophrenia Proneness Instrument, Adult Version.

The CAARMS measures intensity, frequency and duration of subthreshold psychotic symptoms, and has shown to have good predictive validity for predicting transition to psychosis (Yung, Yuen, et al., 2003). Intensity and frequency for each subscale is scored on a 7-point Likert scale and distress caused by the symptom on a 0 – 100 scale. The CAARMS differentiates between three UHR-groups: 1) Trait and State Risk Factor Group (Trait), 2) Attenuated Psychotic Symptoms group (APS) and 3) Brief Limited Intermittent Psychotic Symptoms group (BLIPS). The operationalized UHR criteria for each of these groups are shown in Table 2.4. Notably, the current study did not adopt the later addition of a functional decline criterion to the intake CHR criteria. The total CAARMS symptom severity was operationalised as the sum of the global rating scale score multiplied by the frequency score of the four subscales (Morrison et al., 2012).

Overall functioning was assessed with the Global Assessment of Functioning (adapted from (Hall, 1995)) measure that is part of the CAARMS and is used to establish the level of functioning. It is a numeric scale ranging from 0 (in persistent danger) to 100 (superior functioning) to rate the social, occupational and psychological functioning of participants excluding impairment in functioning due to physical health or environmental limitations.

Table 2.4 Summary of ultra-high risk criteria based on the CAARMS.

Group	Intake criteria checklist
Trait Group	- Family history of psychosis in first-degree relative month, occurred during last year or GAF score of 50 for last year or longer
APS: subthreshold intensity	- Severity scale score of 3-5 on Unusual Thought Content subscale or Non-bizarre Ideas subscale, 3-4 on Perceptual Abnormalities subscale or 4-5 on Disorganized Speech subscales of the CAARMS - Frequency scale score of 3–6 on Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities or Disorganised Speech subscales of the CAARMS - For at least 1 week - Symptoms present in past year
APS: subthreshold frequency	- Severity scale score of 6 on Unusual Thought Content, Non-Bizarre Ideas or Disorganised Speech subscales or 5-6 on Perceptual Abnormalities of the CAARMS - Frequency scale score of 3 on Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities or Disorganised Speech subscales of the CAARMS - Symptoms present in past year
BLIPS Group	- Severity scale score of 6 on Unusual Thought Content, 6 on Non-Bizarre Ideas, 6 on Disorganised Speech subscales or 5-6 on Perceptual Abnormalities of the CAARMS - Frequency scale score of 4-6 on Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities or Disorganised Speech - Each episode of symptoms is present for less than one week and symptoms spontaneously remit on every occasion - Symptoms occurred during last year

APS, Attenuated Psychotic Symptoms; BLIPS, Brief Limited Intermittent Psychotic Symptoms

2.3.3 **Baseline visits**

Following the baseline clinical screening, participants were invited for a second visit that included a battery of questionnaires (Mini International Neuropsychiatric Interview 6.0, Scale for Premorbid Adjustment, Global Functioning Social and Role Scale). The Global Functioning: Social and the Global Functioning: Role measures were developed to measure prodromal functioning

and to cover the age range typical of the prodromal phase, disentangle social from role functioning and provide a brief and easy to use clinician ratings (Cornblatt et al., 2007).

The third visit included administering the Brief Assessment of Cognition in Schizophrenia (BACS) version 3.1 to assess six domains of cognition, namely verbal memory and learning (list learning task), working memory (digit sequencing task), motor speed (token motor task), verbal fluency (semantic fluency task), executive function (Tower of London task) and processing speed (symbol coding task) (Keefe et al., 2004). Following the neuropsychological visit, participants were invited for a brain imaging visit, including an MEG recording and an MRI scan session.

2.3.4 **Follow-up assessments**

CHR participants were followed up for 12 months (at 6, 9 and 12 months). The four positive symptom subscales of the CAARMS instrument, Global Assessment of Functioning and self-report questionnaires were re-administered at every follow-up, namely at 6, 9 and 12 months. Global Functioning: Social and Global Functioning: Role Scale were assessed at 6 and 12 months. The Structured Clinical Interview 1 (SCID-1) for DSM-5 is a semi-structured interview for making the major DSM-5 diagnoses and was administered at 6 and 12 months.

2.3.5 **Data acquisition**

MEG recordings were conducted at the Centre for Cognitive Neuroimaging at the University of Glasgow on average 84.7 (SD = 76.1) days following the first clinical interview. During the MEG recording session, participants were seated in a reclining chair and asked to support their head against the back of the helmet of the MEG dewar to minimize head movement. Participants performed a short practice run to get familiar with the visual letter detection task and we checked that the tones presented were balanced in loudness between the ears. During the recording session, participants were instructed to sit as still as possible, ignore the auditory stimuli and respond as quickly as possible to the target letters by pressing a button on a response pad with their right index finger (LUMItouch, Lightwave Technologies, Surrey, BC, Canada).

MEG data was recorded with a 248-magnetometer whole-head MEG system (MAGNES® 3600 WH, 4-D Neuroimaging, San Diego) in a dimly lit magnetically shielded room. Prior to data acquisition, we attached five head position indicator coils to the participant's head to record the head position within the MEG helmet before and after each block. Blocks with head movements exceeding the threshold of 1.0 cm were repeated to avoid source localization errors. For each participant the positions of the head coils, three anatomical fiducial points (the nasion and the right and left preauricular) and their head shape were digitized using a 3D digitiser (FASTRAK®, Polhemus Inc., VT, USA). We used the digitized fiducial markers and the head shape for subsequent coregistration of the structural MRIs with the MEG data. Neuromagnetic signals were acquired at a 1017.25 Hz sampling rate with a bandwidth of 400 Hz.

After the MEG recording a high-resolution anatomical MRI scan was acquired for each participant using a 3D magnetization-prepared rapid-acquisition gradient echo sequence (160 slices; voxel size: $1mm^3$; FOV: 256 mm; TR: 2300 ms; TE: 3.93 ms). Scanning was performed with a 3-Tesla Siemens Trio scanner.

2.4 MEG stimuli and task

2.4.1 Auditory mismatch negativity paradigm

All sounds were computer-generated complex sinusoidal sounds (400Hz * 800Hz) with 7-ms ascending and descending ramps. Series of four or five brief sounds were presented with a fixed stimulus onset asynchrony (SOA) of 150 ms and with a randomized inter-stimulus interval (ISI) that was jittered between 700 to 1000 ms. Three types of auditory stimuli were presented: standard, deviant and omission trials. Standard trials contained five identical sounds, deviant trials comprised four identical sounds and a fifth duration-deviant sound, and omission trials contained only four identical sounds. The standard sound duration was 80 ms and the deviant sound duration was 40 ms. All sounds were presented at the default level of 81 dB unless a participant’s hearing was too impaired (93 dB) or sensitive (71 dB) to be loud enough or comfortable. The auditory stimuli were presented as three blocks, each block consisting of 200 trials and lasting approximately five minutes. Each block consisted of 120 standard trials that

were presented with a probability of 0.6, 40 deviant trials with a probability of 0.2 and 40 omission trials with a probability of 0.2. The trials were presented in pseudorandomized order so that each block started with three standard trials before delivering the first deviant/omission trials and two deviant trials were never consecutive (Figure 2.1). The auditory stimuli were presented binaurally via MEG-compatible 6-meter-long plastic tubes attached to earplugs using an Etymotic ER-30 system (Etymotic Research, Inc. United States of America). The MEG tasks were presented using Presentation® software (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA).

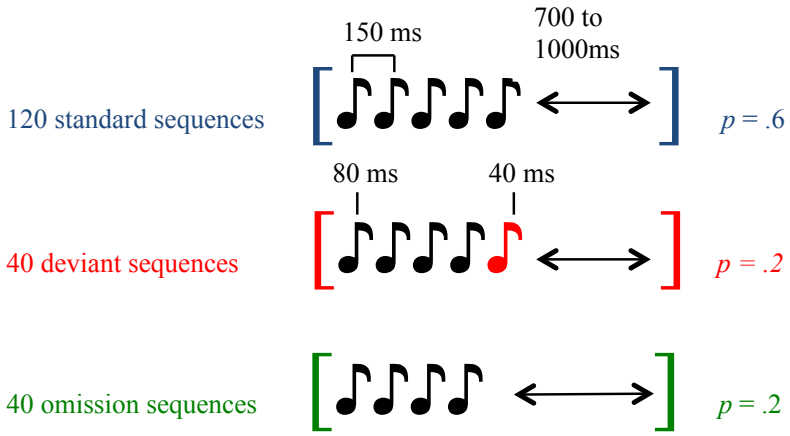


Figure 2.1 Auditory mismatch negativity paradigm. All three types of auditory sequences presented with a SOA of 150 ms. The ISI between two series varied from 700 to 1000 ms.

2.4.2 **Visual letter detection task**

The auditory MMNm paradigm was combined with a visual letter detection task to control for potential attention effects. The visual stimuli consisted of 20 target letters (X) and 100 non-target letters (R, S, T, U, V, W, Y, Z) that were pseudo-randomized throughout the auditory series. Visual targets were always presented during standard trials and were time-locked to the presentation of the first sound. Both target and non-target letters were presented for 150 ms. The font-size was increased when necessary for participants with poor vision without their glasses. Viewing distance was approximately 80 cm.

2.5 Data analyses

2.5.1 MEG data pre-processing

I used an open source software package FieldTrip (Oostenveld, Fries, Maris, & Schoffelen, 2011) in Matlab (MathWorks, Natick, MA, USA) programming environment to pre-process MEG data. I segmented continuous MEG data into epochs of 1400 ms (200 ms pre-stimulus to 1200 ms post-stimulus), filtered epochs to remove power-line noise (50 100 150 Hz) using a discrete 50 HZ Fourier transform filter and used a z-score-based algorithm with a cut-off point of 20 to check semi-automatically for muscle artifacts and superconducting quantum interference device jumps. Then I denoised epochs using the reference sensor data recorded by 23 MEG reference channels and re-sampled the data from 1 kHz to 500 Hz and detected noisy channels by visual inspection and rejected them on a subject-to-subject basis. On average I identified and rejected six bad channels per subject. Subsequently I used an independent component analysis (Bell & Sejnowski, 1995) to detect and remove components containing muscle activity and electrooculographic and electrocardiographic artifacts from the MEG signals using the FieldTrip implemented 'runica' method. On average 3,4 components (minimum of 2 components and maximum of 8 components) per participant were identified as representing muscle, ocular or cardiac artifacts based on the spatial topography and the time course of the components and subsequently removed from the signal. I interpolated the rejected channels using the nearest-neighbour approach. After pre-processing, there were sensor level data for 49 controls, 106 CHR participants and 17 first episode patients, overall 172 participants. The average standard, deviant and omission trial numbers (standard deviations are in parentheses) were 296 (8.7), 113 (5.6) and 112 (5.6) for the controls, 290 (14.7), 111 (6.8) and 110 (5.7) for CHR participants and 288 (9.5), 110 (5.1) and 110 (5.8) for the first episode patients.

Lastly I band-pass filtered the data between 1 Hz and 20 Hz and baseline corrected trials using the average activity between 200 to 0 ms pre-stimulus activity (the first 200 ms of each epoch). Then I averaged the artifact-free trials separately for each condition. For sensor level analyses the averaged axial (ERF) data were transformed to planar gradient configuration using the nearest-

neighbour method to facilitate the topographical interpretation of the data (Hämäläinen et al., 1993). The durMMNm response was computed by subtracting the waveform to the standard stimuli from the waveform to the deviant stimuli and in a similar manner the omiMMNm response was computed by subtracting the waveform to the standard sound from the waveform to the omitted sound. Latencies of both durMMNm and omiMMNm responses refer to the onset of the deviant or omitted sound (600 ms) rather than the onset of the sequence of five sounds.

2.5.2 **Virtual channels**

To assess potential group differences in durMMNm or omiMMNm peak amplitudes in specific regions of interests (ROI), I computed artifact-free virtual channel time-series at seven pre-specified ROIs for each participant. ROIs were defined for the left and right Heschl's gyri (HG), superior temporal gyri (STG) and middle temporal gyri (MTG) and the right inferior frontal gyrus (IFG) (Figure 2.2) based on the Automated Anatomical Labelling atlas (AAL) that is widely used for macroanatomical parcellation. The selection of these seven ROIs was based on previous source localization studies reporting generators of MMN in both frontal and temporal regions including HG, STG and MTG using EEG/MEG (Doeller et al., 2003; Fulham et al., 2014; Marco-Pallarés et al., 2005; Sauer et al., 2017) and DCM (Garrido et al., 2008; Garrido, Kilner, Kiebel, & Friston, 2009). See Figure 2.2 for the exact locations of the nodes that I extracted time courses from and Table 2.5 for the Montreal Neurological Institute (MNI) coordinates of those ROIs.

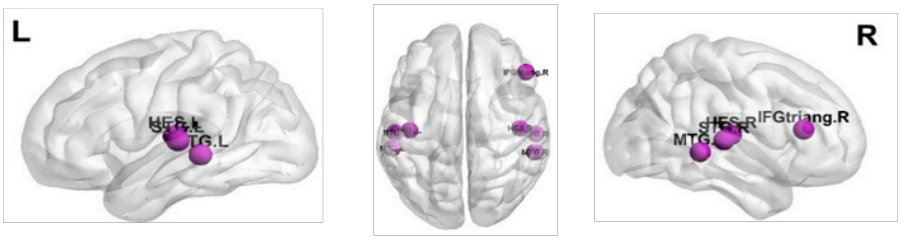


Figure 2.2 Regions of interests used for source level analyses.

Table 2.5 Abbreviations and MNI coordinates of regions of interests.

Node	Abbreviation	MNI coordinate		
		x	y	z
Left heschl's gyrus	L HG	-42	-19	10
Right heschl's gyrus	R HG	46	-17	10
Left superior temporal gyrus	L STG	-53	-21	7
Right superior temporal gyrus	R STG	58	-22	7
Left middle temporal gyrus	L MTG	-56	-34	-2
Right middle temporal gyrus	R MTG	57	-37	-2
Right inferior frontal gyrus	R IFG	50	30	14

Using the Linearly Constrained Minimum Variance (LCMV) beamformer (Veen, Drongelen, Yuchtman, & Suzuki, 1997) and 5 % regularization I computed the spatial filters for the aforementioned seven ROIs and multiplied each of them with the original MEG data to reconstruct standard, deviant and omission source level time-series. To compute the duration and omission MMNm difference waveforms and to average virtual channels across participants, I used absolute values to avoid cancellation due to opposite polarities. This procedure resulted in virtual channel time-series data for 48 controls, 103 CHR participants and 16 first episode patients, overall 167 participants. There was a loss of 1 HC, 3 CHR and 1 first episode patient due to T1 being unavailable and thus source reconstruction was not possible for these participants.

2.6 **Statistical analyses**

2.6.1 **General**

All statistical analyses were performed using R statistical software (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria) or the Statistical Package for Social Sciences (SPSS) version 22 (IBM Corp.).

In general, if the sample size was < 30 and the central limit theorem could not be applied and the Kolmogorov-Smirnov test (sample > n = 50) or the Shapiro-Wilk's test (sample < n = 50) indicated that the normality assumption was violated I used an equivalent non-parametric test. More specifically, in case data did not meet the assumptions of the parametric test, I used the Wilcoxon Rank sum test instead of the (dependent, two-tailed) paired t-test, the Mann-Whitney U test instead of the (independent, two-tailed) unpaired t-test, the Kruskal-

Wallis test instead of a one-way ANOVA, the Friedman Test instead of a one-way ANOVA with repeated measures and Spearman correlation instead of Pearson correlation. Bonferroni correction was applied for further analysis of effects that emerged from ANOVAs to avoid type 1 error and to adjust for multiple comparisons. A two-tailed alpha level of 5 % was considered significant throughout unless otherwise stated. Effect sizes for statistical tests were reported using Cohen's *d* that is calculated as the difference between the means divided by the pooled standard deviation. *D* = 0.2 is considered a small effect size, *d* = 0.5 a medium effect size and *d* = 0.8 a large effect size.

2.6.2 Analyses of demographic and clinical characteristics between groups

I run a one-way analysis of variance (ANOVA) or an independent *t*-test for continuous variables and a chi-square test for categorical variables to investigate any potential group differences in baseline and follow-up demographic and clinical characteristics. Post-hoc pairwise comparisons with Bonferroni correction were performed after a significant omnibus test.

2.6.3 Individual peak latency and amplitude estimation

2.6.3.1 Sensor space

At the sensor level, individual peak latencies, namely the time point with the highest amplitude, were automatically extracted on a subject-to-subject basis using search windows based on visual inspection of grand average planar transformed waveforms extracted from averaged data across twelve sensors of interest (SOI) over auditory regions (Left hemisphere: 'A97', 'A98', 'A129', 'A130', 'A157', 'A158', right hemisphere: 'A112', 'A113', 'A144', 'A145', 'A171', 'A172', highlighted in red in Figure 2.3). Peak latencies were estimated separately for the left and right hemisphere by extracting averaged data across the SOIs over the left and right hemisphere. Peak amplitude values were then computed as the maximum value at the time of the peak latency for both hemispheres.

For the between-condition analyses, individual peak ERF latencies in response to standard and deviant/omitted stimuli were automatically extracted on a subject-by-subject basis from a search window of 170-230 ms post stimulus for

the durMMNm effect and 46 – 56 ms and 110-120 ms for the omiMMNm effect using the quantification method outline above. For the group analyses, the automatic peak detection algorithm was used to extract peak MMNm latencies from averaged data across the SOIs over the left and right hemisphere from individual participant waveforms using a latency window of 160 to 210 ms for durMMNm and 40 to 130 ms for omiMMNm based on the grand average peaks.

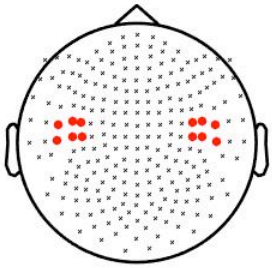


Figure 2.3 MEG sensors of interests used to extract sensor level data.

2.6.3.2 **Source space**

At the source level, individual peak latencies were computed for each ROI (the left and right Heschl's gyri (HG), superior temporal gyri (STG) and middle temporal gyri (MTG) and the right inferior frontal gyrus (IFG)) by extracting activity from a voxel within that ROI. Subsequently peak amplitude values were computed for each ROI using the identified peak latency.

To assess the presence of a statistically significant MMNm effects in each ROI, individual ERF peak amplitudes elicited by standard, deviant and omitted stimuli were automatically extracted from a search window of 160 – 220 ms for durMMNm and 40 – 60 and 110 - 130 ms for omiMMNm based on inspection of grand average waves. To examine potential group differences in duration or omission MMNm peak amplitudes in any ROI, individual MMNm peak amplitudes were extracted from each ROI using the same search windows (160 to 210 ms for durMMNm and 40 to 130 ms for omiMMNm) as for the sensor level data. I performed a non-parametric Kruskal-Wallis H test due to non-normally distributed data to compare MMNm peak amplitudes between groups separately in each ROI.

3 Neuromagnetic Mismatch Negativity in Clinical High Risk and Early Stages of Psychosis

3.1 Introduction

Auditory mismatch negativity (MMN; Näätänen, Gaillard, & Mäntysalo, 1978) and its magnetic counterpart (MMNm; Hari et al., 1984) is a component of the ERP/ERF evoked by an unexpected deviant stimulus presented in a series of repetitive auditory stimuli. Reduced MMN amplitude, a neurophysiological index of an early auditory processing dysfunction, is a robust finding in chronic schizophrenia patients with a large effect size of 1.0 (Cohen's *d*) (Erickson et al., 2016; D. Umbricht & Krljesb, 2005). Moreover, while some findings of original studies examining MMN amplitude in first episode patients have been inconsistent, a recent meta-analysis provided evidence for a medium size MMN reduction (ES = 0.42) in first episode psychosis (Erickson et al., 2016). Most interestingly, recent studies have found MMN deficits to be present in individuals at clinical high risk state for developing psychosis, suggesting MMN amplitude to be compromised prior to psychosis onset and possibly represent a marker of risk for psychosis development (e.g. Shin et al. 2009; Shaikh et al. 2012; Atkinson et al. 2012; Perez et al. 2014). On the other hand, other studies have not been able to replicate this finding (E Bramon, 2004; Hirt et al., 2019; M. Kim et al., 2014; Magno et al., 2008; Price et al., 2005; Salisbury, Kasai, et al., 2007) and thus it remains unclear whether reduced MMN amplitude is present already in the high risk stage of psychosis.

It has been suggested that inconsistent results regarding MMN deficits in CHR individuals might be due to high clinical heterogeneity within the high risk stage (Fusar-Poli, 2015). Indeed, typically CHR studies have not considered the potential existence of CHR subgroups but treated them as one clinical entity (Paolo Fusar-Poli, Cappucciati, et al., 2016; Frauke Schultze-Lutter et al., 2010). Thus, it could be beneficial to stratify neuroimaging data on the basis of CHR individuals that are in the EPS, defined by the presence of BS, and those in the LPS, defined by the presence of APS, as recommended by the two-stage model of clinical risk for psychosis (Häfner et al., 2004; Keshavan, DeLisi, & Seidman, 2011). This theoretical separation of the high risk stage is supported by empirical cross-sectional evidence demonstrating CHR individuals in the EPS to have better

cognitive performance (Frommann et al., 2011), higher P300 amplitude (Frommann et al., 2008) and less pronounced structural abnormalities (Koutsouleris et al., 2009) than CHR individuals in the LPS. However, to date there are no studies comparing MMN in CHR individuals in different high risk stages and accordingly the first goal of the chapter was to explore whether MMNm amplitudes differ between CHR subgroups.

The primary aim of the chapter was to investigate MMNm amplitudes in a large sample of CHR individuals predominantly recruited from the general population and compare them to a smaller sample of first episode patients and controls to examine whether the well-replicated MMN deficiency observed in chronic schizophrenia is present already during the high risk and early stage of psychosis. In addition, as heterogeneous recruitment methods may result in a variance of pre- and post-test risk for psychosis across CHR samples (Paolo Fusar-Poli, Schultze-Lutter, et al., 2016), potentially due to different combinations of risk and protective factors (Os & Guloksuz, 2017), questions have been raised regarding the comparability of samples recruited from different pathways (Oliver, Radua, Reichenberg, Uher, & Fusar-Poli, 2019). Indeed, a recent study found that CHR individuals recruited through the community differed from clinically recruited CHR individuals in terms of symptoms, functioning (Mills, Fusar-Poli, Morgan, Azis, & McGuire, 2017) and the most frequent comorbid diagnosis (Shi et al., 2017). Hence, we also compared CHR individuals recruited from the general population with those recruited through clinical pathways to explore potential group differences in neurophysiological as well as clinical and neuropsychological characteristics.

In addition to examining the presence of reduced MMN in different stages of psychosis, past studies have also examined its association with cognition and functioning. Interestingly, MMN deficits have not only been shown to be associated with cognitive impairments (Baldeweg et al., 2004; Kawakubo & Kasai, 2006; S. H. Lee et al., 2014; Miyanishi et al., 2013; Toyomaki et al., 2007) and poor functioning (Fulham et al., 2014; Hermens et al., 2010; M. Kim et al., 2014; S. H. Lee et al., 2014; Light & Braff, 2005; Rasser et al., 2011) but to directly impact higher cognition and negative symptoms in schizophrenia (Thomas et al., 2017), in line with the notion that early auditory processing

dysfunctions contribute to cognitive impairments (Daniel C. Javitt, 2009). However, much less is known about the association of MMN amplitude with cognition and functioning in the high risk stage of psychosis with previous studies reporting inconsistent results as discussed in the introduction chapter. Hence, the final aim of the chapter was to explore relationships between early auditory sensory information processing as indexed by MMNm amplitude and higher order cognition and functioning in the CHR sample.

3.1.1 Hypotheses

The following hypotheses will be tested:

(1) Compared to controls, the BS + UHR group exhibits the most impaired MMNm peak amplitude, followed by the UHR and finally the BS group.

(2) MMNm peak amplitudes are reduced in CHR individuals compared to healthy controls but to a lesser degree than in first episode patients.

(3) CHR individuals recruited through clinical pathways have a smaller MMNm amplitude compared to community recruited CHR individuals.

(4) Greater levels of auditory processing deficits, indexed by attenuated MMNm amplitudes, are associated with cognitive impairment and poor functioning in CHR individuals.

3.2 Methods

The methodology of the current chapter including the recruitment, participants, study procedure as well as MEG stimuli, recording and data pre-processing are presented in chapter 2 (Methods).

3.2.1 Statistical analyses

3.2.1.1 MMNm analyses in sensor space

In order to evaluate the presence of significant MMNm effects across groups, the individual ERF peak amplitudes elicited by standard and deviant stimuli over the left and right hemisphere were assessed via a 2 x 2 repeated-measures ANOVA

with hemisphere (left, right) and stimulus type (standard, deviant) as within-subjects factors. To assess potential group differences, mixed-design ANOVAs with one within-subjects factor of hemisphere with two levels (left, right) and one between-subjects factor of group were performed for analyses of durMMNm and omiMMNm and post hoc tests were used to confirm the sources of significant ANOVA effects.

In addition to examining whether the HC, CHR and FEP groups differed in their central tendency of MMNm peak amplitude I also used a shift function (Rousselet, Pernet, & Wilcox, 2017) to compare full distributions of peak MMNm amplitudes to examine potential group differences in any part of the MMNm distributions. The deciles (the value at each tenth percentile of the distribution) of each group distribution were computed, the amplitude of Group 1 was subtracted from Group 2 at each decile and 95 % confidence intervals of the decile differences computed using a percentile bootstrap.

3.2.1.2 **MMNm analyses in source space**

Using the individual ERF peak amplitudes elicited by standard, deviant and omitted stimuli I performed a paired samples *t*-test to compare the peak amplitudes to assess the presence of a statistically significant MMNm effect in each ROI. To investigate group differences in MMNm responses, non-parametric Kruskal-Wallis H tests were conducted to compare MMNm peak amplitudes between groups separately in each ROI.

3.2.1.3 **Correlations between MMNm amplitudes and cognition, symptoms and functioning**

We explored associations between both durMMNm and omiMMNm peak amplitude values (overall 18 indices) and cognition (six domains and composite score), symptoms (CAARMS positive symptom severity score) and functioning (GAF score) in the CHR group using non-parametric two-tailed Spearman rank correlations. Due to multiple correlations, we used a more conservative *p* value of .01 for significance.

3.2.1.4 Predicting the GAF score from suicidality, comorbidity and symptom severity

A three stage hierarchical multiple regression with the enter method was conducted with the GAF score as the dependent variable. The presence of suicidal ideation was entered at stage one of the regression (coded as 0 = “no”, 1 = “yes”), comorbidity of mood or anxiety disorders (coded as 0 = “no”, 1 = “yes”) at stage two and finally the CAARMS symptom severity at stage three. The predictor variables were entered in this order to assess whether the severity of APS increases the variance explained in the GAF score over and beyond the presence of suicidal ideation and comorbidity of anxiety/mood disorders.

3.3 Results

3.3.1 Demographic and clinical characteristics

3.3.1.1 HC, CHR and FEP groups

Table 3.1 presents a summary of key demographic and clinical measures contrasting the HC, CHR and FEP groups at baseline. The groups differed in age, years of education, medication, psychological treatment and a family risk for schizophrenia. Post hoc pairwise comparisons showed that compared to controls, CHR participants were significantly more likely to have lower education, use prescription medication, especially anti-depressants (24,5 %), have a first-degree relative with a diagnosis of schizophrenia, received psychological treatment and had a higher level of current suicide risk (53 %) than controls. Compared to first episode patients, CHR participants were significantly younger. First episode patients were significantly more likely to use prescription medication, received psychological treatment and have a first-degree relative with schizophrenia compared to controls.

As expected, the CHR group had significantly lower global, social and role functioning and higher APS severity than the HC group but higher global functioning and lower APS severity than the FEP group. The three groups differed in verbal memory, motor speed, processing speed and the BACS composite score. The post hoc results showed that the CHR group had a significantly poorer motor speed, processing speed and the BACS composite

score than the HC group but better than the FEP group. The FEP group had a significantly poorer verbal memory performance than the HC group.

Table 3.1 Baseline demographic and clinical characteristics of HC, CHR and FEP groups.

Measure	Sub-Measure	HC (n = 49)	CHR (n = 106)	FEP (n = 17)	Statistics	Significance	Post Hoc
Age		22.5 (3.57)	21.7 (4.53)	23.9 (4.08)	H (2) = 7.25	p = .027[a]	CHR < FEP
Gender	Male	16	28	8	x^2 (2) = 3.15	n.s. (.207)	
	Female	33	78	9			
Employment	Full time paid	3	2	0	x^2 (12) = 20.70	n.s. (.06)	
	Part time paid	2	7	1			
	Voluntary	1	1	0			
	Student	41	87	7			
	Unemployed	2	7	2			
Years of Education		16.6 (3.03)	15.1 (3.29)	14.6 (2.58)	H (2) = 8.83	p = .012[a]	HC > CHR
Medication +	Any medication	0	55	9	x^2 (10) = 50.17	p < .001	HC < CHR & FEP
	None	49	50	3			
Treated Mental Health Problems	None	46	38	4	x^2 (4) = 49.97	p < .001	HC< CHR & FEP
	Current	0	17	4			
	Past	3	105	12			
Family History (1st Degree) +	No	49	94	10	x^2 (2) = 6.26	p = .04	HC < CHR & FEP
	Yes	0	10	2			
GAF		87.6 (6.44)	59.0 (13.19)	43.0 (15.72)	H (2) = 95.03	p < .001[a]	HC > CHR & FEP,
GF: Social scale		8.82 (.391)	7.54 (1.074)		U = 722	p < .001[a]	HC > CHR
GF: Role scale		8.57 (.764)	7.50 (1.09)		U = 989.5	p < .001[a]	HC > CHR
CAARMS severity		.73 (2.35)	27.90 (16.75)	89.45 (25.57)	F (2, 163) = 167.25	p < .001	HC < CHR & FEP,
Current Suicide Risk	No	48	49		x^2 (6) = 37.20	p < .001	HC < CHR
	Yes Low	1	25				
	Yes Moderate	0	14				
	Yes High	0	16				
Verbal memory		51.37 (9.04)	48.70 (11.21)	42.00 (13.06)	F (2, 163) = 3.356	p = .037	HC > FEP
Motor speed		81.04 (11.60)	69.29 (15.62)	57.60 (9.28)	F (2, 163) = 16.911	p < .001	HC > CHR & FEP,
Processing speed		73.20 (11.75)	66.47 (13.50)	52.55 (14.40)	F (2,164) = 12.20	p < .001	HC > CHR & FEP,
Verbal fluency		58.29 (13.89)	56.88 (12.78)	53.45 (9.75)	F (2, 163) = .654	n.s. (.521)	
Executive function		18.65 (1.77)	18.18 (2.47)	17.82 (3.37)	F (2, 162) = .904	n.s. (.407)	
Working memory		21.06 (2.77)	20.63 (4.04)	20.09 (4.13)	F (2, 164) = .396	n.s. (.674)	
BACS composite score		303.19 (24.85)	280.60 (40.49)	248.00 (30.79)	F (2, 159) = 11.61	p < .001	HC > CHR & FEP, CHR > FEP

HC, healthy control; CHR, clinical high risk; FEP, first episode psychosis; n.s., non-significant; GAF, Global Assessment of Functioning; GF, global functioning; CAARMS, comprehensive assessment of at risk mental states; BACS, brief assessment of cognition in schizophrenia; [a] Non-normal distribution in the sample (Kolmogorov–Smirnov test; $p < .05$). Frequencies are reported for categorical variables, group means and standard deviations (in parenthesis) are reported for continuous variables, $p > 0.05$ listed as non-significant, + medication and 1st degree family history of schizophrenia was an exclusion criterion for controls.

Compared to controls, CHR individuals were significantly more likely to have the following psychiatric disorders based on the Mini International Neuropsychiatric Interview: major depressive episode (current and past), panic disorder (lifetime and current), social phobia (current), obsessive-compulsive disorder (current) and generalised anxiety disorder (Appendix A.1).

3.3.1.2 **Community vs clinically recruited CHR groups**

Twelve out of 106 (11.3 %) CHR individuals were recruited through clinical pathways. The clinically referred CHR group differed from the community recruited CHR group (n = 94) in employment, years of education, role functioning and the BACS composite score (Table 3.2).

Table 3.2 Baseline demographic and clinical variables of community and clinically recruited CHR groups.

Measure	Sub-Measure	Community recruited (n = 94)	Clinical referrals (n = 12)	Statistics	Significance
Age		21.97 (4.60)	20 (3.72)	*U* = 405	n.s. (.121)
Gender	Male	24	4	$x^2(1) = .333$	n.s. (.394)
	Female	70	8		
Handedness	Left	3	1	$x^2(2) = 5.130$	n.s. (.077)
	Right	58	5		
	Amdidextrous	10	4		
Employment	Full time paid	2	0	$x^2(5) = 24.65$	*p* < .001
	Part time paid	6	0		
	Voluntary	1	0		
	Student	79	8		
	Unemployed	3	4		
Years of Education		15.43 (3.12)	12.67 (3.70)	*U* = 259	*p* = .002
Medication	Any medication	46	9	$x^2(1) = 2.89$	n.s. (.08)
	None	48	3		
Treated Mental Health Problems	None	34	4	$x^2(2) = .781$	n.s. (.677)
	Current	14	3		
	Past	45	5		
Family History (1st Degree)	No	86	10	$x^2(1) = .829$	n.s. (.315)
	Yes	8	2		
Global Assessment of Functioning		59.31 (13.60)	56.25 (9.40)	*t* (103) = .755	n.s. (.452)
GF: Social scale		7.59 (1.067)	7.17 (1.03)	*U* = 426.5	n.s. (.165)
GF: Role scale		7.58 (1.067)	6.83 (1.15)	*U* = 338	*p* = .018
CAARMS severity		28.59 (17.28)	22.50 (10.92)	*U* = 445	n.s. (.255)
Comorbid anxiety/depression	No	35	5	$x^2(1) = .046$	n.s. (.533)
	Yes	56	7		
Suicidal ideations	No	44	5	$x^2(1) = .162$	n.s. (.464)
	Yes	48	7		
BACS composite score		284.40 (37.591)	249.55 (53.038)	*t* (100) = 11.247	*p* = .007

GF, global functioning; CAARMS, comprehensive assessment of at risk mental states; BACS, brief assessment of cognition in schizophrenia; n.s., non-significant.

3.3.2 **MMNm analyses**

The results of subgroup analyses showed no significant differences in MMNm amplitudes between the three CHR subgroups, namely BS, UHR and BS + UHR (Appendix A.2), and thus the CHR subgroups were grouped into one CHR sample, which was used in the subsequent analyses.

3.3.2.1 **Sensor level analyses**

3.3.2.1.1 Condition effect across groups

At the sensor level analysis, visual inspection of grand average planar transformed waveforms revealed a peak latency of 200 ms post stimulus for standard sounds and 185 ms for deviant sounds (Figure 3.1A). A 2 x 2 repeated-measures ANOVA revealed a significant interaction (F (1, 171) = 22.15, p < .01) between stimulus type and hemisphere, which was due to higher ERF peak amplitudes to deviant compared to standard stimuli over the right hemisphere (Table 3.3). In analysis of the omiMMNm, grand average omiMMNm waveforms derived from averaged data across the twelve SOIs revealed two peaks: 52 ms

and 115 ms after the omitted stimulus (Figure 3.1B). A 2 x 2 repeated-measures ANOVA was performed on the ERF peak amplitudes in both time intervals of interest (TOI; 46 – 56 ms and 110 – 120 ms after the stimulus omission). There was a significant interaction (F (1, 171) = 22.13, p < .01) between stimulus type and hemisphere in the first TOI (46 – 56 ms), which was due to higher ERF peak amplitudes elicited by omitted compared to standard stimuli over the right hemisphere. In the second TOI (110 – 120 ms) there was a significant main effect of stimulus type (F (1,171 = 33.78, p < .01) and a significant main effect of hemisphere (F (1,171) = 23.05, p < .01), indicating that the ERF responses were higher over the right hemisphere compared to the left hemisphere across stimulus types. There was no significant interaction (F (1, 171) = .47, p = .49) between stimulus type and hemisphere in the second TOI. The distributions of individual ERF peak amplitudes elicited by standard, deviant and omitted sounds are presented in Appendix A.3.

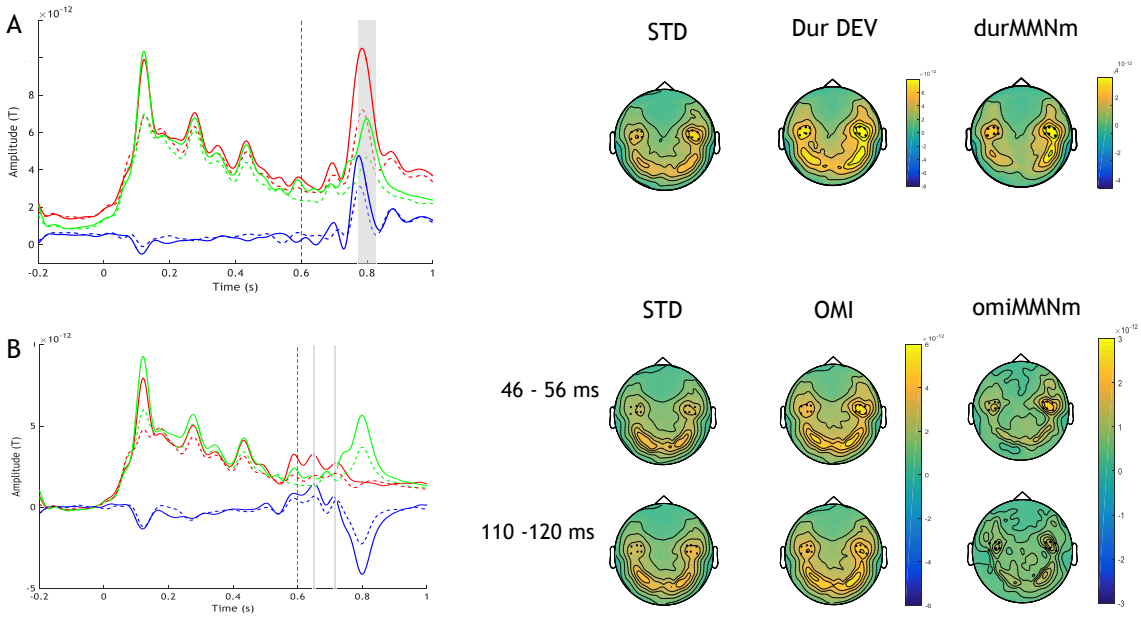


Figure 3.1 Sensor level durMMNm and omiMMNm waveforms and topographic plots. Time courses of grand average planar ERF responses to standard sounds (green line), deviant sounds (red line) and MMNm difference waveform (blue line) extracted from averaged data across the six left (dashed line) and right (solid line) sensors of interests as marked by the black dots in the topographic plots. The dotted line at the time point of 0.6 seconds indicates the fifth standard and deviant sound onset. Topographic maps of standard, deviant and MMNm waveforms in the TOIs (grey shaded areas) which were used to extract individual ERF peak amplitudes. The top panel (A) presents the durMMNm effect and the bottom panel (B) presents the omiMMNm effect. STD, standard; Dur DEV, duration deviant; OMI, omission.

Table 3.3 Sensor level means and standard deviations of ERF peak amplitudes to standard and deviant stimuli over the left and right hemisphere.

	Stimulus		
Hemisphere	Standard	Deviant	STD vs DEV *d*
durMMNm			
Left	5.24 (2.62)	8.32 (4.74)	0.8
Right	7.22 (3.20)	11.79 (5.34)	1.04
omiMMNm 1st TOI			
Left	2.46 (1.20)	3.64 (1.92)	0.74
Right	3.13 (1.41)	5.06 (2.48)	0.96
omiMMNm 2nd TOI			
Left	3.01 (1.38)	3.78 (1.97)	0.45
Right	3.63 (1.76)	4.55 (2.64)	0.41

3.3.2.1.2 Group effect

In the sensor level analysis of durMMNm amplitudes, grand average waveforms extracted from the twelve SOIs revealed peak latencies of 174, 174 and 182 ms post stimulus for the HC, CHR and FEP group, respectively (Figure 3.2). A 2 x 3 mixed-design ANOVA revealed a significant main effect of hemisphere (F (1, 169) = 25.18, p < .01). However, there was no significant main effect of group (F (2, 169) = .32, p = .73) or group by hemisphere interaction (F (2, 169) = .93, p = .40) (Table 3.4). Similarly for omiMMNm, the ANOVA revealed a significant main effect of hemisphere (F (1, 169) = 18.12, p < .01) but no significant main effect of group (F (2, 169) = .43, p = .65) or group by hemisphere interaction (F (2, 169) = .48, p = .62) (Figure 3.3 & Table 3.4). The distributions of individual durMMNm and omiMMNm peak amplitudes are presented in Appendix A.3.

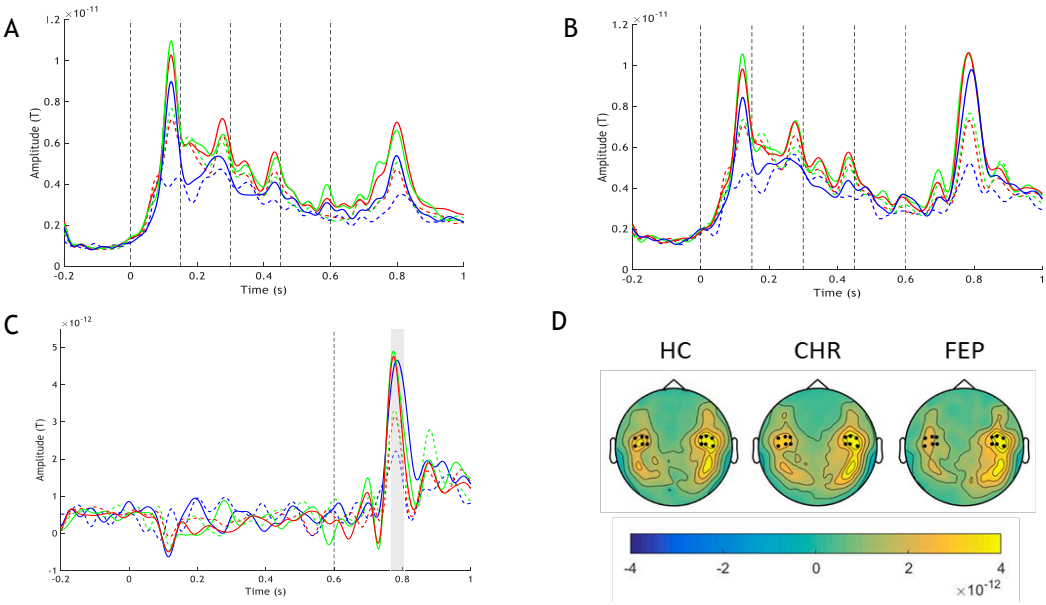


Figure 3.2 Sensor level durMMNm waveforms and topographic plots for HC, CHR and FEP groups. Grand average standard (A), deviant (B) and durMMNm (C) waveforms for the HC (green line), CHR (red line) and FEP (blue line) group extracted from the six left (dashed line) and right (solid line) MEG sensors as indicated by the black dots in the topographic plots. (D) Topographic maps of the durMMNm responses for the HC, CHR and FEP group in the

interval of 160 to 210 ms (grey-shaded area) which was used to extract individual peak amplitudes. HC, healthy control; CHR, clinical high risk; FEP, first episode psychosis.

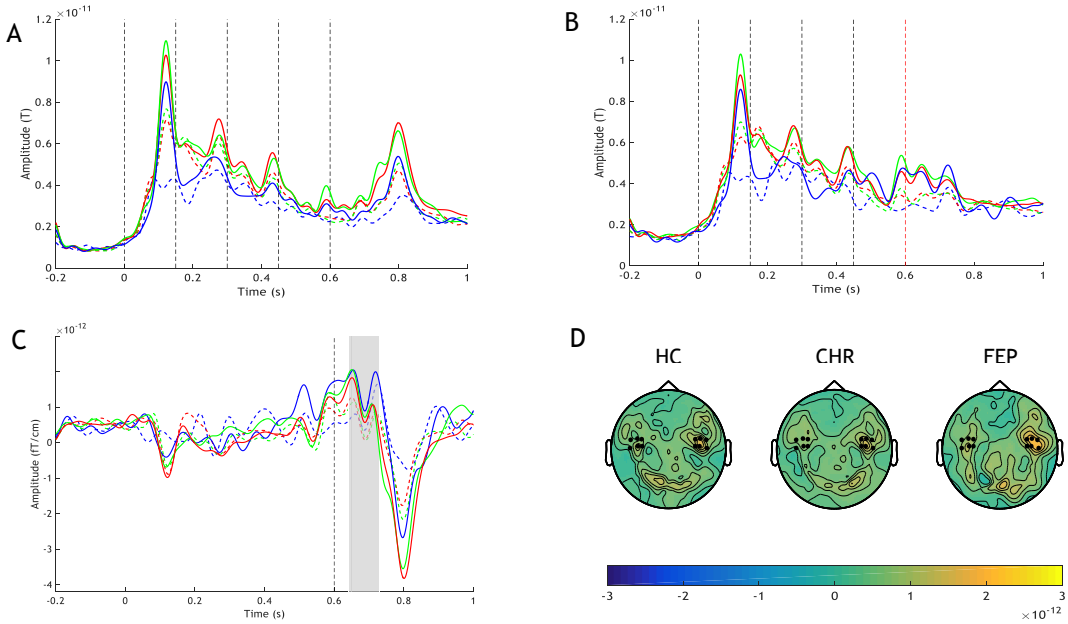


Figure 3.3 Sensor level omiMMNm waveforms and topographic plots for HC, CHR and FEP groups. Grand average standard (A), deviant (B) and omiMMNm (C) waveforms for the HC (green line), CHR (red line) and FEP (blue line) group extracted from the six left (dashed line) and right (solid line) MEG sensors of interests marked by the black dots in the topographic plots. (D) Topographic maps omiMMNm responses for the time interval of 40 to 130 ms indicated by the grey shaded area that was used to extract individual omiMMNm peak amplitudes. HC, healthy control; CHR, clinical high risk; FEP, first episode psychosis.

Table 3.4 Sensor level means and standard deviations of MMNm peak amplitudes for HC, CHR and FEP groups and effect sizes of group differences over the left and right hemisphere.

	Group				
Hemisphere	HC (n = 49)	CHR (n = 106)	FEP (n = 17)	HC vs CHR *d*	HC vs FEP *d*
durMMNm					
Left	4.57 (4.65)	4.14 (3.52)	3.08 (2.05)	0.10	0.41
Right	6.12 (4.49)	5.80 (4.47)	6.16 (3.46)	0.07	0.01
omiMMNm					
Left	2.79 (1.69)	2.66 (1.62)	2.74 (1.70)	0.07	0.03
Right	3.57 (2.52)	3.38 (2.19)	4.03 (2.21)	0.08	0.2

3.3.2.1.3 Shift function

In addition to comparing central tendencies of the three groups, I used the shift function to examine whether the three groups differed in any part of their distributions of MMNm peak amplitudes over the left or right hemisphere. The shift function revealed that the durMMNm amplitude distributions of HC and CHR groups were identical; however, there was a significant group difference in the right tail of the peak amplitude distribution of the durMMNm extracted from SOIs over the left hemisphere between the HC and the FEP group. The significant difference for decile 9 indicates that the groups did not differ for smaller

durMMNm amplitudes but only in terms of higher amplitudes (Figure 3.4A). For the omiMMNm distributions, the shift function revealed no significant group differences in any parts of the omiMMNm distributions (Figure 3.4B).

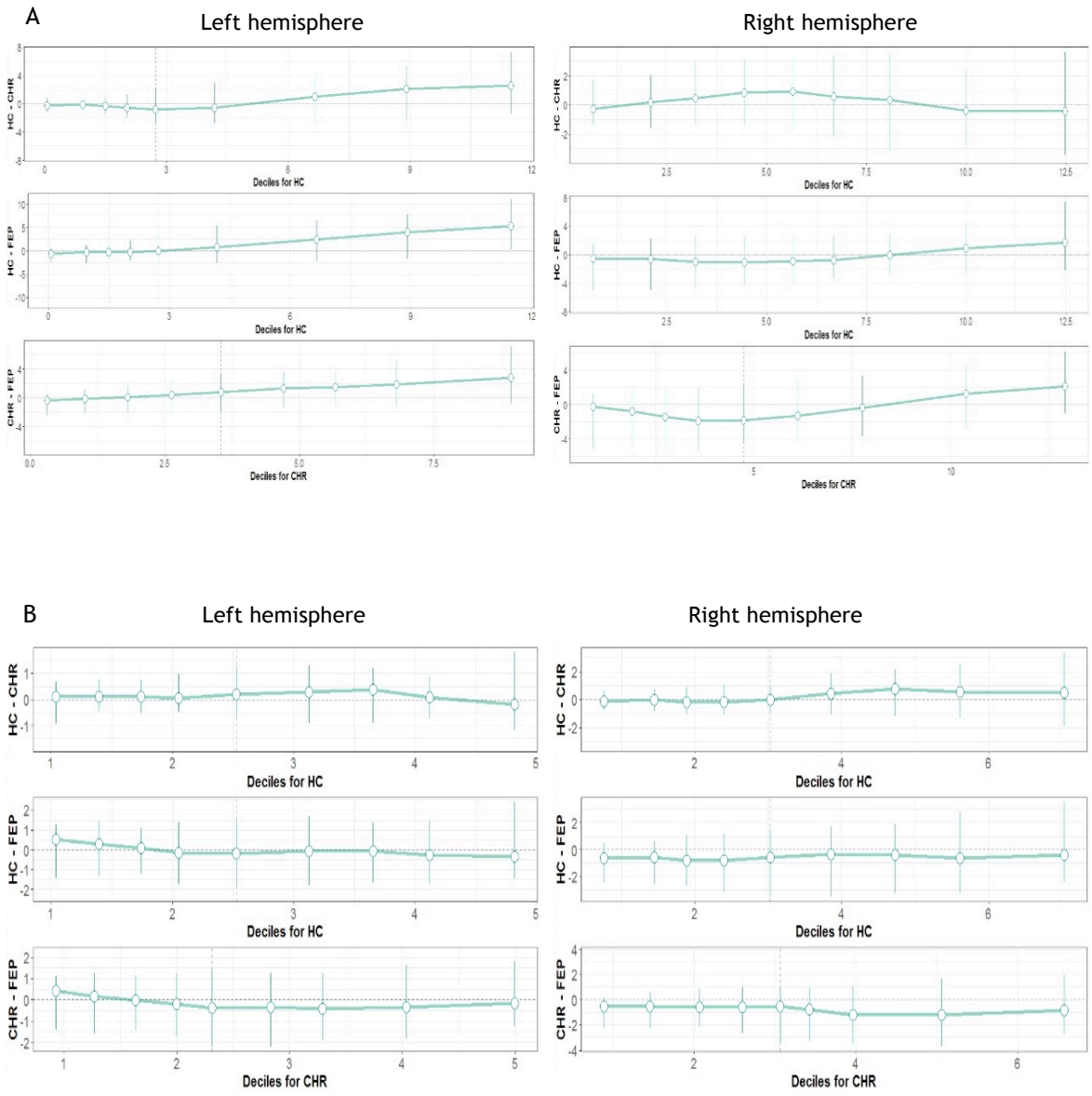


Figure 3.4 Shift function comparing MMNm peak amplitude distributions between HC, CHR and FEP groups. Data are shown for the left and right hemisphere amplitudes. The x-axis shows the MMNm deciles for the first group of the comparison. The y–axis shows the MMNm difference scores (group 1 – group 2) for each decile, as a function of group 1 deciles. Positive differences mean that group 1 had higher MMNm amplitudes than group 2. The vertical line indicates the 95% bootstrap confidence interval of the MMNm differences. HC, healthy control; CHR, clinical high risk; FEP, first episode psychosis. The top panel (A) presents durMMNm and the bottom panel (B) omiMMNm.

3.3.2.2 **Virtual channel analyses**

3.3.2.2.1 Condition effect

At the source level paired samples *t*-tests on the ERF peak amplitudes revealed a significant effect of stimulus type (standard, deviant) in each ROI (Figure 3.5A). For omiMMNm, the results revealed significantly higher ERF peak amplitudes for omitted compared to standard stimuli in each ROI in the first TOI (46 – 56 ms). In the second TOI of 110 to 130 ms, *t*-tests revealed significantly higher amplitudes to omitted compared to standard stimuli in L HG, L STG, L MTG and R IFG (Figure 3.5B & Table 3.5).

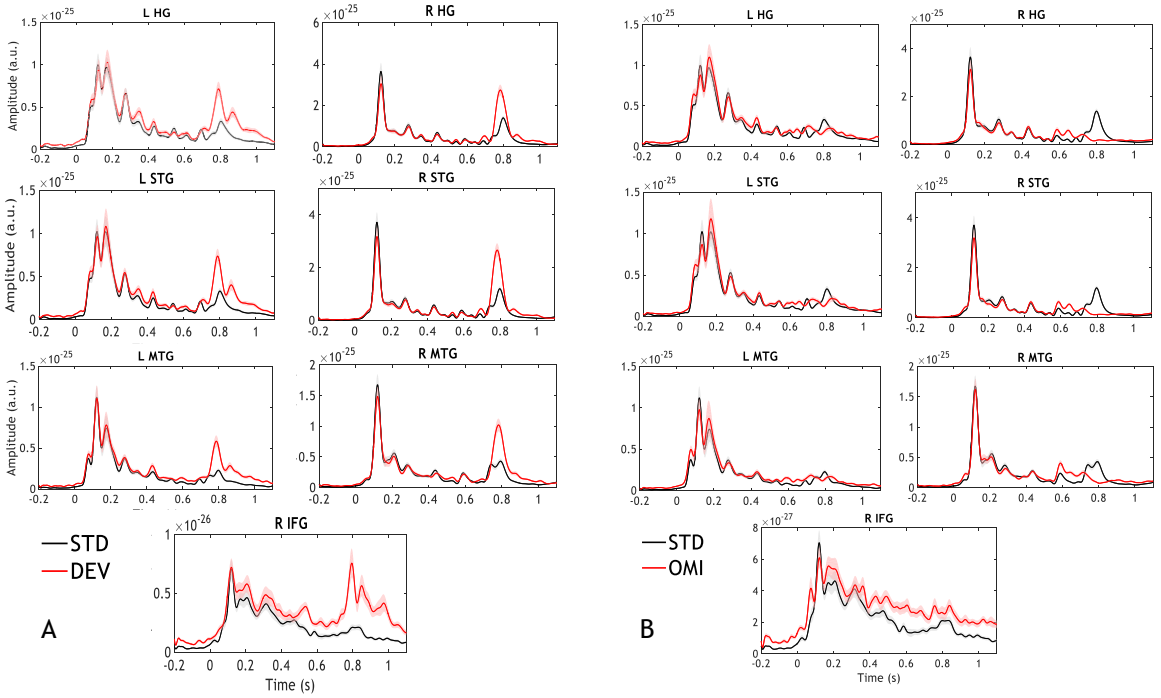


Figure 3.5 Virtual channel standard, deviant and omission time-series from each ROI. Grand averaged virtual channel waveforms with SEM error bars (shaded area) in response to standard (in black line) and deviant stimuli (in red line) plotted separately for each ROI. The onset of the deviant sound was at 0.6 seconds. Absolute values of the time series in ROIs are given. The left panel (A) contrasts the standard and duration deviant waveforms and the right panel (B) contrasts the standard and omission waveforms. L, left; R, right; HG, Heschl's gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus; IFG, inferior frontal gyrus; STD, standard; DEV, deviant; OMI, omission.

Table 3.5 Virtual channel means and standard deviations of ERF peak amplitudes to standard and deviant stimuli and statistical results comparing the ERF responses separately in each ROI.

ROI	Stimulus		Statistics	STD vs DEV *d*
	Standard	Deviant		
durMMNm				
L HG	4.96 (5.27)	11.19 (12.30)	t(166) = 7.87, *p* < .001	0.41
R HG	16.08 (15.11)	36.53 (37.56)	t(166) = 8.99, *p* < .001	0.71
L STG	4.68 (5.03)	10.86 (12.45)	t(166) = 7.56, *p* < .001	0.65
R STG	13.88 (12.87)	34.23 (36.0)	t(166) = 9.19, *p* < .001	0.75
L MTG	3.32 (3.83)	8.47 (10.55)	t(166) = 7.07, *p* < .001	0.64
R MTG	6.02 (7.50)	14.46 (15.77)	t(166) = 9.62, *p* < .001	0.68
R IFG	0.39 (0.39)	1.27 (1.85)	t(166) = 6.54, *p* < .001	0.08
omiMMNm 1st TOI				
L HG	1.56 (1.65)	2.82 (3.78)	t(166) = 4.59, *p* < .001	0.43
R HG	2.86 (3.38)	7.02 (9.30)	t(166) = 7.14, *p* < .001	0.59
L STG	1.30 (1.55)	2.40 (3.36)	t(166) = 5.09, *p* < .001	0.42
R STG	2.43 (2.91)	6.40 (7.93)	t(166) = 7.90, *p* < .001	0.66
L MTG	.93 (1.24)	1.82 (2.70)	t(166) = 4.77, *p* < .001	0.42
R MTG	1.32 (1.56)	3.23 (4.34)	t(166) = 6.23, *p* < .001	0.58
R IFG	.20 (.29)	.38 (.45)	t(166) = 4.69, *p* < .001	0.47
omiMMNm 2nd TOI				
L HG	2.17 (2.44)	3.41 (4.47)	t(166) = 3.46, *p* = .001	0.34
R HG	4.68 (7.31)	5.58 (7.95)	t(166) = 1.22, *p* = .221	0.11
L STG	1.94 (2.26)	2.76 (3.61)	t(166) = 2.75, *p* = .006	0.27
R STG	4.70 (6.45)	4.83 (6.75)	t(166) = 0.19, *p* = .846	0.01
L MTG	1.58 (2.17)	2.38 (3.82)	t(166) = 2.61, *p* = .010	0.25
R MTG	3.51 (4.68)	3.33 (5.58)	t(166) = -.36, *p* = .719	0.03
R IFG	.22 (.27)	.33 (.36)	t(166) = 2.89, *p* = .004	0.34

Uncorrected critical *p*-values listed. HG, Heschl's gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus; IFG, inferior frontal gyrus.

3.3.2.2.2 Group effect

The results of non-parametric Kruskal-Wallis H tests showed no significant main effect of group on durMMNm (Figure 3.6) or omiMMNm (Figure 3.7) peak amplitudes in any of the ROIs (Table 3.6).

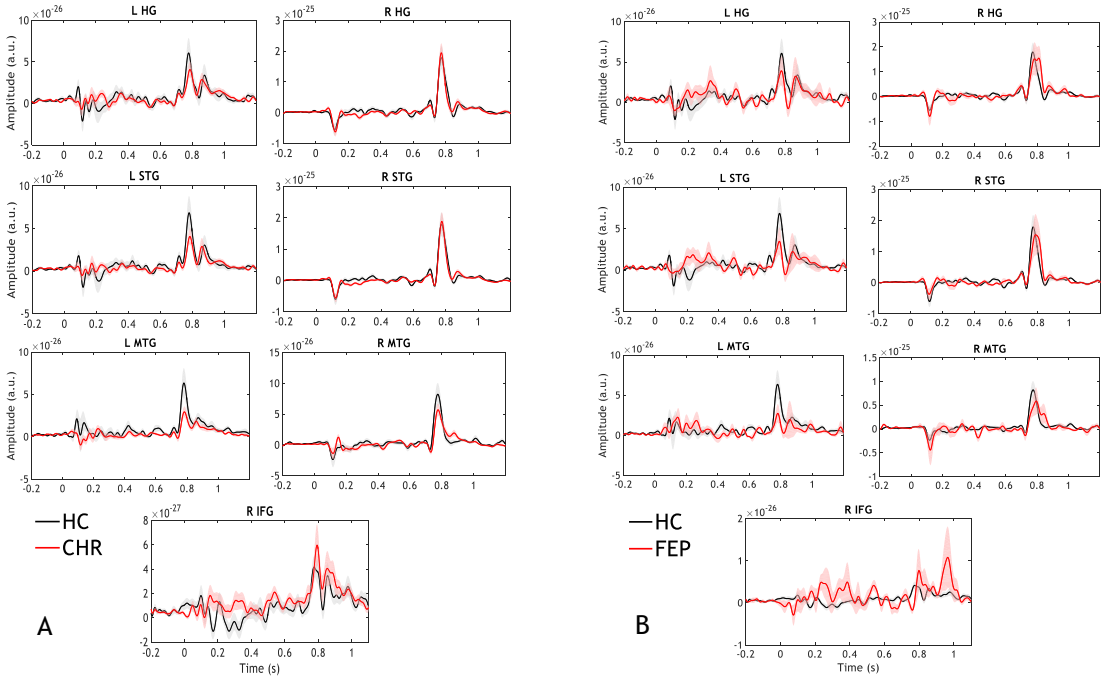


Figure 3.6 Virtual channel durMMNm time-series from each ROI for HC, CHR and FEP groups. Grand mean durMMNm virtual channel waveforms with SEM error bars (shaded

area) comparing (A) controls (in black) with clinical high risks (in red) and (B) controls (in black) with first episode patients (in red) in each ROI. The onset of the deviant sound was at 0.6 seconds. Absolute values are given. L, left; R, right; HG, Heschl's gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus; IFG, inferior frontal gyrus.

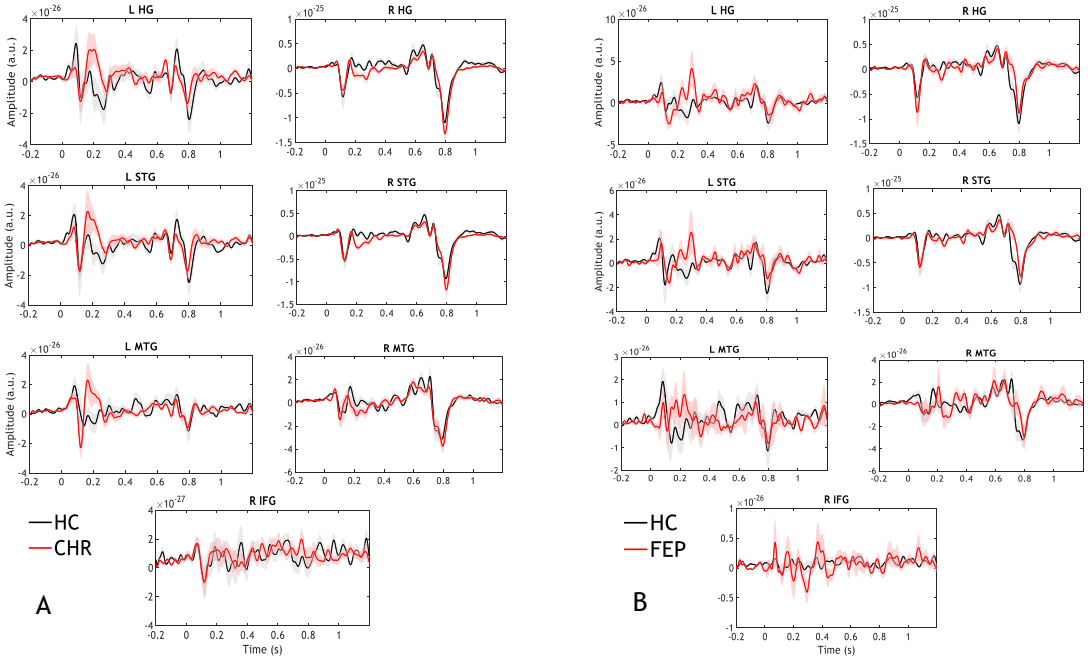


Figure 3.7 Virtual channel omiMMNm time-series from each ROI for HC, CHR and FEP groups. Grand mean omiMMNm virtual channel waveforms with SEM error bars (shaded area) comparing (A) controls (in black) with clinical high risks (in red) and (B) controls (in black) with first episode participants (in red) in each ROI. The onset of the deviant sound was at 0.6 seconds. Absolute values are given. L, left; R, right; HG, Heschl's gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus; IFG, inferior frontal gyrus.

Table 3.6 Virtual channel results of group differences in MMNm amplitudes between HC, CHR and FEP groups at each ROI. Means and standard deviations of MMNm peak amplitudes for each group, effect sizes of group differences and statistical results comparing the three groups separately in each ROI.

	Group							
ROI	HC (n = 48)	CHR (n = 103)	FEP (n = 16)	HC vs CHR *d*	HC vs FEP *d*	x^2	df	*p*
durMMNm								
L HG	8.88 (12.78)	8.40 (10.70)	6.43 (7.23)	0.04	0.24	0.62	2	0.73
R HG	25.72 (28.42)	25.92 (33.64)	26.78 (26.00)	0.01	0.04	0.91	2	0.63
L STG	9.93 (14.51)	7.86 (10.11)	5.23 (6.80)	0.17	0.41	0.87	2	0.65
R STG	25.40 (29.98)	24.36 (30.18)	23.30 (26.17)	0.03	0.07	0.31	2	0.86
L MTG	9.08 (13.40)	5.50 (7.19)	4.08 (4.85)	0.27	0.5	3.15	2	0.21
R MTG	12.10 (13.36)	9.47 (10.67)	9.18 (11.79)	0.22	0.23	1.76	2	0.41
R IFG	.88 (.78)	1.05 (1.87)	1.12 (2.17)	0.1	0.15	0.96	2	0.62
omiMMNm								
L HG	4.30 (5.03)	4.09 (4.51)	4.88 (5.16)	0.04	0.11	0.41	2	0.81
R HG	9.03 (9.30)	8.37 (9.92)	7.59 (5.51)	0.07	0.19	0.92	2	0.63
L STG	3.92 (4.53)	3.12 (3.28)	3.99 (3.60)	0.20	0.02	1.39	2	0.50
R STG	8.42 (8.10)	7.33 (8.49)	6.74 (5.74)	0.13	0.24	2.60	2	0.27
L MTG	3.81 (5.05)	2.71 (3.56)	2.33 (2.50)	0.25	0.34	2.38	2	0.30
R MTG	5.71 (7.32)	4.20 (5.60)	3.94 (3.84)	0.23	0.30	1.80	2	0.41
R IFG	0.49 (.52)	.56 (.61)	0.47 (.51)	0.12	0.04	0.16	2	0.92

Uncorrected critical *p*-values listed. HC, healthy controls; CHR, clinical high risk; FEP, first episode participants; L, left; R, right; HG, Heschl's gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus; IFG, inferior frontal gyrus.

3.3.3 **Clinically vs. community recruited CHR individuals**

3.3.3.1 **Sensor level**

For durMMNm, a 2 x 2 mixed-design ANOVA on the ERF amplitudes revealed a significant main effect of recruitment pathway (F (1, 104) = 59.84, p = .03), indicating an attenuated durMMNm amplitude across hemispheres in clinically referred CHR individuals compared to community recruited CHR individuals. There was also a main effect of hemisphere (F (1, 104) = 4.03, p = .047) but no hemisphere by recruitement pathway interaction (F (1, 104) = .83, p = .36) (Figure 3.8A). There was no significant main effect of recruitment pathway (F (1, 104) = 125.66, p = .14), hemisphere (F (1, 104) = 3.34, p = .07) or group by hemisphere interaction on omiMMNm peak amplitudes (F (1, 104) = .23, p = .63 (Figure 3.8B & Table 3.7).

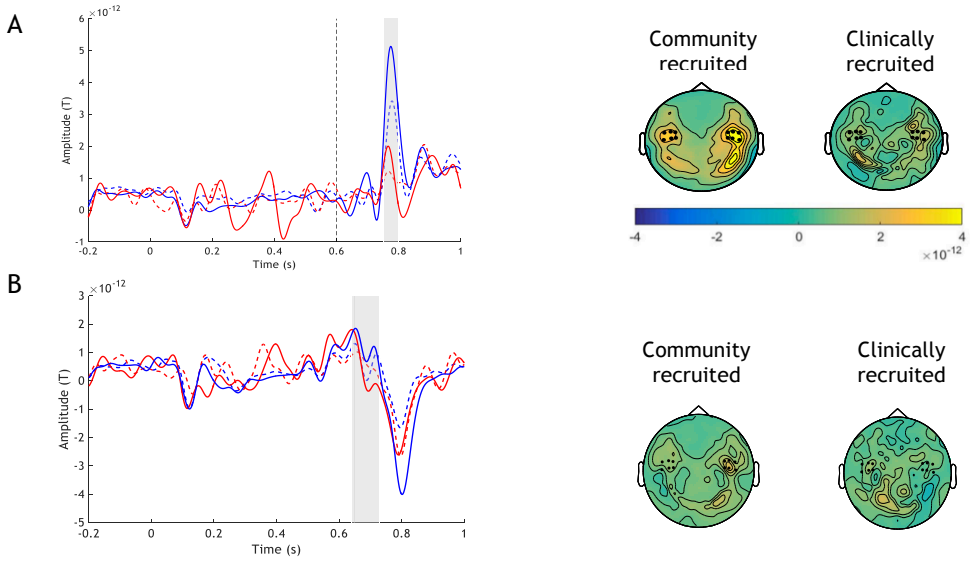


Figure 3.8 Sensor level MMNm waveforms and topographic plots for the community and clinically recruited CHR groups. Grand average MMNm waveforms for the community (blue line) and clinically referred CHR (red line) groups extracted from the six left (dashed line) and right (solid line) SOIs as indicated by the black dots in the topographic plots. Topographic maps of the MMNm responses for each group in the TOIs (grey shaded areas), which were used to extract individual MMNm peak amplitudes. The panel (A) presents the durMMNm effect and the panel (B) presents the omiMMNm effect.

Table 3.7 Sensor level means and standard deviations of MMNm peak amplitudes for community and clinically recruited CHR groups and effect sizes of group differences over the left and right hemisphere.

	Group		
Hemisphere	Community recruited CHR (n = 94)	Clinically recruited CHR (n = 12)	Community vs Clinically recruited CHR *d*
durMMNm			
Left	4.35 (3.62)	2.57 (2.11)	0.60
Right	6.13 (4.57)	3.24 (2.50)	0.78
omiMMNm			
Left	2.72 (1.67)	2.15 (1.10)	0.37
Right	3.48 (2.59)	2.60 (1.35)	0.43

3.3.3.2 **Virtual channels**

One community and two clinically recruited CHR individuals did not have T1 available and thus the sample sizes used for source space are different compared to those used for analyses in sensor space. The results of Mann-Whitney U tests showed that the community recruited CHR group had a higher durMMNm amplitude in the left MTG compared to the clinically recruited CHR group (Figure 3.9A & Table 3.8). However, this effect is not significant when corrected for multiple comparisons. The group-level analyses in source space showed no effect of recruitment pathway on omiMMNm amplitude in any ROI (Figure 3.9B & Table 3.8).

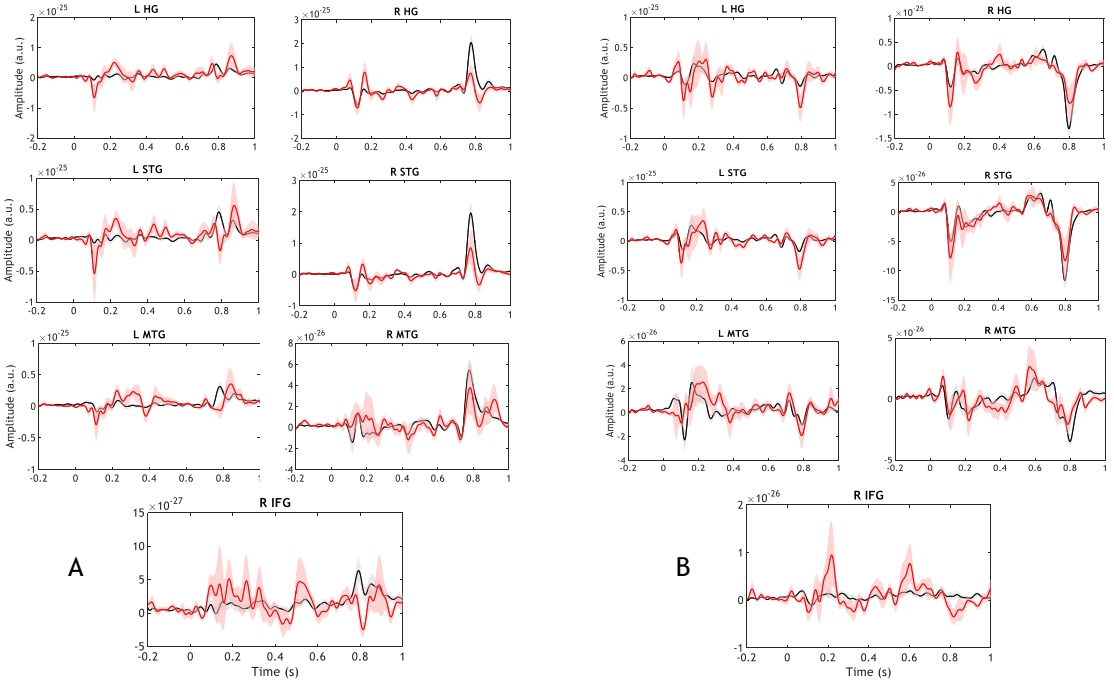


Figure 3.9 Virtual channel MMNm waveforms for the community and clinically recruited CHR groups. Grand mean MMNm virtual channel waveforms with SEM error bars (shaded area) comparing CHR individuals recruited from the community (in black) and clinical pathways

(in red) in each ROI. The onset of the deviant sound was at 0.6 seconds. Absolute values are given. Figure (A) presents the durMMNm effect and the figure (B) presents the omiMMNm effect. L, left; R, right; HG, Heschl's gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus; IFG, inferior frontal gyrus.

Table 3.8 Virtual channel results of group differences in MMNm amplitudes between community and clinically recruited CHR groups. Means and standard deviations of MMNm peak amplitudes for both groups, effect sizes of group differences and statistical results for each ROI. Uncorrected critical *p*-values listed.

	Group			
	Community recruited	Clinically recruited	Community vs Clinically	
ROI	CHR (n = 93)	CHR (n = 10)	recruited CHR *d*	Statistics
durMMNm				
L HG	8.46 (10.93)	7.82 (8.72)	0.06	U = 436, p = .747
R HG	27.51 (34.83)	11.11 (12.50)	0.63	U = 350, p = .200
L STG	8.14 (10.47)	5.34 (5.56)	0.33	U = 427, p = .672
R STG	25.68 (31.00)	12.15 (17.81)	0.53	U = 342, p = .171
L MTG	5.85 (7.37)	2.30 (4.26)	0.59	U = 281, p = .040
R MTG	9.79 (10.96)	6.49 (7.27)	0.35	U = 407, p = .518
R IFG	1.11 (.48)	.48 (.57)	1.19	U = 347, p = .189
omiMMNm				
L HG	4.12 (4.57)	3.77 (4.19)	0.08	U = 458, p = .938
R HG	8.85 (10.28)	3.90 (3.14)	0.65	U = 321, p = .109
L STG	3.15 (2.79)	2.79 (2.65)	0.13	U = 460, p = .956
R STG	7.72 (8.80)	3.68 (2.84)	0.62	U = 370, p = .290
L MTG	2.70 (3.68)	2.68 (2.23)	0.01	U = 405, p = .504
R MTG	4.45 (5.82)	1.87 (1.28)	0.61	U = 372, p = .300
R IFG	.55 (.60)	.71 (.75)	0.24	U = 385, p = .373

3.3.4 Correlations of MMNm amplitude with cognitive and clinical measures in CHR

Spearman rank correlations were calculated between MMNm peak amplitudes and six cognitive domains, BACS composite score, APS severity as well as social, role and global functioning scores in the CHR group. Due to multiple correlations, a more conservative *p*-value of .01 was used for significance to minimise the likelihood of type 1 errors.

3.3.4.1 Cognitive measures

In the CHR group, a significant positive correlation between processing speed and durMMNm amplitude over the right hemisphere (r = .24, p = .01) and in the right HG (r = .25, p = .01) was observed (Figure 3.10).

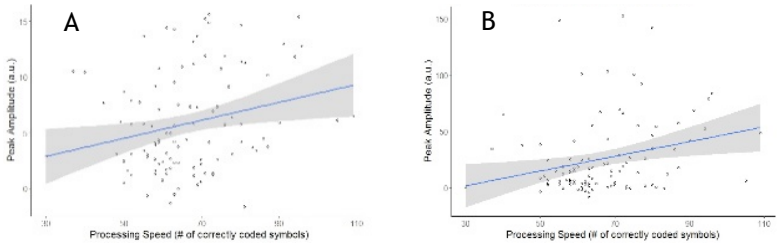


Figure 3.10 Correlations between processing speed and durMMNm (A) over the right hemisphere and (B) in the right HG in the CHR sample.

3.3.4.2 **Clinical measures**

There were no significant correlations between MMNm amplitudes and severity of APS, social, role or global functioning scores in the CHR sample.

3.3.5 **Predicting the GAF score from suicidality, comorbidity and symptom severity**

There was no multicollinearity between the three independent variables as indicated by tolerance (0.93 - 0.96) and Variance Inflation Factor values (VIF: 1.04 – 1.08). The hierarchical multiple regression revealed that the model one with the presence of suicidal ideation as an independent variable was significant and accounted for 16.1 % of the variation in the GAF score. Adding the comorbidity variable explained an additional significant 4.4 % of the variation in the GAF scare. Introducing the APS severity also added significantly to the prediction model by explaining further 8.1 % of the variance. When all three independent variables were included in the model, they accounted for 28.6 % of the GAF score but comorbidity was not a significant predictor of the GAF score when controlling for other two variables. The presence of suicidal ideation was the most important predictor for the GAF score followed by the severity of APS (Table 3.9).

Table 3.9 Summary of hierarchical regression analysis for variables predicting the GAF score in CHR individuals.

		Standardized Coefficients (β)	*t*	*p*	95 % C.I. for β	Tolerance	VIF	R^2	ΔR^2
Step 1								0.161	0.161
	(Constant)		36.263	.000	60.88 - 67.93				
	Suicidality	-.401	-4.402	.000	-15.66- -5.93	1.000	1.000		
Step 2								0.205	0.044
	(Constant)		31.233	.000	63.13- 71.7				
	Suicidality	-.359	-3.944	.000	-14.52- -4.8	.961	1.041		
	Comorbidity	-.214	-2.347	.021	-10.87- -0.91	.961	1.041		
Step 3								0.286	0.081
	(Constant)		27.855	.000	67.65- 78.03				
	Suicidality	-.345	-3.978	.000	-13.92- -4.65	.959	1.043		
	Comorbidity	-.160	-1.811	.073	-9.22- 0.42	.929	1.077		
	Symptom severity	-.291	-3.356	.001	-0.37- -0.1	.960	1.042		

3.4 **Discussion**

3.4.1 **Neurophysiological findings**

Before assessing any potential group differences in MMNm peak amplitudes, the presence and characteristics of MMNm responses to duration and omission

deviants were examined in the sensor and source space across groups. Analyses of differences between standard and deviant conditions confirmed that the auditory MMNm paradigm successfully elicited significant durMMNm and omiMMNm responses. In line with previous findings in the literature, the visual inspection of ERFs revealed that the durMMNm amplitude peaked at around 175 ms after the onset of the duration deviant stimulus (Jacobsen & Schröger, 2003) and omiMMNm around 50 to 120 ms after the sound omission (Bendixen, Schroger, & Winkler, 2009; Salisbury, 2012). Moreover, we observed a stronger MMNm response over the right hemisphere compared to the left hemisphere at the sensor and source level. This matches previous studies showing MMN to be right lateralized for simple tone stimuli in contrast to left lateralized for language paradigms (Levänen et al., 1996). Furthermore, the right IFG showed significant activation as a response to both deviant types, providing evidence for a frontal MMNm source, associated with involuntary attention switching (Giard, Perrin, Pernier, & Bouchet, 1990), in addition to temporal sources, associated with sensory memory and change detection (Rinne et al., 2000). The inconsistent findings in the literature regarding the presence of a frontal MMN generator might be due to variability in the imaging technique (Rinne et al., 2000) and auditory paradigm employed (MacLean, Blundon, & Ward, 2015).

In contrast to our expectation, the CHR subgroups did not differ in duration or omission MMNm amplitudes, suggesting the two subgroups to be characterised by similar MMNm profiles. In light of recent meta-analytical evidence showing that the APS and BLIPS groups are two separate subgroups, the BLIPS subgroup having a significantly higher psychosis risk than the APS subgroup (Paolo Fusar-Poli, Cappucciati, et al., 2016), future studies could separate CHR individuals into these subgroups to investigate MMN amplitudes between them. Unfortunately, the current CHR sample only included individuals meeting the APS, not the BLIPS criteria, and thus we could not stratify our MMNm results according to these two subgroups.

The main aim of the chapter was to investigate MMNm peak amplitudes in CHR individuals, first episode patients and controls to examine whether MMNm deficits are present during the first episode psychosis and even prior to psychosis onset. Against our expectations, we found no evidence for MMNm deficiency to be a feature of the high risk or first episode stage of psychosis. Furthermore, the

shift function revealed that the MMNm amplitude distributions of HC and CHR groups were identical, converging with the finding based on the mean amplitude. The current finding of intact MMNm amplitude in CHR individuals replicates previous findings (Atkinson et al., 2017; Bodatsch et al., 2011; Brockhaus-Dumke et al., 2005; Higuchi et al., 2013; Hirt et al., 2019; Koshiyama et al., 2017; Lepock et al., 2019; Mondragón-Maya et al., 2013) but is in contrast with studies reporting reduced MMN in CHR individuals (Atkinson et al., 2012; Hsieh et al., 2012; Jahshan et al., 2012; Daniel C. Javitt & Sweet, 2015; Koshiyama et al., 2017; Lavoie et al., 2018; Nagai, Tada, Kirihara, Yahata, et al., 2013; Perez et al., 2014; Shaikh et al., 2012; Shin et al., 2009; Solís-Vivanco et al., 2014). The observed effect sizes for MMNm differences between CHR individuals and controls in the current study are smaller both in sensor (d = 0.07 to 0.10) and source space (d = 0.01 to 0.27) than those previously reported in the CHR literature ranging from small (d = 0.21; Mondragón-Maya et al., 2013) to large (d = 0.76; (Atkinson et al., 2012), with a recent meta-analysis reporting CHR individuals to exhibit a modest MMN reduction (d = 0.40) (Erickson et al., 2016).

Unexpectedly, we found no robust evidence for MMNm deficits in first episode patients either. However, a comparison of entire distributions of MMNm amplitudes revealed lower durMMNm amplitudes in the right tail of the distribution among first episode participants compared to controls, indicating that the groups differed only in high durMMNm amplitudes. Our finding that first episode patients did not differ from controls with respect to the mean MMNm amplitude is in line with previous studies that observed unaffected MMN amplitudes during the early stage of psychosis (Magno et al., 2008; Mondragón-Maya et al., 2013; Salisbury et al., 2017; D. Umbricht et al., 2006) but in contrast with other studies (e.g. Atkinson, Michie, & Schall, 2012b; Higuchi et al., 2013a; Kaur et al., 2011) and a recent meta-analysis reporting a medium MMN impairment in first episode patients (Erickson et al., 2016). Collectively, based on our findings it appears that MMNm deficiency is not present during the high risk or first episode stage of psychosis, not supporting the notion of MMNm to be a candidate marker for early stages of psychosis (Koshiyama et al., 2017; Nagai, Tada, Kirihara, Araki, et al., 2013). Given the robustness of MMN deficits in chronic schizophrenia (Erickson et al., 2016), it might be that MMN deficiency

is related to illness progression, possibly reflecting grey matter loss (Rasser et al., 2011; Salisbury, Kasai, et al., 2007) and NMDA receptor glutamate dysfunction (D.C. Javitt et al., 1996; Rosburg & Kreitschmann-Andermahr, 2016).

The analyses comparing the clinically and community recruited CHR individuals revealed that the clinically referred CHR group had an attenuated duration MMNm amplitude over the right and left hemisphere as well as lower employment rate, education, cognition and role functioning compared to community recruited CHR group. Given that the two CHR groups differed in some measures that have been suggested to be associated with transition to psychosis, namely role functioning (T. D. Cannon et al., 2008) and cognition (Paolo Fusar-Poli, Deste, et al., 2012), it could be that the clinical CHR individuals had an elevated risk of psychosis compared to the community CHR individuals. However, our results are based on a small sample (n = 12) and thus should be interpreted with caution. Nevertheless, our data suggest that future studies should monitor the recruitment strategies and characteristics of CHR samples recruited from different pathways to reduce heterogeneity across CHR samples.

In line with our hypothesis based on previous research showing reduced MMN to be associated with cognitive dysfunction in first episode and schizophrenia patients, we found speed of information processing deficits to be weakly associated with reduced MMNm over the right hemisphere and in the right HG in the CHR group. This is in line with a CHR study that also found durMMNm amplitude to be associated with neuropsychological performance (r = 0.55) but with a different domain, verbal fluency (Higuchi et al., 2013). The observed lack of significant correlations between MMNm and symptoms is in line with previous studies conducted in CHR (Atkinson et al., 2012; Perez et al., 2014; Solís-Vivanco et al., 2014) and schizophrenia samples (Erickson et al., 2017). Further, unlike several studies conducted in schizophrenia patients (Friedman, Sehatpour, Dias, Perrin, & Javitt, 2012; Light & Braff, 2005; Rasser et al., 2011), we found no evidence for MMNm to be associated with social, role or global functioning in the CHR group. This is in line with the majority of previous CHR studies (Jahshan et al., 2012; Shin et al., 2009; Solís-Vivanco et al., 2014) but in contrast with a recent study that found evidence for duration MMN to be associated with global functioning already in the early stages of psychosis (Koshiyama, Kirihara, Tada, Nagai, Fujioka, Koike, et al., 2018). Given the scarce and inconsistent evidence

whether MMN is associated with cognition and functioning in the high risk stage of psychosis, more research is warranted.

3.4.2 **Clinical findings**

As expected, we found that the largely community recruited CHR sample differed from controls on several demographic, clinical and neuropsychological measures. Firstly, in line with previous studies using clinically recruited CHR samples, CHR individuals had lower global (Hui et al., 2013), role and social functioning compared to controls (e.g. Cornblatt et al., 2007). However, the current CHR sample was characterised by a slightly higher global functioning score (GAF mean = 59) compared to that of a recent meta-analysis reporting a mean GAF score of 50 in the CHR population. Nonetheless, the observed pattern that the functional level of CHR individuals was closer to first episode patients than controls was the same as found in the aforementioned meta-analysis (Paolo Fusar-Poli et al., 2015). The current CHR sample also had slightly higher social (7.54) and role functioning (7.50) scores compared to the range of scores (5.0 to 6.67) previously reported in CHR studies (Addington et al., 2011; Cornblatt, 2011; Niendam et al., 2007). Unfortunately data was not available for social and role functioning in first episode patients to assess whether the extent of social and role deficits in the CHR sample is more similar to first episode patients than controls as reported in previous studies (Addington et al., 2008; S. J. Lee et al., 2017). The slightly higher functioning CHR sample compared to previous CHR samples is likely be due to the fact that the current CHR sample was mainly community recruited instead of clinically referred from special early psychosis services.

Secondly, our findings showed that 61.2 % of CHR individuals met either anxiety and/or depressive diagnosis, and were more likely to use medication and receive psychological treatment compared to controls. Specifically, 28.2 % of CHR individuals reported both anxiety and depressive symptoms (current or past), 22.3 % had anxiety symptoms alone and only 10.7 % had depressive symptoms alone. The prevalence rate of 61.2 % of anxiety and/or depressive disorders observed in the current study is comparable to a previous study reporting that 69 % of CHR individuals had one or more mood/anxiety diagnoses at baseline (Woods et al., 2009). Similarly another study found that 62 % of CHR individuals

met the clinical criteria for at least one current comorbid disorder (Salokangas et al., 2012). However, our finding of a higher number of anxiety disorders compared to depressive disorders in the CHR sample is contrary to that of a recent meta-analysis that reported a higher baseline prevalence rate of depressive disorders (41 %) compared to anxiety disorders (15 %) (Paolo Fusar-Poli et al., 2014). On the other hand, our finding is consistent with a recent study that found the general anxiety disorder to be the most common mental disorder in their community recruited CHR sample (Shi et al., 2017). Therefore, one possible explanation for the conflicting findings regarding the most prevalent comorbid disorder in the CHR population may be that there is a difference in the most frequent comorbid diagnosis between community and clinical CHR samples.

Thirdly, our findings show that CHR individuals reported higher levels of current suicide risk than controls, demonstrating that high prevalence rates of suicidal ideations can be found not only in chronic schizophrenia (Skodlar et al., 2008) patients but also in the high risk stage of psychosis. We found a high prevalence rate of 53 % of at least low suicidal risk in the CHR sample, which is slightly smaller compared to a prevalence of 66 % reported in a recent meta-analysis (Taylor et al., 2015), potentially because the current CHR sample was slightly better functioning overall than previous CHR samples in the literature. Finally, the CHR group had poorer neuropsychological performance compared to the control group but better than the first episode group, replicating the findings from CHR samples recruited from clinical pathways (Paolo Fusar-Poli, Deste, et al., 2012; Keefe et al., 2006; Lencz et al., 2006) and extending them to a community CHR sample.

The current finding of APS to be associated with the presence of comorbid depressive/anxiety disorders as well as global, role and social functioning (Appendix A.4) is in line with a previous study indicating the clinical significance of APS in the general population (Frauke Schultze-Lutter, Michel, et al., 2014). Furthermore, our finding of APS contributing to global functioning over and beyond the presence of suicidal ideations and comorbidity suggests that APS by themselves are functionally disabling even before reaching the diagnostic threshold. The overall explained variance in global functioning using the three variables was moderate (28.6 %). However, the presence of suicidal ideation

explained a higher amount of variance in global functioning than APS, suggesting that suicidal thoughts have a stronger association with global functioning than the severity of APS in the community CHR population.

3.4.3 **Limitations and conclusions**

The sample size of the clinically referred CHR group (n = 12) is considered small for a neuroimaging study and thus the results should be interpreted with caution until replicated with a minimum sample of 20 participants as recommended by Simmons and colleagues (2011). Secondly, the CHR and FEP groups were not completely anti-psychotic free, some of them being on multiple medications and thus we cannot rule out the influence of medication on our results.

In conclusion, the findings in this chapter suggest that MMNm deficits are not a feature of the earliest stages of psychosis. In the light of our data and the consistently reported reduced MMN in chronic schizophrenia in the literature (Erickson et al., 2016; D. Umbricht & Krljesb, 2005), it could be that MMN deficits relate to disease progression and emerge later in the chronic stage of the disorder. However, future longitudinal studies following individuals to progress through different clinical stages of psychosis with multiple recordings are required to confirm this. Lastly, the small positive associations between MMNm and speed of information processing in the CHR sample provide preliminary support for MMNm to be linked with cognition in the high risk stage. From the clinical point of view, our data contributes to the existing literature by demonstrating that similar to clinically presenting CHR individuals, the community CHR individuals exhibit several clinical concerns in addition to APS, indicating that the community CHR population deserves access to clinical care regardless of APS and potential future transition to psychosis.

4 Effective Connectivity Underlying the Neuromagnetic Mismatch Negativity in Individuals at Clinical High Risk for Psychosis

4.1 Introduction

The increased interest in functional brain connectivity, namely the interaction between different cerebral areas, since the early 1960s has resulted in several different mathematical models for computing connectivity that can be applied to a number of neurophysiological signals including EEG and MEG signals (Sakkalis, 2011). The analysis methods for functional integration are typically divided into two different categories, those measuring functional connectivity and those measuring effective connectivity (Friston, 1994). While functional connectivity is defined as the temporal correlation between remote neurophysiological events, operationalised as statistical dependencies of time-series from different brain regions, effective connectivity is defined as the influence that one neural system has over another, describing the dynamic interaction within brain networks allowing causality to be assessed (Friston, Frith, & Liddle, 1993).

Granger-causality (Granger, 1969) and dynamic causal modelling (DCM) (Friston et al., 2003) are two widely adopted effective connectivity approaches in neuroimaging to determine causal interactions between different brain areas. The key difference between the two methods is that the Granger-causality technique is data driven whereas DCM is not an exploratory but a model-based approach. The most frequent application of DCM is to compare different underlying mechanisms that could explain the recorded imaging data (K. E. Stephan et al., 2010). More specifically, DCM tests a number of competing hypotheses about how observed data were generated by comparing connectivity models that are pre-specified by sources that are connected by different types of connections (forward, backward and lateral) and rules determining which connections are allowed to change (modulations). Bayesian model selection (BMS) is used to select the model that best explains the given data using exceedance probability, namely the likelihood of a specific model being more frequent than other models (Klaas E Stephan, Penny, Daunizeau, Moran, & Friston, 2009). Model comparison process is typically then followed by obtaining

posterior parameter estimates (task effect modulations) of the winning model and entering them into a second-level frequentist test to compare groups in these parameters (Penny, Stephan, Mechelli, & Friston, 2004). Although DCM was originally developed for effective connectivity analysis of fMRI data in 2003 (Friston, 2003), it was later extended to analyse evoked responses in EEG and MEG data (David et al., 2006; Kiebel, David, & Friston, 2006).

In addition to healthy populations, DCM has been applied to psychiatric disorders to examine the neural mechanisms underlying perceptual and cognitive disruptions (Heinzle & Stephan, 2017) and indeed several psychiatric illnesses have been linked to connectivity abnormalities (Greicius, 2008; Menon, 2011). Especially since it was proposed that abnormal functional integration of distributed brain regions, i.e. dysconnectivity, plays a key role in the pathophysiology of schizophrenia two decades ago (Friston & Frith, 1995; Klaas E. Stephan, Friston, & Frith, 2009), several studies have investigated alterations in effective connectivity in different stages of psychosis. For instance, previous DCM studies have examined connections within the working memory frontoparietal network (Owen, McMillan, Laird, & Bullmore, 2005) to understand the network dysfunctions underlying the well-established working memory impairment in psychosis. Indeed, in line with the dysconnectivity hypothesis, schizophrenia patients exhibit a reduced influence of prefrontal connectivity over parietal cortex during a working memory task (Deserno, Sterzer, Wustenberg, Heinz, & Schlagenhauf, 2012). Interestingly, there is evidence for the same impaired top-down connectivity (Schmidt et al., 2013) in first episode patients and CHR individuals, suggesting this abnormal connectivity to be related to emerging psychosis and unlikely to be solely due to the illness progression.

DCM has been also used to assess the mechanisms underlying the resistance of schizophrenia patients to the hollow mask illusion, namely why patients do not perceive the hollow mask as a concave mask but as a normal convex face. Previous studies using both fMRI (Danai Dima et al., 2009) and EEG data (Danai Dima, Dietrich, Dillo, & Emrich, 2010) have found a weaker top-down influence and a stronger bottom-up connection in patients compared to controls during the hollow mask presentation. These findings provide further support for the disconnection hypothesis of schizophrenia (Friston & Frith, 1995; Klaas E.

Stephan et al., 2009) and in terms of predictive coding (Friston, 2005; Rao & Ballard, 1999) suggest that the abnormal illusory perception in psychosis emerges as a result of aberrant dynamic interaction between bottom-up sensory input and top-down predictions.

A few studies have also employed DCM to examine the effective connectivity underlying the well-replicated and robust MMN deficiency in schizophrenia patients (D. Umbricht & Krljesb, 2005). The first DCM study to examine connectivity during an auditory roving oddball MMN paradigm in schizophrenia patients found evidence for abnormal connectivity in the backward connection from the right IFG to STG, providing evidence for aberrant top down connectivity within the MMN brain network in schizophrenia (D. Dima et al., 2012). Moreover, the patients also exhibited a decreased intrinsic inhibitory self-connectivity in the right primary auditory cortex, which the authors interpreted to reflect a loss of adaptation within local neurons resulting in inability to form a memory trace of the sound. Another more recent study employed DCM for MMN in a group of patients with a psychotic illness as well as their first-degree unaffected relatives to specifically examine potential group differences in terms of intrinsic inhibitory changes (Ranlund et al., 2016). The results revealed a disrupted intrinsic connectivity within the right IFG in patients as well unaffected relatives, suggesting similar connectivity abnormalities in patients with psychosis as well as in individuals at (genetically) at risk for psychosis, suggesting abnormal gain control/excitability of the neural population to be a potential endophenotype for psychosis.

However, no studies to date have examined effective connectivity in the brain network underlying the MMNm generation in CHR individuals. Accordingly, the aim of chapter 4 was to use DCM to investigate the underlying effective connectivity network of duration change detection in CHR individuals to examine whether alterations within the MMNm network are present already prior to illness onset. Based on previous findings in the literature and the disconnection hypothesis it was hypothesised that compared to controls, CHR individuals show abnormal duration deviant-induced changes within the MMNm network, especially connections integrating the frontal cortex.

4.2 **Methods**

The recruitment process, study procedure as well as MEG stimuli, recording and data pre-processing are described in chapter 2 (Methods).

4.2.1 **Participants**

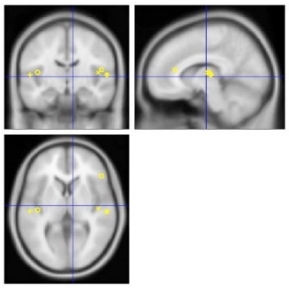
The CHR group consisted of 103 individuals (27 males; 76 females) aged between 16 to 35 years old (mean = 21.76 years, SD = 4.57) with normal to corrected vision who fulfilled one of the clinical CHR inclusion criteria based on the positive symptom subscales of the CAARMS (Yung et al., 2005) or/and the SPI-A (Schultze-Lutter et al., 2007). The control group consisted of 48 individuals (15 males; 33 females; mean age = 22.58 years, SD age = 3.55). More detailed information regarding the demographic and clinical characteristics of the two groups is provided in chapter 2 (Methods), section 2.2.

4.2.2 **Dynamic causal modelling**

We used DCM for event related fields as implemented in SPM12 (Statistical Parametric Mapping). The MEG data pre-processing and the generation of virtual-channel time-series in response to the standard and duration deviant stimuli was done using FieldTrip. I imported the standard and duration deviant time-series for five ROIs, namely bilateral Heschl's gyrus (HG), bilateral superior temporal gyrus (STG) and the right inferior frontal gyrus (rIFG), directly into SPM12. The five ROIs and their coordinates in the Montreal Neurological Institute (MNI) space are show in Figure 4.1. The selection of these specific ROIs to form the asymmetrical three-level hierarchical brain network was based on previous EEG/MEG (Doeller et al., 2003; Fulham et al., 2014; Marco-Pallarés et al., 2005) and DCM (Garrido et al., 2008; Garrido, Kilner, Kiebel, et al., 2009) studies reporting MMN to be generated in both frontal and temporal sources. Moreover, using our own MEG data, MMNm analyses at the source level in chapter 3 confirmed the presence of significant MMNm responses elicited by duration deviant tones in these five ROIs. The left and right HG were selected as cortical input for processing the auditory information and the canonical microcircuit neural model was used as the neural mass model to describe neural activity (Bastos et al., 2012). DCM was applied to ERFs to standard and duration deviant

sounds from 0 to 250 ms post stimulus onset to ensure modelling of the MMNm response itself rather than later components (Garrido et al., 2008).

A



B

Region	Abbreviation	MNI coordinate x	y	z
Left heschl's gyrus	L HG	-42	-19	10
Right heschl's gyrus	R HG	46	-17	10
Left superior temporal gyrus	L STG	-53	-21	7
Right superior temporal gyrus	R STG	58	-22	7
Right inferior frontal gyrus	R IFG	50	30	14

Figure 4.1 The source network used for DCMs of MMNm. (A) The distribution of five sources used for the DCM analysis, namely the left and right Heschl's gyrus, left and right superior temporal gyrus and right inferior frontal gyrus and (B) their coordinates in MNI space (mm).

4.2.3 **Bayesian Model Selection**

Before investigating potential group differences in effective connectivity underlying the MMNm response, I used BMS to examine which modulatory connections best explained the difference between ERFs to standard and duration deviant tones in the pre-defined five source network model in healthy controls. I specified six candidate dynamic causal models, each allowing for a different subset of connections to be modulated between (extrinsic) and within (intrinsic) five sources to test hypotheses that the differences in ERF responses to standard and duration deviant tones were caused by changes in 1) forward connections (F-models) 2) backward connections (B-models) or 3) in both backward and forward connections (FB-models). Figure 4.2 displays the entire model space, in which the first row of models allowed for changes only in extrinsic connections and the second row of models allowed for changes in both extrinsic as well as intrinsic inhibitory self-connections. I used the random-effects (RFX) BMS method that accounts for heterogeneity across subjects and allows different subjects to use different models to determine the most likely model that generated the observed duration MMNm response relative to other models (Klaas E Stephan et al., 2009).

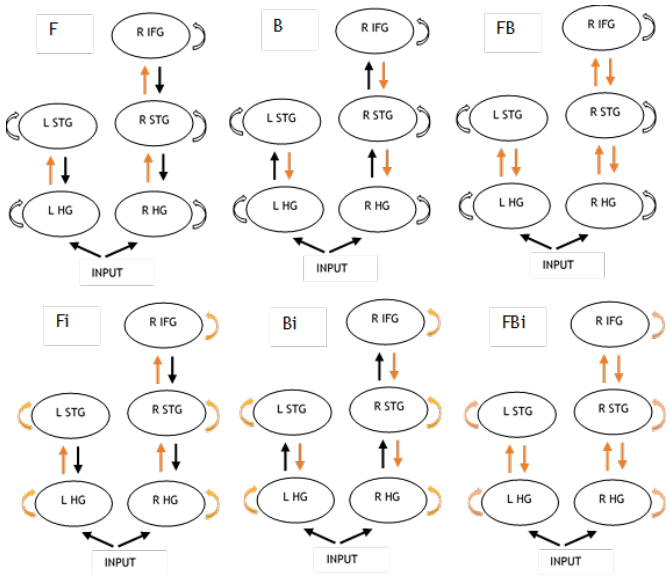


Figure 4.2 DCM model space including all six models used for BMS. The models have the same network structure including five nodes and each model received auditory input at bilateral Heschl's gurys but they differed in modulations of connections. Orange colour indicates modulated connections. F, forward; B, backward; FB, forward and backward.

4.2.4 Statistical Analyses

4.2.4.1 Group differences in modularity connections

After the RFX-BMS, the posterior parameter estimates of the winning model were extracted for each subject to quantify the rate of changes in coupling strengths between five selected regions induced by the duration deviant condition (DCM.Ep.B values). Subsequently potential group differences in these modulatory connections were examined by comparing the posterior coupling means between the CHR and HC group using independent samples *t*-tests.

4.3 Results

4.3.1 Bayesian model selection

The application of the (RFX) BMS, which penalises for increased model complexity (Penny et al., 2004), to the entire model space revealed that the winning model in the HC group with the highest exceedance probability that best explained the responses to deviants compared to standards was the one that allowed for modulations of both forward and backward connections (FB model). The exceedance probability for the best FB model was 0.54 and 0.46 for the next best FBi model (Figure 4.3A). Accordingly, the FB model was used in the subsequent analysis to assess potential group differences in stimulus dependent

changes in effective connectivity during the deviant sound processing between the CHR and HC group.

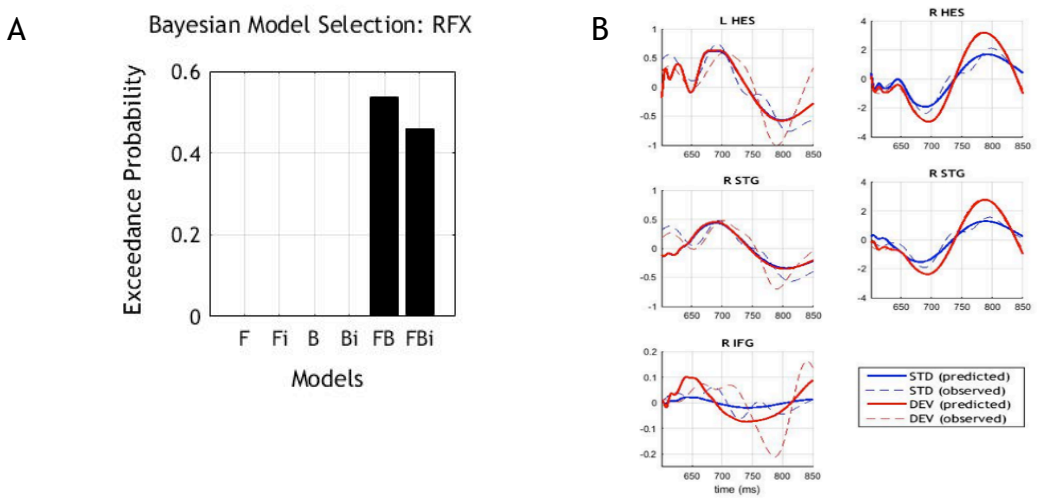


Figure 4.3 RFX-BMS results and model fit. (A) Random effects Bayesian model selection results among all models expressed relative to other models. The winning model for explaining the effect of the deviant stimulus was the FB model that included modulations of both forward and backward connections. (B) Model fits of the winning FB model presenting predicted (solid line) and observed (dashed line) ERF responses to standard (blue) and deviant (red) tones.

4.3.2 **Group differences in modularity connections**

Figure 4.4 A shows that on average all forward and backward connection strengths increased as indicated by values > 1 when the duration deviant stimulus was presented in the HC and CHR group. The subject specific coupling parameters of the FB model were entered into independent *t*-tests to assess group differences between the HC and CHR group. The results did not reveal a group difference in any of the forward or backward connections (Figure 4.4A & B). The distributions of individual coupling changes between different regions in the HC and CHR group are displayed in Figure 4.4C.

A

Connection	HC (n = 48)	CHR (n = 103)	*t*	*p*	ES (*d'*)
LHG to LSTG	2.19 (3.34)	1.86 (2.18)	0.69	0.49	0.12
RHG to RSTG	2.01 (1.70)	2.18 (2.49)	-0.42	0.67	0.08
RSTG to RIFG	1.98 (1.15)	1.95 (1.35)	0.14	0.88	0.02
LSTG to LHG	2.85 (3.22)	2.60 (3.26)	0.44	0.66	0.08
RSTG to RHG	3.77 (3.25)	3.85 (4.30)	-0.11	0.91	0.02
RIFG to RSTG	1.97 (1.55)	1.72 (1.22)	1.11	0.27	0.18

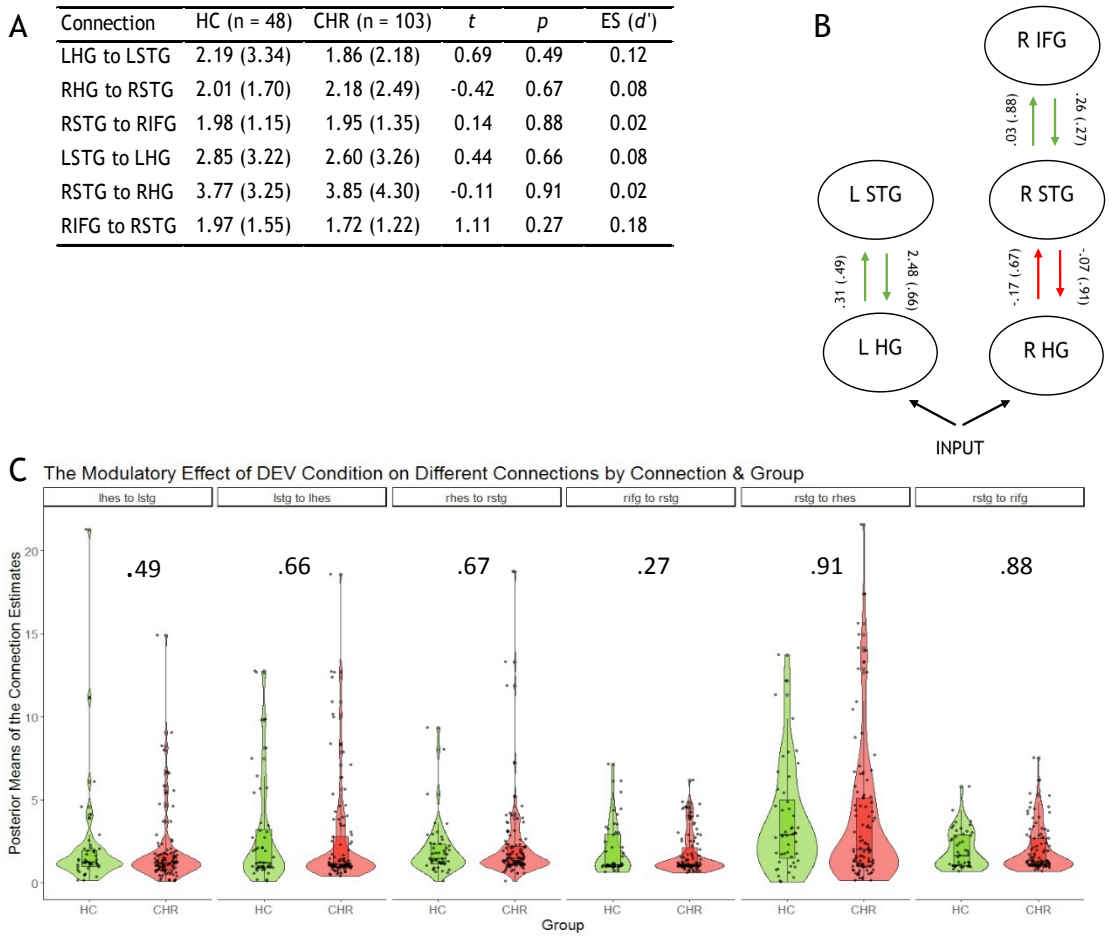


Figure 4.4 Comparison of coupling changes between the HC and CHR group. (A) Mean DCM modulatory posterior estimates for all extrinsic connections in the HC and CHR group and the results for the between-group comparison of deviant-induced modulations in different connections. Coupling changes are presented as scaling effects comparing deviants to standards, 1 indicating no change, < 1 indicating a decrease in the coupling strength as a response to deviants and > 1 indicating an increase in the coupling strength as response to deviants. (B) Group differences in mean coupling changes (HC minus CHR) and *p*-values (in brackets) for all connections between controls and CHR individuals. Green colour indicates a higher modulatory effect of the deviant condition in the HC group compared to the CHR group. The red colour indicates a smaller modulatory effect in the HC group compared to the CHR group. (C) The distributions of individual coupling parameters in the HC (green) and CHR group (red) for each connection.

4.4 Discussion

In the current chapter, effective connectivity underlying the duration MMNm response was modelled using DCM to assess the presence of aberrant effective connectivity in CHR individuals compared to healthy controls. To this end, we first assessed how the neural coupling was modulated by the duration deviant stimulus in an asymmetrical three level model including bilateral HG and STG and the right IFG in healthy controls to determine the model that best explained the MMNm effect as accurately as possible with minimal complexity. The selected network architecture of five nodes was based on previous DCM studies

demonstrating them to underlie the MMN generation (Garrido et al., 2008) and our own results in chapter 3 confirming the presence of a significant duration MMNm response in all five brain regions.

The model selection results revealed that the model that allowed for changes in extrinsic forward and backward connections (FB-model), but not intrinsic connections, had the highest exceedance probability and was most likely to explain the observed duration MMNm response in healthy controls. Notably, the exceedance probability of the winning FB model (54 %) was not that different compared to the next best model FBi (46 %) but overall there was more evidence for the FB than the FBi model. The finding that the FBi model with the highest number of parameters was not the winning model demonstrates that in DCM the most complex model is not necessarily the best model as the models are penalised for complexity (K. E. Stephan et al., 2010). Moreover, it is worth mentioning that although the model fit of the winning FB model was good, as demonstrated by the comparison of the predicted and observed ERF responses to standard and deviants tones, it might be that another unexplored network model could fit our duration MMNm data better as BMS chooses an optimal model from a set of pre-defined models considered (K. E. Stephan et al., 2010). Yet, this is unlikely considering the good model fit as well as previous validations of the MMN network structure and thus the current cortical network can be assumed to be a good index of the real network generating the MMN response (Garrido, Kilner, Kiebel, et al., 2009; Garrido, Kilner, Kiebel, Stephan, & Friston, 2007).

Our finding that the MMNm effect emerges from modulations in all bidirectional extrinsic connections is in line with an early DCM study that also found that modulations of both forward and backward connections best explained the MMN response during a classic oddball paradigm in controls (Garrido et al., 2007). On the other hand, our results are in contrast with a DCM study reporting that the best model explaining MMN elicited in a roving paradigm was the one with changes in both feedforward and backward extrinsic connections as well as changes in bilateral intrinsic connections within primary auditory cortices (Garrido et al., 2008). However, although our winning model did not include changes in intrinsic connections, we cannot rule out the possibility that also those connections contribute to the MMNm effect, especially considering the

relative high confidence for the second best FBi model that included intrinsic changes.

We observed that the duration MMNm response was on average mediated by increased forward and backward connections in both HC and CHR groups, suggesting all extrinsic connections to be important in processing a deviant stimulus. According to theoretical accounts of predictive coding, increases in bottom-up forward connections convey the prediction error between the sensory predictions and the actual stimulus input to update the model at higher levels whereas the top-down backward connections convey predictions trying to cancel the prediction error at lower levels (Garrido et al., 2007). However, against our hypothesis, CHR individuals did not exhibit aberrant modulations of feedforward or backward connections induced by duration deviants in the frontotemporal MMNm network compared to controls. Given that an abnormal effective connectivity from the right IFG to the right STG has been observed in schizophrenia patients (D. Dima et al., 2012), we expected especially this connection to be altered in the CHR group. However, this lack of observed reduction of top down connectivity may suggest top-down processing and efficient signalling of predictions at this stage of psychosis.

Moreover, our finding is in contrast with previous effective connectivity findings in CHR individuals during different tasks reporting the CHR state to be associated with disrupted frontotemporal connectivity (Crossley et al., 2009; Schmidt et al., 2013). Overall, in light of our data and previous evidence for extrinsic and intrinsic dysconnectivity in the MMN network in patients with schizophrenia (D. Dima et al., 2012; Ranlund et al., 2016), it appears that the underlying effective connectivity network of change detection is intact in the high risk state for psychosis and the disrupted connectivity may emerge later as a consequence of the illness.

5 The Utility of MMNm Amplitude for Predicting Outcomes in CHR Individuals

5.1 Introduction

The notion of indicated prevention in psychosis, namely targeting individuals with subthreshold psychotic symptoms thought to be in the pre-psychotic illness stage to prevent or delay the onset of a first episode of psychosis (Klosterkötter, 2008), has received an increasing clinical and research interest since the introduction of the UHR paradigm 25 years ago (Yung & McGorry, 1996). However, although CHR individuals have an elevated risk of developing a psychotic disorder within a short period of time compared to the general population, most of them do not transition to psychosis (T. D. Cannon et al., 2008), raising concerns regarding early intervention in the CHR population (De Koning et al., 2009; McGorry et al., 2009). Given that accurate identification of individuals truly at risk for developing psychosis is a prerequisite for safe and meaningful early intervention, a number of neuroimaging measures have been studied as potential markers for improving psychosis prediction in CHR individuals.

It has been suggested that reduced MMN amplitude, a neurophysiological measure of early auditory processing dysfunction, is one of the most promising markers for psychosis prediction in CHR individuals (Näätänen, Shiga, Asano, & Yabe, 2015). Indeed, previous studies comparing MMN amplitudes of CHR individuals who transitioned to psychosis (CHR-T) and who did not (CHR-NT) have found MMN deficits only in CHR-Ts and not CHR-NTs, suggesting MMN amplitude to have value for predicting progression from the high risk state to first episode psychosis (Bodatsch et al., 2011; Higuchi et al., 2013; Lavoie et al., 2018; Perez et al., 2014; Shaikh et al., 2012). However, other studies, including the largest published CHR study to date, could not replicate these findings (Atkinson et al., 2017; Hsieh et al., 2012). Moreover, although there is tentative meta-analytical evidence showing a large effect size (d = 0.79) of MMN impairment in CHR-Ts (Erickson et al., 2016), the majority of previous studies have been limited by insufficient statistical power due to small sample sizes. Accordingly, the first aim of this chapter was to examine whether MMNm amplitudes in the sensor and source space differ between individuals who transitioned from the CHR state to

full-blown psychosis and who did not within 12 months. To this end, we followed up the CHR group introduced in chapter 3 and assessed their symptom levels and functioning at 12 months.

As a result of declining transition rates in CHR studies (Lim et al., 2018; Yung et al., 2007) and recent evidence showing that CHR individuals have unfavourable outcomes irrespective of transition to psychosis (Beck et al., 2019; A. Lin et al., 2015), the UHR approach has been criticised for its focus on psychosis as the only outcome of interest. Consequently, the field has slowly started to move towards assessing and predicting other clinically relevant outcomes as well. CHR-NTs have been typically divided into those who remitted from their initial CHR state and those who sustained subthreshold psychotic symptoms, meta-analytical evidence indicating that around 46 % of CHR individuals no longer meet the UHR criteria at a 2-year follow-up (Simon et al., 2013).

It is important to acknowledge that despite a high proportion of CHR individuals remitting from their APS, they continue to have a poor level of functioning (Addington et al., 2011; T. Y. Lee, Kim, et al., 2014) and a high prevalence of non-psychiatric disorders that are associated with poor outcome (Rutigliano et al., 2016). Yet, to date the question of how many CHR individuals recover both symptomatically and functionally has remained relatively unexplored as previous studies have mainly focused on examining symptomatic remission (Woods et al., 2014). To address this gap in the existing literature, we used an operational definition of remission based on the criteria suggested by Lee and colleagues (2014) which takes into account both symptomatic and functional outcomes. Furthermore, due to the focus on the onset of psychosis as the predominantly only outcome of interest in the CHR literature, there is a lack of research examining whether reduced MMNm amplitude is associated with persistent CHR status and low functioning. Hence, the second objective of the chapter was to assess the symptomatic and functional remission rates in UHR individuals at 12 months and examine whether MMNm amplitude can differentiate UHR individuals who achieved full remission (CHR-R) from those who did not (CHR-NR).

Despite extensive research efforts, it has proven difficult to predict outcomes of CHR individuals based on clinical and cognitive measures (Seidman et al., 2010) and it has been suggested that combining imaging measures with clinical and

neuropsychological measures may improve outcome prediction. However, while previous studies have investigated the utility of MMN amplitude in predicting transition to psychosis (Bodatsch et al., 2011; Perez et al., 2014), its ability to predict the severity of APS or global functioning in CHR individuals remains unknown. Moreover, it is important to investigate whether adding MMNm data to more easily obtained and economically feasible clinical and neuropsychological measures improves outcome prediction in CHR individuals. Accordingly, the third and final goal of the chapter was to determine whether MMNm amplitude can predict the severity of APS and global functioning at 12 months above and beyond clinical and neuropsychological predictors.

5.1.1 Hypotheses

The following hypotheses will be tested:

(1) CHR individuals who transitioned to psychosis within 12 months show an attenuated MMNm peak amplitude response compared to CHR individuals who did not transition and controls.

(2) UHR individuals who did not achieve symptomatic and functional remission at 12 months show reduced MMNm amplitude compared to remitters and controls.

(3) MMNm amplitude contributes to the prediction of the severity of APS and GAF in UHR individuals at 12 months above and beyond clinical and cognitive predictor variables.

5.2 Methods

The recruitment, participants, study procedure as well as MEG stimuli, recording and data pre-processing are outlined in chapter 2 (Methods).

5.2.1 Transition criteria

We used the transition criteria based on the definition by Yung and colleagues (1998) that requires the presence of at least 1 positive psychotic symptom

several times a week for longer than one week. Transition to psychosis was confirmed by a DSM-5 diagnosis on the SCID.

5.2.2 **Remission criteria**

Symptomatic and functional remission, referred as a full remission in this thesis, was defined a priori as an UHR individual (excluding individuals with only BS at baseline) not meeting the UHR criteria as based on the CAARMS (see General Methods 1.4.2. for the operationalised UHR criteria) and a GAF score of ≥ 60 at 12 months. Although the GAF score of ≥ 60 out 100 is an arbitrary choice as a cut-off point for functional remission, it was chosen as it is frequently used to divide patients with mild functional impairment from those with moderate to severe functional impairment in clinical practice.

5.2.3 **Changes in symptom severity and global functioning**

Symptom change from baseline to a 12-month follow-up visit was calculated by subtracting the total severity of the positive symptom subscales of the CAARMS at baseline from scores at 12 months. Similarly, change in GAF score during the 12-month follow-up period was calculated by subtracting GAF/social scores at baseline from scores at 12 months.

5.2.4 **Statistical analyses**

Changes in the severity of APS and GAF over time was compared in those UHR individuals who achieved full remission and who did not by a mixed-design ANOVA with one between-subjects factor of group (remitters vs non-remitters) and one within-subjects factor of time (baseline vs 12 months).

To examine potential group differences in MMNm amplitudes at the sensor level, mixed-design ANOVAs with one within-subjects factor of hemisphere with two levels (left, right) and one between-subjects factor of group were performed for durMMNm and omiMMNm amplitudes. To investigate group differences in MMNm responses at the source level, non-parametric Kruskal-Wallis H tests were conducted to compare MMNm peak amplitudes between groups separately in each ROI.

Two separate two-stage hierarchical multiple regressions with the enter method were conducted with the severity of APS and the GAF score at 12 months as the dependent variable. Baseline role and social functioning, GAF score, APS severity and BACS composite score were entered simultaneously as predictor variables at stage one of the regression and the durMMNm amplitude over the right hemisphere was entered at stage two. Because of high collinearity between cognitive subtest scores and MMNm amplitudes in sensor and source space, only duration MMNm amplitude extracted from the six SOIs over the right hemisphere and the overall BACS cognitive score were selected.

5.3 Results

5.3.1 Demographic and clinical characteristics

5.3.1.1 CHR individuals with and without follow-up information

MMNm data were recorded for 106 CHR participants at baseline. 65 (61 %) of these participants had 12-month follow-up data available (Figure 5.1). The CHR individuals with follow-up data had a lower prevalence of suicidal ideations and a higher GAF score, APS severity and level of education than CHR participants without follow-up data. The groups did not differ in any other demographic or clinical characteristics or, most importantly, MMNm peak amplitude (Appendix B.1).

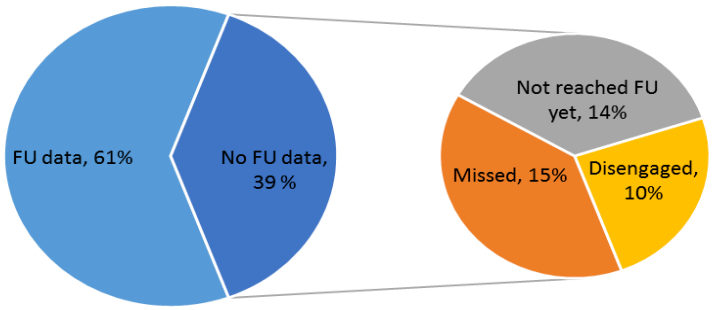


Figure 5.1 CHR individuals with and without 12 month follow-up data. 15 out of 41 (37 %) CHR participants without follow up data had not yet reached the 12-month follow-up visit, 16 (39 %) had reached the follow-up but missed it and 10 (24 %) had disengaged during the 12-month follow-up period. FU, follow-up.

5.3.1.2 CHTs vs CHR-NTs

CHR individuals were divided into those who transitioned to psychosis (CHR-T) and those who did not (CHR-NT) during the 12-month follow-up period. Of the 65

CHR participants with follow-up data, 5 (7.7 %) had experienced a transition to psychosis during 12 months. The CHR-T group differed from the CHR-NT group only by having a lower social functioning score at baseline with a non-significant trend (p = .08) in the GAF score and age (Table 5.1).

Table 5.1 Baseline characteristics of CHR-NT and CHR-T groups.

Measure	Sub-Measure	CHR-NT (n = 60)	CHR-T (n = 5)	Statistics	Significance
Age		22.23 (4.56)	18.60 (2.07)	t (63) = 1.76	n.s. (.08)
Gender	Male	14	1	x^2(1) = .865	n.s. (.99)
	Female	46	4		
Employment	Full time paid	1	0	x^2(4) = .551	n.s. (.97)
	Part time paid	3	0		
	Voluntary	1	0		
	Student	54	5		
	Unemployed	1	0		
Years of Education		15.73 (3.68)	13.60 (2.30)	t (63) = 1.27	n.s. (.21)
Medication +	Any medication	31	3	x^2(1) = .128	n.s. (.72)
	None	29	2		
Treated Mental Health Problems	None	22	1	x^2(2) = 2.59	n.s. (.27)
	Current	8	2		
High risk stage	EPS	15	1	x^2(2) = .062	n.s. (.80)
	LPS	45	4		
Clinically referred	No	55	5	x^2(1) = .451	n.s. (.50)
	Yes	5	0		
	Past	30	2		
Family History (1st Degree) +	No	53	5	x^2(1) = .654	n.s. (.99)
	Yes	7	0		
CAARMS severity		29.72 (15.97)	39.0 (20.86)	t (63) = - 1.22	n.s. (.23)
GAF		61.90 (12.81)	51.80 (5.40)	t (63) = 1.74	n.s. (.08)
GF: Social scale		7.67 (1.02)	6.60 (1.14)	t (63) = 2.23	p = .03
GF: Role scale		7.67 (1.05)	7.40 (1.34)	t (63) = .53	n.s. (.60)
Current Suicide Risk	No	34	3	x^2(3) = 4.125	n.s. (.25)
	Yes Low	11	0		
	Yes Moderate	7	0		
	Yes High	7	2		
BACS composite score		277.50 (42.45)	284.0 (53.47)	t (63) = -.29	n.s. (.77)

CHR-NT, clinical high risk non-transitioners; CHR-T, clinical high risk transitioners; CAARMS, comprehensive assessment of at risk mental states; GAF, Global Assessment of Functioning; GF, global functioning; BACS, brief assessment of cognition in schizophrenia; n.s., non-significant. P > 0.05 listed as non-significant.

5.3.1.3 **Remitters vs non-remitters**

Out of 60 CHR-NTs, 43 (71.6 %) met the UHR criteria based on the CAARMS at baseline (excluding the BS only group). Out of these 43, 30 (70 %) participants remitted symptomatically and no longer met the UHR criteria at 12 months whereas 25 (58 %) participants remitted functionally. Only 17 (39.5 %) participants achieved the predefined full remission incorporating symptomatic and functional remission (CHR-R) and 26 (60.5 %) did not (CHR-NR) (Figure 5.2).

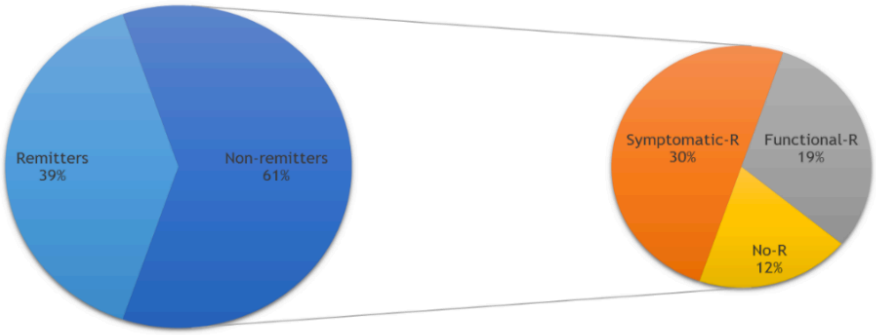


Figure 5.2 UHR individuals grouped according to their symptomatic and functional outcome at 12 months. Of the 26 (60.5 %) participants who did not fully remit (CHR-NR), 13 (30.2 %) participants remitted only symptomatically, while 8 (18.6 %) participants remitted only functionally and 5 (11.6 %) participants did not remit symptomatically or functionally. R, remission.

At baseline, the CHR-R group had a higher GAF and role functioning score than the CHR-NR group but they did not differ in any other measure. In terms of group differences in GAF change over time, a mixed-design ANOVA revealed a significant time (baseline, 12 months) and group (remitter, non-remitters) interaction (F (1, 41) = 4.20, p = .047), indicating that only CHR-Rs, not CHR-NRs, showed an improvement in the GAF score. Similarly there was a significant group difference in the change in the severity of APS (Time x Group: F (1, 41) = 6.71, p =.01) and social functioning (Time x Group: F (1, 39) = 6.79, p = .01) over time. However, there was no significant change in role functioning over 12 months in the CHR-R or CHR-NR group (Time: F (1, 39) = .08, p = .78) and there was no significant group difference in change in role functioning between the two groups (Time x Group: F (1, 39) = 2.46, p .13). It has to be noted that although CHRs showed a higher GAF improvement than CHR-NRs, the data show large individual differences in effect sizes and overlap between groups and indeed the group difference in the GAF change was just below the significance level of 0.05 (p = .047) (Figure 5.3).

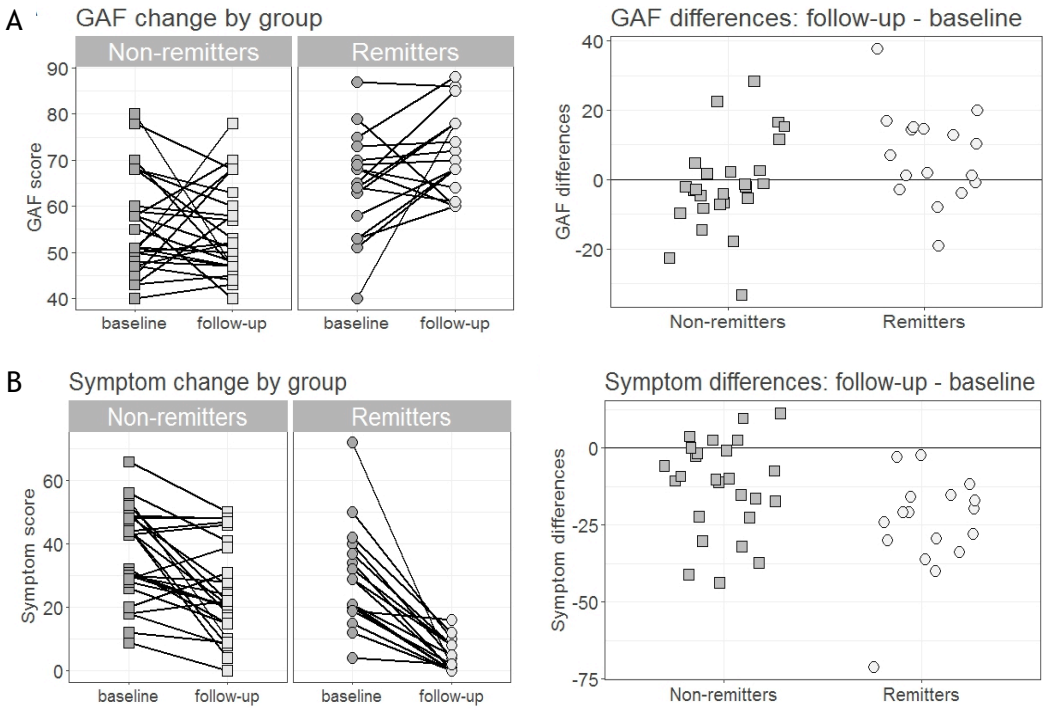


Figure 5.3 GAF and APS change in CHR-NR and CHR-R groups over 12 months. (A) Paired observations of GAF scores at baseline and 12 months for CHR-R and CHR-NR groups and the changes in GAF score over 12 months. A positive score indicates an improvement in the GAF score. (B) Stripchart of paired observations showing the severity of APS in CHR-R and CHR-NR groups at baseline and 12 months and the changes in symptom severity over 12 months. A negative score indicates an improvement in the symptom severity. GAF, Global Assessment of Functioning.

As expected, controls were less likely to use medication, have mental health problems and a first-degree relative with a diagnosis schizophrenia than both the CHR-R and CHR-NR group. Controls also had higher global, social and role functioning and lower APS severity and suicide risk than the both CHR groups. The HC group had a higher BACS composite score than the CHR-NR group but not the CHR-R group (Table 5.2).

Table 5.2 Characteristics of CHR-NR, CHR-R and HC groups at baseline and 12 months.

Measure	Sub-Measure	HC (n = 49)	CHR-NR (n = 26)	CHR-R (n = 17)	Statistics	Significance	Post Hoc Comparisons
Age		22.5 (3.57)	22.65 (5.34)	22.00 (4.20)	H (2) = .43	n.s. (.808)	
Gender	Male	16	6	4	$x^2(2) = .999$	n.s. (.61)	
	Female	33	20	13			
Handedness	Left	4	1	2	$x^2(4) = 2.15$	n.s. (.708)	
	Right	37	11	10			
	Amdidextrous	8					
Employment	Full time paid	3	1	0	$x^2(10) = 4.513$	n.s.(.921)	
	Part time paid	2	1	1			
	Voluntary	1	0	1			
	Student	41	23	15			
	Unemployed	2	1	0			
Years of Education		16.6 (3.03)	15.38 (4.23)	15.71 (3.04)	H (2) = 3.77	n.s. (.152)	
Medication	Any medication	0	12	10	$x^2(2) = 30.53$	$p < .001$	HC < CHR-NR & CHR-R
	None	49	14	7			
Treated Mental Health Problems	None	46	10	4	$x^2(4) = 42.530$	$p < .001$	HC < CHR-NR & CHR-R
	Current	0	2	4			
	Past	3	14	9			
Family History (1st Degree)	No	49	23	15	$x^2(2) = 6.03$	$p = .049$	HC < CHR-NR & CHR-R
	Yes	0	3	2			
GAF		87.6 (6.44)	56.31 (10.94)	64.71 (11.36)	F (2,90) = 116.41	$p < .001$	HC > CHR-NR & CHR-R, CHR-R > CHR-NR
GF: Social scale		8.82 (.391)	7.54 (1.10)	7.65 (.862)	H (2) = 43.05	$p < .001$	HC > CHR-NR & CHR-R
GF: Role scale		8.57 (.764)	7.31 (1.19)	8.06 (.66)	H (2) = 30.30	$p < .001$	HC > CHR-NR & CHR-R, CHR-R > CHR-NR
CAARMS total		0.73 (.235)	36.85 (14.76)	29.18 (16.20)	F (2,90) = 112.97	$p < .001$	HC < CHR-NR & CHR-R
Current suicide risk	No	49	14	9	$x^2(2) = 30.51$	$p < .001$	HC < CHR-NR & CHR-R
	Yes low	0	5	3			
	Yes moderate	0	2	4			
	Yes high	0	4	1			
BACS		303.19 (24.85)	268.12 (46.37)	279.94 (44.47)	F (2, 90) = 8.61	$p < .001$	HC > CHR-NR
Follow-up characteristics							
GAF		NA	54.77 (1.94)	71.65 (2.269)	t (41) = -5.58	$p < .001$	
GF: Social scale		NA	6.88 (1.177)	8.07 (.884)	U = 86	$p = .003$	
GF: Role scale		NA	7.08 (1.129)	8.33 (.617)	U = 64	$p < .001$	
CAARMS total		NA	24.69 (14.94)	4.53 (4.96)	t (41) = 5.36	$p < .001$	
Change in GAF		NA	- 1.54 (13.38)	6.94 (13.07)	t (41) = -2.05	$p = .047$	
Change in Social scale		NA	- .654 (1.23)	.33 (1.047)	U = 109.5	$p = .017$	
Change in Role scale		NA	- 0.231 (1.24)	.33 (.816)	U = 138	n.s. (.103)	
Change in CAARMS total		NA	- 12.15 (15.14)	- 24.65 (15.96)	t (41) = 2.59	$p = .013$	

HC, healthy controls; CHR-NR, clinical high risk non-remitters; CHR-R, clinical high risk remitters; CAARMS, comprehensive assessment of at risk mental states; GAF, Global Assessment of Functioning; GF, global functioning; BACS, brief assessment of cognition in schizophrenia; n.s., non-significant. P > 0.05 listed as non-significant.

5.3.1.4 Symptom and functioning levels of the entire UHR sample at 12 months

Among the 43 UHR participants with 12-month follow-up data, there was a significant improvement in the severity of APS from baseline (M = 33.81, SD = 15.62) to 12 months (M = 16.72, SD = 15.55) (t = 6.80, p < .01). However, there was no significant change in the GAF score from baseline (M = 59.63, SD = 11.73) to 12 months (M = 61.44, SD = 12.71), (t = 6.80, p = .39) (Figure 5.4). Similarly there was no significant improvement in role functioning (t = .14, p = .89) from baseline (M = 7.56, SD = 1.07) to 12 months (M = 7.54, SD = 1.14) or in social functioning (t = 1.50, p = .14) from baseline (M = 7.61, SD = 1.02) to 12 months (M = 7.32, SD = 1.21). Pearson correlation analysis showed that there was no significant relationship between symptomatic and functional remission (r = -.05, p = .78).

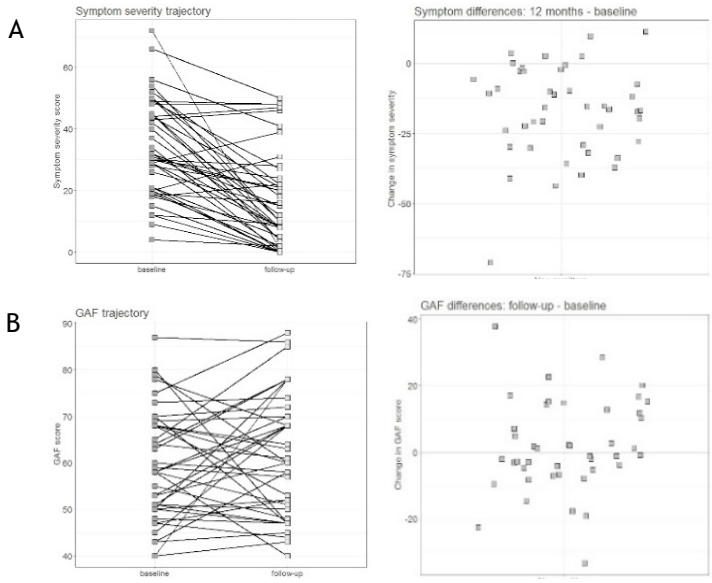


Figure 5.4 GAF and APS change in the entire UHR group over 12 months. (A) Change in the severity of APS and (B) the GAF score from baseline to a 12-month follow-up among UHR individuals. GAF, Global assessment of functioning.

5.3.2 **MMNm analyses**

5.3.2.1 **Transition effect on MMNm**

5.3.2.1.1 Sensor level

For durMMNm, a 2 x 3 mixed-design ANOVA with one within-subjects factor of hemisphere (left, right) and one between-subjects factor of group (HC, CHR-T, CHR-NT) revealed a significant main effect of hemisphere (F (1, 111) = 10.87, p < .01) but no significant main effect of group (F (2, 111) = .18, p = .84) or group by hemisphere interaction (F (2,111) = .60, p = .55). Similarly for omiMMNm, there was a significant main effect of hemisphere (F (1, 111) = 12.98, p = < .01) but no significant main effect of group (F (2, 111) = .76, p = .47) or group by hemisphere interaction (F (2, 111) = 2.19, p = .12) (Table 5.3).

Table 5.3 Means and standard deviations of MMNm peak amplitudes for the CHR-NT, CHR-T and HC groups over the left and right hemisphere.

	Group					
Hemisphere	CHR-NT (n = 60)	CHR-T (n = 5)	HC (n = 49)	CHR-NT vs CHR-T *d*	HC vs CHR-NT *d*	HC vs CHR-T *d*
durMMNm						
Left	4.18 (3.47)	4.10 (4.58)	4.57 (4.65)	0.02	0.01	0.10
Right	6.03 (4.43)	7.96 (6.23)	6.12 (4.49)	0.36	0.02	0.34
omiMMNm						
Left	2.80 (1.80)	2.63 (1.07)	2.79 (1.69)	0.10	0.01	0.11
Right	3.33 (2.25)	5.44 (1.76)	3.57 (2.51)	1.05	0.10	0.86

HC, healthy controls; CHR-NT, clinical high risk non-transitioners; CHR-T, clinical high risk transitioners.

5.3.2.1.2 Virtual channels

Kruskal-Wallis tests did not reveal a significant main effect of group on dur*MMN*m or omi*MMN*m peak amplitudes in any of the ROIs (Table 5.4).

Table 5.4 Virtual channel means and standard deviations of MMNm peak amplitudes in the CHR-NT, CHR-T and HC group, effect sizes of group differences and statistical results comparing the groups on MMNm peak amplitudes in each ROI.

	Group						
ROI	CHR-NT (n = 60)	CHR-T (n = 5)	HC (n = 48)	CHR-NT vs CHR-T *d*	HC vs CHR-NT *d*	HC vs CHR-T *d*	Statistics
durMMNm							
L HG	7.50 (8.26)	11.10 (12.00)	8.88 (12.78)	0.35	0.13	0.18	H(2) = 0.69, *p* = .71
R HG	26.74 (31.69)	21.74 (25.19)	25.72 (28.42)	0.17	0.03	0.15	H(2) = 0.07, *p* = .97
L STG	7.38 (8.39)	10.22 (9.22)	9.93 (14.51)	0.32	0.22	0.02	H(2) = 0.44, *p* = .80
R STG	24.19 (27.04)	28.53 (35.60)	25.40 (29.98)	0.14	0.04	0.1	H(2) = 0.09, *p* = .96
L MTG	4.90 (6.49)	5.16 (7.24)	9.08 (13.40)	0.04	0.4	0.36	H(2) = 2.78, *p* = .25
R MTG	9.72 (11.31)	12.40 (16.74)	12.10 (13.36)	0.19	0.2	0.02	H(2) = 0.83, *p* = .66
R IFG	1.07 (2.19)	.62 (.40)	.88 (.78)	0.29	0.12	0.42	H(2) = 1.07, *p* = .59
omiMMNm							
L HG	3.96 (4.14)	1.80 (1.94)	4.30 (5.03)	0.67	0.07	0.66	H(2) = 1.79, *p* = .41
R HG	8.17 (10.05)	13.28 (16.11)	9.03 (9.30)	0.38	0.09	0.32	H(2) = 1.09, *p* = .58
L STG	2.91 (2.94)	1.47 (1.89)	3.92 (4.53)	0.58	0.26	0.71	H(2) = 2.59, *p* = .27
R STG	7.11 (8.09)	10.48 (11.44)	8.42 (8.10)	0.34	0.16	0.21	H(2) = 2.83, *p* = .24
L MTG	2.89 (4.24)	1.29 (.73)	3.81 (5.05)	0.53	0.2	0.7	H(2) = 3.10, *p* = .21
R MTG	3.89 (5.52)	6.62 (6.12)	5.71 (7.32)	0.47	0.28	0.13	H(2) = 3.50, *p* = .17
R IFG	.47 (.57)	.41 (.45)	0.49 (.52)	0.12	0.004	0.16	H(2) = 0.47, *p* = .79

Uncorrected critical *p*-values listed. HC, healthy controls; CHR-NT, clinical high risk non-transitioners; CHR-T, clinical high risk transitioners; ROI, region of interest; HG, Heschl's gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus; IFG, inferior frontal gyrus.

5.3.2.2 **Remission effect on MMNm**

5.3.2.2.1 Sensor level

A 2 x 3 mixed-design ANOVA revealed a significant main effect of hemisphere (F (1, 89) = 8.34, p = .01) but no significant main effect of group (F (2, 89) = 1.44, p = .24) or group by hemisphere interaction (F (2, 89) = .16, p = .85) on dur*MMN*m (Table 5.5 & Figure 5.5). In analysis of omi*MMN*m responses, the ANOVA revealed a significant main effect of hemisphere (F (1, 89) = 6.21, p = .02), but no main effect of group (F (2, 89) = .37, p = .70) or hemisphere by group interaction (F (2, 89) = .15, p = .86) (Table 5.5 & Figure 5.5). The distributions of individual MMNm peak amplitudes for each group are presented in Appendix B.2.

Table 5.5 Means and standard deviations of MMNm peak amplitudes for the CHR-NR, CHR-R and HC groups and the effect sizes of group differences over the left and right hemisphere.

	Group			
Hemisphere	CHR-NR (n = 26)	CHR-R (n = 17)	HC (n = 49)	CHR-R vs CHR-NR *d*
durMMNm				
Left	4.60 (3.37)	3.23 (3.26)	4.57 (4.65)	0.41
Right	6.48 (4.70)	4.31 (3.89)	6.12 (4.49)	0.50
omiMMNm				
Left	3.09 (2.02)	2.49 (1.45)	2.79 (1.69)	0.34
Right	3.55 (2.11)	3.24 (2.26)	3.57 (2.52)	0.14

HC, healthy controls; CHR-R, clinical high risk remitters; CHR-NR, clinical high risk non-remitters.

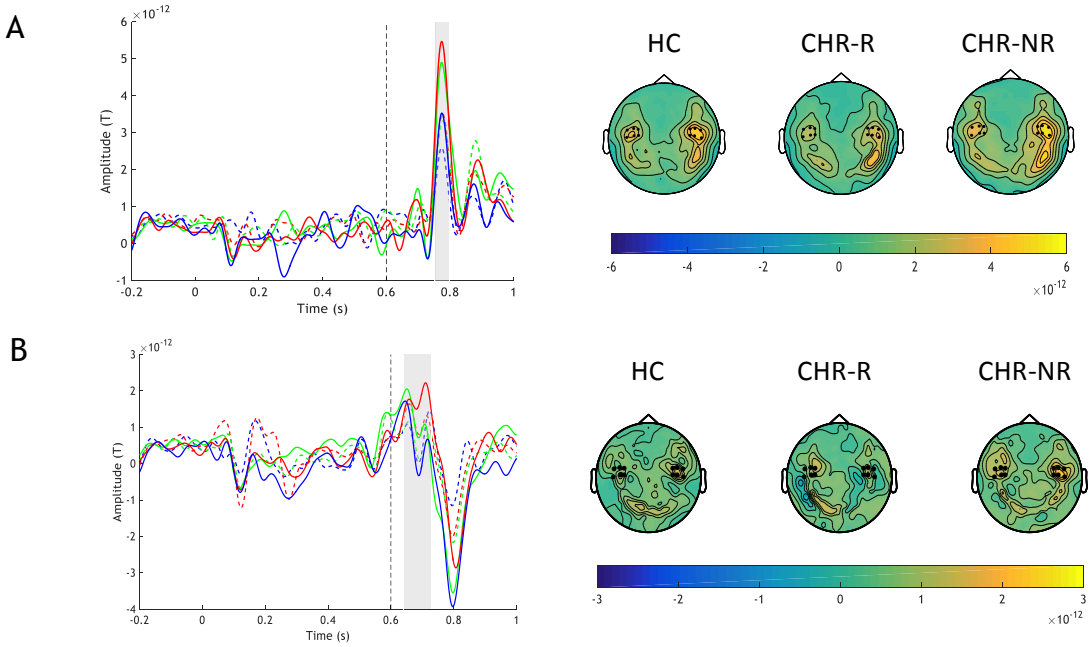


Figure 5.5 DurMMNm and omiMMNm waveforms and topographic plots for the CHR-R, CHR-NR and HC groups. Grand average MMNm waveforms for the HC (green line), CHR-R (blue line) and CHR-NR (red line) groups derived from the six left (dashed line) and right (solid line) MEG sensors as marked by the black dots in the topographic plots and topographic maps of MMNm components over the left and right hemisphere for each group in the TOIs (grey shaded area) which were used to extract individual MMNm peak amplitude values. The top panel (A) presents the durMMNm effect and the bottom panel (B) presents the omiMMNm effect. HC, healthy controls; CHR-R, clinical high risk remitters; CHR-NR, clinical high risk non-remitters.

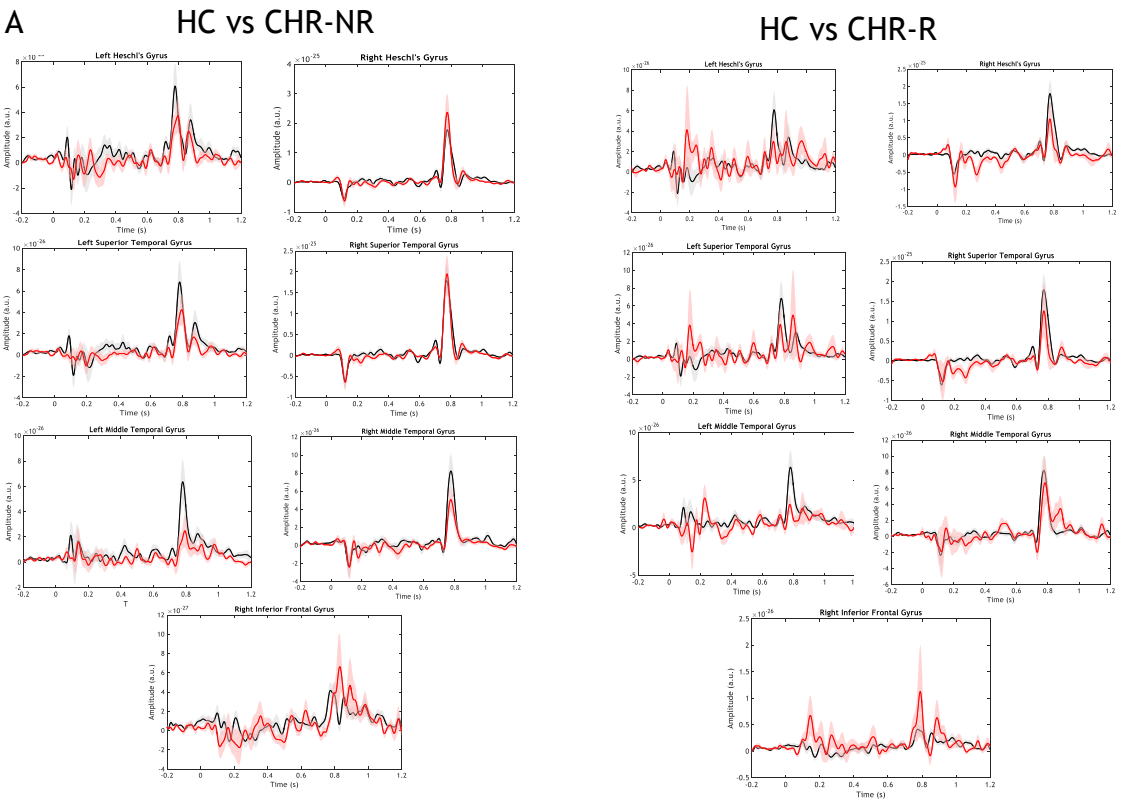
5.3.2.2.2 Virtual channels

The results of Kruskal-Wallis tests suggested a group effect on omiMMNm peak amplitude in the right MTG. However, this effect is not significant when corrected for multiple comparisons. The results did not reveal any other group effects on durMMNm or omiMMNm peak amplitudes in any of the ROIs (Figure 5.6 & Table 5.6).

Table 5.6 Means and standard deviations (in parentheses) of MMNm peak amplitudes in the CHR-NR, CHR-R and HC group, effect sizes of group differences and statistical results comparing the groups on MMNm peak amplitudes in each ROI.

	Group						
ROI	CHR-NR (n = 26)	CHR-R (n = 17)	HC (n = 48)	CHR-NR vs CHR-R *d*	HC vs CHR-NR *d*	HC vs CHR-R *d*	Statistics
durMMNm							
L HG	7.97 (8.11)	5.88 (6.46)	8.88 (12.78)	0.29	0.09	0.3	X^2 (2) = 0.47, p = .79
R HG	30.00 (36.49)	16.46 (20.92)	25.72 (28.42)	0.45	0.13	0.37	X^2 (2) = 1.96, p = .38
L STG	8.27 (8.44)	6.40 (7.71)	9.93 (14.51)	0.23	0.14	0.3	X^2 (2) = 0.65, p = .72
R STG	24.85 (26.43)	17.56 (27.71)	25.40 (29.98)	0.27	0.02	0.27	X^2 (2) = 2.04, p = .36
L MTG	5.44 (7.57)	3.92 (4.34)	9.08 (13.40)	0.25	0.33	0.52	X^2 (2) = 2.48, p = .29
R MTG	7.80 (7.30)	10.38 (14.66)	12.10 (13.36)	0.22	0.4	0.12	X^2 (2) = 1.37, p = .51
R IFG	.80 (1.27)	1.55 (3.65)	.88 (.78)	0.27	0.08	0.25	X^2 (2) = 1.77, p = .41
omiMMNm							
L HG	3.45 (4.05)	3.30 (2.53)	4.30 (5.03)	0.04	0.19	0.25	X^2 (2) = 0.15, p = .93
R HG	7.85 (7.83)	8.07 (9.44)	9.03 (9.30)	0.03	0.14	0.1	X^2 (2) = 0.52, p = .77
L STG	2.89 (3.07)	2.68 (2.17)	3.92 (4.53)	0.08	0.266	0.35	X^2 (2) = 0.44, p = .80
R STG	6.16 (5.87)	8.95 (9.55)	8.42 (8.10)	0.35	0.32	0.06	X^2 (2) = 1.78, p = .41
L MTG	3.14 (5.60)	2.97 (2.68)	3.81 (5.05)	0.04	0.13	0.21	X^2 (2) = 2.53, p =. 28
R MTG	2.37 (2.74)	6.40 (7.83)	5.71 (7.32)	0.69	0.6	0.09	X^2 (2) = 6.41, p = .04
R IFG	.43 (.61)	.46 (.50)	0.49 (.52)	0.05	0.11	0.06	X^2 (2) = 0.98, p = .61

Uncorrected critical *p*-values listed. HC, healthy controls; CHR-R, clinical high risk remitters; CHR-NR, clinical high risk non-remitters; ROI, region of interest; HG, Heschl's gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus; IFG, inferior frontal gyrus.



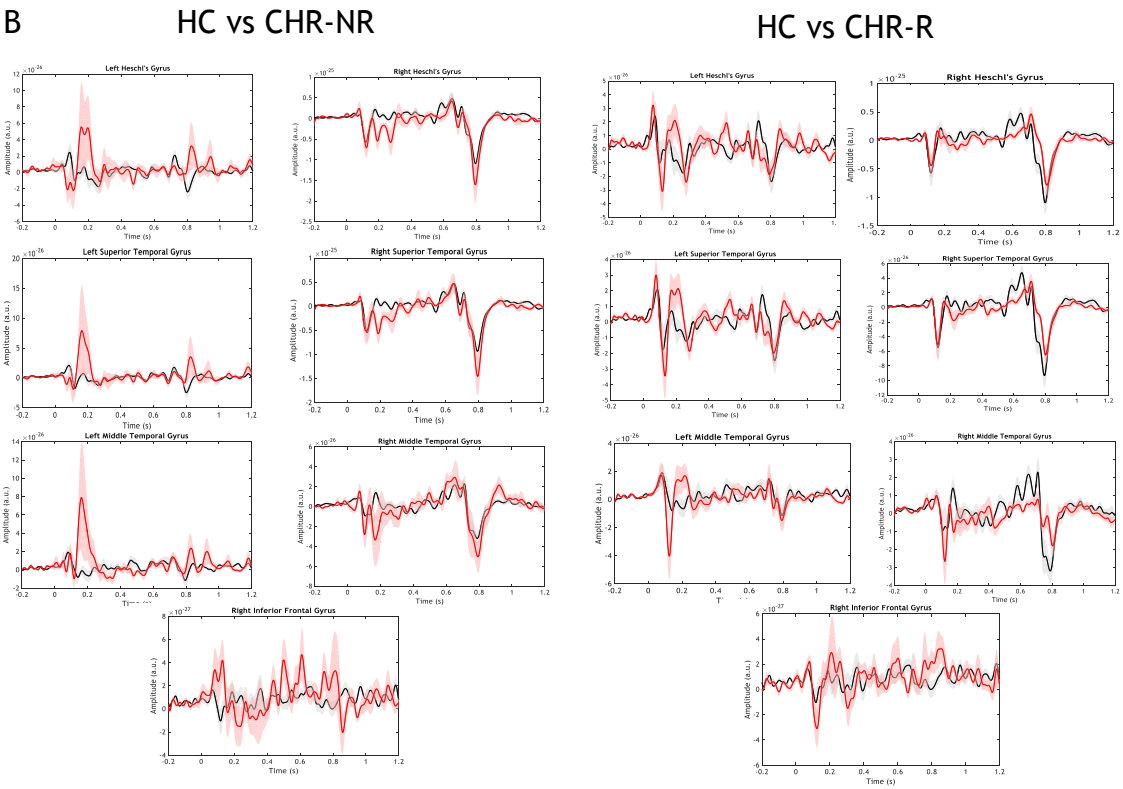


Figure 5.6 Virtual channel durMMNm (A) omiMMNm (B) waveforms for the HC, CHR-R and CHR-NR groups. Grand average MMNm virtual channel time series with SEM error bars (shaded areas) comparing controls (black line) with CHR-NRs (red line) (left panel) and controls with CHR-Rs (right panel) in each ROI. The onset of the deviant sound was at 0.6 seconds. Absolute values are given. HC, healthy controls; CHR-R, clinical high risk remitters; CHR-NR, clinical high risk non-remitters.

5.3.3 **Prediction models**

5.3.3.1 **Predicting symptom levels at 12 months**

There was no multicollinearity between the six independent variables as indicated by tolerance (0.75 - 0.88) and Variance Inflation Factor values (VIF: 1.14 – 1.33). The regression revealed that the model one with five clinical and cognitive variables was significant (F (5, 37) = 3.20, p = .01, R^2 = .30) against a null model (no predictors) and accounted for 30 % of the variation in the severity of APS at 12 months. The duration MMNm amplitude explained an additional 5.2 % of the APS at 12 months but the R^2 change was not significant (ΔF (1, 36) = 2.92, p = .10, R^2 = .052). The baseline APS severity was the only significant predictor of the APS severity at 12 months when controlling for other four factors (β = .43, p = .01). The positive regression coefficient suggests that as the baseline symptom severity increases by 1 point, the symptom level at 12 months goes up by 0.43 points (Table 5.7).

Table 5.7 Summary of multiple hierarchical regression analysis for variables predicting the APS severity at 12 months in CHR individuals.

		Standardized Coefficients	*t*	*p*	Tolerance	VIF	R^2	ΔR^2
Step 1							0.302	0.302
	(Constant)		1.654	.107				
	Baseline Role	.127	.832	.411	.808	1.237		
	Baseline Social	-.102	-.676	.503	.826	1.211		
	Baseline GAF	-.180	-1.138	.262	.753	1.329		
	Baseline APS	.425	2.757	.009	.792	1.263		
	Baseline BACS	-.238	-1.578	.123	.827	1.210		
Step 2							0.355	0.052
	(Constant)		1.542	.132				
	Baseline Role	.194	1.259	.216	.756	1.322		
	Baseline Social	-.130	-.875	.388	.816	1.225		
	Baseline GAF	-.192	-1.240	.223	.751	1.331		
	Baseline APS	.377	2.460	.019	.765	1.308		
	Baseline BACS	-.272	-1.832	.075	.812	1.232		
	DurMMNm	.244	1.710	.096	.879	1.138		

GAF, Global Assessment of Functioning; CAARMS, comprehensive assessment of at risk mental states; BACS, brief assessment of cognition in schizophrenia.

5.3.3.2 **Predicting global functioning at 12 months**

A two-step hierarchical multivariate regression was used with the GAF score at 12 months as the dependent variable. Baseline role and social functioning, GAF score, APS severity and BACS composite score were entered at step one and the durMMNm amplitude was incorporated into the model at step two. No sources of multicollinearity were present among predictor variables (Tolerance: 0.75 - 0.88, VIF: 1.14 – 1.33).

The results of the regression analysis revealed that the overall model with five clinical and cognitive factors was statistically significant compared to a null model (F (5, 37) = 3.04, p = .02, R^2 = .29)), indicating that the model with the full set of variables successfully predicted the GAF score at 12 months. The model accounted for 30 % of the variation in the GAF score at 12 months. However, the durMMNm variable did not explain any additional variation in the GAF score and the R^2 change was not significant (ΔF (1, 36) = .04, p = .84, R^2 = .01). In the predictive model with five factors (excluding the durMMNm amplitude), the baseline role functioning score (ß = .37, p = .02) was the only significant predictor of the GAF score when other predictors in the model were hold constant. The positive regression coefficient indicates that as the baseline role functioning goes up by 1 point, the GAF score at 12 months improves by 0.24 points (Table 5.8).

Table 5.8 Summary of multiple hierarchical regression analysis for variables predicting the GAF at 12 months in CHR individuals.

		Standardized Coefficients (ß)	*t*	*p*	Tolerance	VIF	R^2	ΔR^2
Step 1							0.291	0.291
	(Constant)		2.019	.051				
	Baseline Role	.373	2.420	.021	.808	1.237		
	Baseline Social	-.123	-.805	.426	.826	1.211		
	Baseline GAF	.241	1.509	.140	.753	1.329		
	Baseline APS	-.193	-1.238	.224	.792	1.263		
	Baseline BACS	-.101	-.664	.511	.827	1.210		
Step 2							0.292	0.001
	(Constant)		2.004	.053				
	Baseline Role	.364	2.258	.030	.756	1.322		
	Baseline Social	-.119	-.768	.448	.816	1.225		
	Baseline GAF	.242	1.497	.143	.751	1.331		
	Baseline APS	-.186	-1.162	.253	.765	1.308		
	Baseline BACS	-.097	-.622	.538	.812	1.232		
	DurMMNm	-.031	-.207	.837	.879	1.138		

GAF, Global Assessment of Functioning; CAARMS, comprehensive assessment of at risk mental states; BACS, brief assessment of cognition in schizophrenia.

5.4 Discussion

5.4.1 Transition to psychosis

The first aim of the chapter was to investigate whether CHR-Ts show reduced baseline duration MMNm amplitude compared to CHR-NTs and controls. However, we were unable to find evidence for group differences in MMNm amplitudes and thus the current study does not provide evidence for MMNm amplitude to be associated with transition to psychosis in CHR individuals. Our results are in contrast with two recent meta-analyses reporting MMN deficits in CHR-Ts compared CHR-NTs (Bodatsch, Brockhaus-Dumke, Klosterkötter, & Ruhrmann, 2015; Erickson et al., 2016). On the other hand, our findings are in line with the largest longitudinal CHR study in the literature suggesting MMN not to be a promising marker for psychosis prediction in CHR individuals (Atkinson et al., 2017).

Similar to several previous studies among clinically recruited CHR individuals (Lim et al., 2018; Yung et al., 2007), the majority of the current CHR sample did not experience a psychotic episode during the 12 month follow-up period. More specifically, only 5 out of 65 CHR individuals with follow-up data available experienced a transition to psychosis. CHT-NTs and CHR-Ts differed only in social functioning at baseline but not in any other demographic, clinical or neuropsychological characteristic. This is consistent with a previous CHR study

that reported poor baseline social functioning to predict psychosis onset (Cornblatt et al., 2007). On the other hand, despite a trend towards poorer global functioning and younger age of CHR-Ts compared to CHR-NTs, our results are in contrast with studies reporting baseline functioning and symptom severity to be associated with transition to psychosis (e.g. T. D. Cannon, Cadenhead, Cornblatt, Woods, et al., 2008). However, similar to previous longitudinal CHR studies examining MMN amplitude as a marker for predicting psychosis onset, our findings are limited by the lack of statistical power due to a small sample of CHR-Ts (n = 5), resulting in increased probability of a type 2 error. Hence, these results should be interpreted with caution until replicated in a larger, ideally in a sample of > 20 participants (Simmons et al., 2011).

5.4.2 **Symptomatic and functional remission**

Besides examining MMNm peak amplitude as a potential marker for transition to psychosis, we also sought to determine whether MMNm amplitude can discriminate UHR individuals who achieved the predefined full remission (no longer met the UHR criteria & the GAF score ≥ 60) from those who did not. In contrast to our expectations, UHR individuals who sustained the initial UHR state for psychosis and low functioning at 12 months did not show reduced MMNm. Our finding is inconsistent with a recent study that reported CHR-NRs to have reduced duration MMN amplitudes compared to CHR-Rs (Kim et al., 2018). The conflicting results are unlikely due to the operationalisation of remission or the quantification of the MMN amplitude as both studies were similar in these aspects. However, Kim and colleagues (2018) had a 6-year follow-up period that was substantially longer than the current follow-up period of 12 months. Moreover, Kim and colleagues (2018) recruited CHR individuals from a special early detection centre for people at risk for psychosis and both CHR-R and CHR-NR groups in their study had substantially lower global functioning at baseline and follow-up compared to those in the current study. Thus, it could be that these inconsistent findings are due to variability in the follow-up period or different CHR samples.

Previous studies have reported variable remission rates of CHR-Ts, potentially due to several reasons, such as the recruitment strategy, the length of the follow-up period and the lack of standardised definition and criteria of remission

(Polari et al., 2018). We used the definition based on both symptomatic and functional outcome, given that previous research has showed that remission from APS does not translate to a good functional outcome in CHR individuals (Addington et al., 2011). IN line with this, we observed that although 70 % of UHR individuals remitted from their initial UHR status, only 39.5 % achieved full remission at 12 months. This remission rate is almost identical to a 39.7 % symptomatic and functional remission rate at 2 years reported in a study among clinically recruited CHR individuals (T. Y. Lee, Kim, et al., 2014), suggesting similar full remission rates in clinical and community CHR samples. Given that 70 % of the current UHR sample achieved symptomatic remission but only 58 % functional remission and the lack of correlation between functional and symptomatic remission, the current study replicates previous findings among clinical CHR individuals indicating that despite being symptom free, CHR individuals do not in general reach optimal functioning levels (Addington et al., 2011; T. Y. Lee, Kim, et al., 2014).

The current study revealed that CHR-Rs had better baseline global and role functioning compared to CHR-NR, suggesting these two measures to be associated with later symptomatic and functional remission. The existing literature on demographic and clinical profiles of remitters and non-remitters is conflicting. While some studies have not find evidence for symptom levels and functioning to be associated with a long-term outcome (M. Kim et al., 2018, 2015), others have found differences in baseline positive symptoms, antipsychotic medication (T. Y. Lee, Kim, et al., 2014), negative symptoms and mood/anxiety symptoms between CHR-Rs and CHR-NRs (Schlosser et al., 2012). At 12 months, as expected, CHR-Rs had lower symptom levels and better functioning than CHR-NRs. Nonetheless, CHR-Rs still had poorer social and global functioning than healthy controls, suggesting that CHR-Rs continued to function poorly despite an improvement in symptoms and functioning over time.

5.4.3 Predicting symptom levels and global functioning at 12 months

The final aim of the chapter was to investigate whether incorporating duration MMNm data with clinical and neuropsychological measures improves the prediction of symptom levels or global functioning at 12 months in UHR

individuals. Against our hypotheses, the results revealed that MMNm amplitude did not contribute to the prediction of the severity of APS or global functioning above and beyond clinical and cognitive predictor variables. The full set of five baseline clinical and cognitive variables accounted for moderate ~30 % of the variance in both symptom level and global functioning at 12 months. The baseline symptom level was the only significant predictor of later symptoms when controlling for other variables, while baseline role functioning was the only reliable predictor of global functioning at 12 months. Our findings are in contrast with the aforementioned study that in addition to group differences in MMN found it also to predict functional and symptomatic improvement (M. Kim et al., 2018).

5.4.4 Clinical outcomes of UHR individuals at 12 months

Regarding the outcome of the entire UHR sample at 12 months, approximately 92 % UHR individuals did not transition to psychosis and 70 % no longer met the UHR criteria, suggesting that the majority of individuals identified to be at the high risk state of psychosis represent false positives in our study. The low transition rate and the high symptomatic remission rate could be due to recruiting CHR individuals from the community resulting in a dilution of psychosis risk enrichment and subsequent transition rate as demonstrated by recent meta-analytical evidence (Paolo Fusar-Poli, Schultze-Lutter, et al., 2016). Interestingly though, none of the CHR-Ts in the current study were clinically referred but came from the community, suggesting that the clinically referred CHR individuals did not have an elevated risk of psychosis compared to community recruited CHR individuals. Moreover, the CHR-T group included CHR individuals with both BS and APS and none of the CHT-Ts had a known family history of psychosis, overall suggesting that the recruitment pathway, high risk stage and family history were not associated with transition to psychosis in the current study.

Considering that only 30 % of the current UHR sample still met the clinical UHR criteria at 12 months, it is possible that the majority of the UHR sample recruited from the community had transient APS, which have been shown to be common in the general population (I. Kelleher & Cannon, 2011). Alternatively, APS might have been related to the co-presence of depressive/anxiety disorders,

which were present in 61 % of the current sample at baseline. Indeed, we observed that CHR individuals with a comorbid anxiety/depressive disorder had a higher APS severity than CHR individuals without a comorbid disorder at baseline (Appendix B.3). This findings is consistent with descriptions of anxiety and depression to be associated with psychotic symptomatology in clinical (J. T.W. Wigman et al., 2011; Johanna T.W. Wigman et al., 2012) and non-clinical CHR samples (Shi et al., 2017). Thus, it is possible that most CHR individuals were not at risk for developing psychosis but exhibited a depressive/mood disorder with transient APS.

Last but not least, it is important to note that despite the UHR sample showing a significant decrease in the severity of APS over 12 months, they did not improve significantly in terms of social, role or global functioning. These findings extend the current CHR literature by showing that similar to CHR individuals recruited through clinical services, community CHR individuals remain at a poor functional status despite remitting from their symptoms and highlights the importance of adding functioning as an outcome evaluation in CHR studies.

5.4.5 **Limitations and conclusions**

Several limitations of the current study need to be kept in mind when interpreting the results in chapter 5. Firstly, the low number of CHR-Ts resulted in underpowered statistical comparisons making it difficult to detect potential small group differences, a common challenge in the CHR field overall. To avoid this limitation in future studies, it might be beneficial to limit recruitment to clinically referred CHR individuals who are seeking help for mental health problems, as suggested by the European Psychiatric Association (F. Schultze-Lutter et al., 2015), to obtain samples with a higher pre-test enrichment and potentially higher subsequent transition rates (Paolo Fusar-Poli, Schultze-Lutter, et al., 2016) or pool data from several studies. Secondly, the 12-month follow-up period was relatively short considering meta-analytical evidence suggesting that CHR individuals have an elevated risk for developing psychosis up to 3 years with the risk increasing over the years (Paolo Fusar-Poli, Bonoldi, et al., 2012). Therefore, the current follow-up period of 12 months might not be long enough to determine the final outcome of CHR individuals. Lastly, MMNm amplitude was assessed only cross-sectionally at baseline and thus we do not have longitudinal

data to determine whether MMNm amplitude changed along with symptoms or functioning.

In conclusion, chapter 5 sought to extend the existing literature by examining whether MMNm amplitude differentiates UHR individuals who achieved the predefined symptomatic and functional remission from those who did not in addition to aiming to replicate past findings suggesting MMN to be able to distinguish CHR-Ts from CHR-NTs. However, contrary to our hypotheses and some recent findings, we found no evidence for an effect of transition or remission on MMNm amplitude in the current study. Furthermore, the current results revealed that neither symptom levels nor global functioning of CHR-NTs at 12 months was predicted by baseline duration MMNm amplitude, overall questioning the predictive utility of MMNm in the high risk stage of psychosis. Instead, the results showed that baseline symptoms predicted symptoms at 12 whereas global functioning was reliable predicted by baseline role functioning. From the clinical perspective, baseline role functioning was highlighted as a key variable in our study as it was associated with full remission and predicted global functioning at 12 months. This finding suggests that CHR individuals with low role functioning should receive additional clinical support as they are more likely to sustain subthreshold psychotic symptoms and poor functioning than CHR individuals with higher role functioning. Overall, the follow-up analysis of the entire UHR sample revealed that there was a significant improvement in APS but not in functioning over 12 months, demonstrating that individuals who meet the UHR criteria for developing psychosis in the community are characterised by long-lasting poor functioning regardless of symptomatic remission.

6 General Discussion

6.1 Overview

Higher order cognitive as well as early sensory information processing deficits are core characteristics of established schizophrenia (Harvey, 2012; Nuechterlein, Dawson, & Green, 1994) but have also been observed early on in the illness in first episode patients and even in CHR individuals as discussed in the introduction chapter (chapter 1). Advancements in neuroimaging methods, such as EEG and MEG, have enabled examining non-invasively the neurophysiological basis of these perceptual and cognitive disturbances and have revealed impairments in several neural correlates of early and late sensory processing in different stages of psychosis. Previous work has shown a large MMN(m) deficit in chronic schizophrenia and pointed towards a moderate impairment in first episode patients (Erickson et al., 2016). Moreover, previous studies have suggested MMN alterations to occur even prior to the onset of psychosis, potentially representing a marker of risk for psychosis development. However, unlike robust findings of reduced MMN in chronically ill patients with schizophrenia, evidence on reduced MMN in CHR individuals as well as first episode patients is more inconsistent. Accordingly, the first aim of the thesis was to investigate MEG recorded MMNm amplitudes in CHR individuals and compare them to first episode patients and controls (chapter 3). A further goal of chapter 3 was to explore whether duration MMNm is associated with cognitive performance and functioning in CHR individuals. In addition to using a conventional approach to compare MMNm amplitudes between CHR individuals and healthy controls, I employed dynamic causal modelling to assess effective connectivity underlying the MMNm generation to determine whether CHR individuals exhibit aberrant connectivity compared to controls (chapter 4).

The introduction of the UHR paradigm and criteria over two decades ago allowed the early detection of individuals at risk for developing a first episode of psychosis (Yung & McGorry, 1996) and currently targeting individuals with subthreshold psychotic symptoms who are actively seeking help is considered the most appropriate prevention strategy for psychosis (Klosterkötter, 2008; McGorry, Killackey, & Yung, 2008) and to reduce DUP (Millan et al., 2016), a valuable prognostic indicator in schizophrenia (Cechnicki, Hanuszkiewicz,

Polczyk, & Bielańska, 2011). However, in contrast to transition rates to psychosis in early CHR studies, there has been a decline over the years and more recent rates range from 10 % to 20 % over 2-3 years (Simon & Umbricht, 2010; Yung et al., 2008). This has raised concerns regarding stigmatising (Corcoran, Malaspina, & Hercher, 2005) and treating unnecessarily false positive individuals and recent research efforts have been focused on finding measures to improve outcome prediction in CHR individuals (Thompson, Marwaha, & Broome, 2016). To this end, by following-up the CHR group for 12 months, I aimed to assess the utility of baseline MMNm amplitude as a marker predicting psychosis development as well as functional and symptomatic remission at 12 months. Lastly, I also examined whether MMNm data improves prediction of symptom severity and global functioning at 12 months above and beyond clinical and neuropsychological measures in CHR individuals (chapter 5).

6.2 Key findings and their implications

6.2.1 Neurophysiological findings

One common criticism of previous CHR studies is that they have treated CHR individuals as one clinical entity, overlooking heterogeneous clinical phenotypes within the high risk stage, which may impede the discovery of biomarkers. In chapter 3, the large sample of CHR individuals (*n* = 106) made it possible to address this limitation by examining MMNm amplitudes according to more homogeneous CHR subgroups (Frauke Schultze-Lutter et al., 2010). However, the results revealed similar MMNm responses in CHR subgroups.

The main aim of chapter 3 was to investigate the presence of MMNm amplitude deficiency in CHR individuals. However, we did not find any significant group differences in MMNm amplitudes to duration deviants or sound omissions between CHR individuals and controls either on the sensor level or in source space ROIs. Moreover, the results of the shift function between the CHR and HC group revealed similar MMNm amplitude distributions in the two groups, providing further evidence that MMN deficiency is not present during the high risk stage of psychosis. Our finding corroborates previous findings of intact MMN amplitude in CHR individuals (Bodatsch et al., 2011; Brockhaus-Dumke et al., 2005; Higuchi et al., 2013; Hirt et al., 2019). Similar to our data, the largest

published CHR study to date (UHR = 80, HC = 58) did not find evidence for reduced MMN in CHR individuals (Atkinson et al., 2017). On the other hand, our result is in contrast with studies that have suggested the CHR state to be characterised by MMN deficits. For instance, Atkinson and colleagues (2012) found reduced MMN amplitude to duration deviants in CHR individuals using EEG. This finding was replicated by Shin and colleagues (2012) using MEG. Notably, despite most MMN studies in the early psychosis literature using EEG, it is unlikely that the current finding is due to the imaging method as there is evidence for reduced MMN amplitude in CHR individuals in both EEG (Atkinson et al., 2012) and MEG studies (Shin, Jung, et al., 2012). Overall our finding challenges the notion that reduced duration MMN is a marker for early stages of psychosis whereas frequency MMN attenuation might only emerge later in the chronic phase (Koshiyama, Kirihara, Tada, Nagai, Fujioka, Koike, et al., 2018; Nagai, Tada, Kirihara, Yahata, et al., 2013; Todd et al., 2008). This notion is also opposed by previous studies that found reduced frequency MMN amplitudes in CHR individuals (Perez et al., 2014) and recent onset schizophrenia patients (Hay et al., 2015).

In chapter 4 we examined effective connectivity underlying the duration MMNm response using dynamic causal modelling (Friston et al., 2003) in CHR individuals and controls. As expected, the results indicated that that the model that allowed for changes in extrinsic forward and backward connections (FB-model) had the highest exceedance probability (54 %) compared to the next best model FBi (46 %) and was most likely to explain the observed MMNm response in controls. However, there were no significant group differences in any of the forward or backward connections within the MMNm brain network between CHR individuals and controls. Thus, based on our data and previous DCM studies it appears that the frontotemporal network dysfunctions are not present in the high risk state of psychosis but only in later illness stages (D. Dima et al., 2012; Ranlund et al., 2016).

It is possible that the lack of detecting small/moderate group differences in MMNm amplitudes or connectivity between CHRs and controls is due to insufficient power as the post-hoc power analysis showed that finding a moderate impairment (d = 0.40) with power of .80 would require a sample size

of 100 participants per group. On the other hand, the lack of reduced MMNm amplitude in CHR individuals and the modest replicability of attenuated MMN in CHR individuals in the literature overall might be due to the possibility that MMN impairments are only present in prodromal individuals (Bodatsch et al., 2011; Higuchi et al., 2013). However, our analysis in chapter 5 using clinical-follow up information to compare CHR individuals with and without conversion to full-blown psychosis within 12 months did not find evidence for reduced MMNm amplitude in CHR-Ts compared to CHT-NTs, suggesting MMN not to be reduced in the prodromal phase of psychosis. This finding is inconsistent with two recent meta-analyses (Bodatsch et al., 2015; Erickson et al., 2016). On the other hand, our data are consistent with findings by Hsieh and colleagues (2012) as well as a recent large CHR study that actually reported increased MMNm amplitude in CHR-Ts compared to CHR-NTs (Atkinson et al., 2017). However, both of these studies were limited by small sample sizes of CHR-Ts (n = 6 and n = 7, respectively), resulting in insufficient statistical power. Likewise, the majority of the current CHR sample (92 %) did not transition to psychosis within 12 months and thus the low number of CHR-Ts (n = 5) is a clear limitation of the current analysis and limits firm conclusions from the present results. In fact, Erickson and collagues (2016) pointed out that the effect size estimations for CHR-Ts and CHR-NTs in the aforementioned meta-analyses may also be unreliable due to studies with small samples.

In addition to examining whether MMNm amplitude is related to progression to psychosis in CHR individuals in chapter 5, we also investigated whether it is associated with persistence of subthreshold psychotic symptoms and poor functioning at 12 months. However, our data provide no evidence for our hypothesis that MMNm peak amplitude is attenuated in CHR-NRs compared to CHR-Rs. Lastly, the results of the regression models in chapter 5 revealed that adding the MMNm amplitude value to a model with clinical and neuropsychological measures did not improve predicting the severity of symptoms or daily functioning at 12 months and thus our study does not support the use of MMNm amplitude in addition to non-imaging measures for predicting outcome in CHR individuals.

Interestingly, the results from chapter 3 indicated intact mean MMNm amplitudes on the sensor and source level in first episode patients as well. The

shift function results revealed a group difference in the high end of the left hemisphere MMNm amplitude distribution, suggesting a group effect only on the high MMNm amplitudes. Our finding of a normal mean MMNm in first episode patients is in line with previous reports of unaffected MMN amplitudes in first episode patients (Magno et al., 2008; Mondragón-Maya et al., 2013; Salisbury et al., 2002; D. Umbricht et al., 2006). On the other hand, there are previous studies that have pointed towards MMN deficits to be present already in this population, with a recent meta-analysis reporting a medium (d = 0.42) MMN impairment in first episode psychosis (e.g. R. Atkinson, Michie, & Schall, 2012; Higuchi et al., 2013; Kaur et al., 2011). However, the current sample of 17 first episode patients is small and could have resulted in insufficient statistical power to detect small to medium group differences in central tendencies of MMNm amplitudes. Indeed, to have 80 % power to detect a medium effect size of 0.5, a sample size of 64 would be required. Future MMN studies could benefit from data pooling from several studies which is supported by a study that validated MMN for use in multi-site studies in schizophrenia research (Light et al., 2015).

Previous studies examining MMN in high risk and early stages of psychosis have employed a variety of deviant types to evoke MMN, ranging from deviants that differ on a simple feature dimension such as frequency, duration or intensity to more complex deviants breaking abstract rules. Our study employed a simple oddball paradigm including a duration deviant tone and sound omission. Given the recent meta-analytical evidence reporting larger MMN impairments to simple compared to complex deviants in schizophrenia patients (Avissar et al., 2018), it is unlikely that the MMNm paradigm contributed to the current neurophysiological null results. Another noteworthy methodological strength of the current study is that in line with recommendations for utilising MMN in clinical research, the MMNm auditory task was combined with a visual distractor task, making the recording conditions optimal by eliminating potential attention-related components (Duncan et al., 2009).

The overarching finding that emerged from the MMNm data presented in this thesis suggests normal preattentive auditory processing of change detection in high risk, prodromal and early stages of psychosis, not supporting MMNm to be a marker for early stages of psychosis. Instead, these findings might suggest that

MMN is a potential marker for disease progression, reflecting GM loss (Rasser et al., 2011; Salisbury, Kuroki, Kasai, Shenton, & McCarley, 2007) and/or NMDA-R hypofunction (D.C. Javitt et al., 1996). This interpretation is in line with cross-sectional studies that did not observe reduced duration MMN in first episode patients but only in recent onset and chronic schizophrenia patients (Magno et al., 2008; D. S. G. Umbricht, Bates, Lieberman, Kane, & Javitt, 2006). It could also be that the inconsistent MMN findings in high risk and early psychosis literature are related to the heterogeneity of long term outcomes in these populations; ranging from early sustained recovery to treatment resistant schizophrenia (Suvisaari et al., 2018). Thus, individuals with a favourable long-term outcome might exhibit intact MMN amplitudes and effective connectivity in contrast to those with a non-favourable outcome who might have begun development of chronic illness related brain pathology and exhibit MMN deficiencies already in earlier stages of psychosis. However, future longitudinal studies with multiple clinical and neurophysiological measures ideally following CHR individuals across different illness stages are warranted to confirm the time point when the deficiencies in the amplitude and the underlying connectivity of MMN occur and whether they index emerging psychosis or progression to schizophrenia.

Lastly, the results in chapter 3 indicated a weak positive association between MMNm amplitude and processing speed but no associations with symptoms or global functioning. While several studies have reported reduced MMN to correlate with poor functioning in chronic schizophrenia (Friedman et al., 2012; Light & Braff, 2005; Rasser et al., 2011), the evidence in the high risk stage is inconsistent, the majority of studies not reporting an association between MMN and functioning (Jahshan et al., 2012; Shin et al., 2009; Solís-Vivanco et al., 2014) but see (Koshiyama, Kirihara, Tada, Nagai, Fujioka, Koike, et al., 2018).

6.2.2 **Clinical findings**

To date, this is the first MMNm study in a large sample of community CHR individuals. Our analyses comparing clinically and community recruited CHR individuals revealed an attenuated duration MMNm amplitude in the clinically recruited CHR sample as well as poorer role functioning and neuropsychological performance compared to the community recruited CHR sample. The current

findings are consistent with a recent study that also found community CHR individuals to have higher role functioning compared to CHR individuals presented to clinical services (Mills et al., 2017). In contrast with our study, however, the authors also found lower symptom severity and general psychopathology in the clinically referred CHR sample. These findings have practical implications for how future CHR samples are recruited as well as assessing and documenting in detail characteristics of community and clinical CHR samples to increase the homogeneity, comparability and replicability of samples. However, it is important to note that the current clinically recruited sample was small (*n* = 12) and therefore the findings should be interpreted with caution.

The findings of chapter 3 contribute to the existing literature by demonstrating that similar to clinically recruited CHR samples, community recruited CHR individuals are also characterised by impaired functioning, high prevalence of suicidal ideation and comorbid diagnosis in addition to APS. Furthermore, our results indicated that APS explained variance in global functioning over and beyond the prevalence of suicidal ideation and comorbidity, demonstrating that APS are associated with significant disability even before they reach the diagnostic threshold. This supports a recent proposal of Mcgorry and colleagues (2018) that the term 'subthreshold states', namely the stage 1b in the clinical staging model, might be unhelpful as these individuals are in need for clinical care even before traditional diagnoses. Lastly, it is important to note that despite the majority of the current CHR sample being recruited from the general population, about half of the sample (52 %) was not medication-free at the time of recruitment and 63.2 % of them had previous or current clinical care and hence the current CHR sample should not be viewed as a medication-naïve and non-help-seeking sample. Taken together, the identification of CHR individuals, even through non-clinical pathways, seems to provide an important opportunity for early intervention and thus it is important to systematically assess general psychopathology in addition to APS and offer appropriate support.

In chapter 5, the clinical follow up data revealed that the majority of the current CHR sample (92 %) did not transition to psychosis within 12 months and only 5 CHR individuals developed psychosis. Considering the proactive

recruitment of CHR participants from the community in our study, the transition rate could have been expected to be lower than in studies including clinically recruited CHR samples due to a diluted pre-test risk of psychosis (Paolo Fusar-Poli, Rutigliano, et al., 2016; Paolo Fusar-Poli, Schultze-Lutter, et al., 2016; Oliver et al., 2019). However, this explanation is not supported by our data as none of the clinically referred CHR individuals transitioned to psychosis within the follow-up period of 12 months. Alternatively, the low number of CHR-Ts in our study might result partially from the high prevalence of CHR individuals with past or current psychological intervention (65 %) and medication (52 %), as evidence shows that CBT treatment may reduce psychosis risk at 12 months (Stafford, Jackson, Mayo-Wilson, Morrison, & Kendall, 2013) and a specific form of psychological treatment is associated with a lower transition rate than nonspecific psychiatric care (Paolo Fusar-Poli, Bonoldi, et al., 2012). However, unfortunately the nature of the treatment received was not documented in our study and this remains speculative. Nonetheless, it is important to note that the observed outcomes at 12 months in the current thesis might not reflect the natural course of CHR individuals recruited from the general population.

The results from chapter 5 revealed that 70 % of the UHR-NTs no longer met the UHR criteria at 12 months. However, despite achieving symptomatic remission, these individuals did not necessarily improve functionally as demonstrated by the finding that less than half (40 %) of UHR-NTs achieved the full remission criteria. The regression results in chapter 5 showed that the baseline APS severity was the only significant predictor of the severity of APS at 12 months whereas the baseline role functioning was the only predictor of global functioning over time. The finding that baseline role functioning was the only measure associated with achieving full remission as well as being a significant predictor of daily functioning at 12 months might have research and clinical implications. Future studies should assess role functioning more systematically with the instrument specifically designed for prodromal individuals (Cornblatt et al., 2007) and monitor and offer additional clinical interventions to CHR individuals with low role functioning. While vocational and educational interventions have been used with first episode (Killackey et al., 2013) and schizophrenia patients (Bio & Gattaz, 2011), the current data suggest that role functioning could be an important target already in the high risk state of

psychosis. Collectively, our 12-month follow-up results demonstrated that despite a significant improvement in APS over 12 months, CHR individuals did not improve significantly in social, role or global functioning. This is in line with previous studies that indicated that symptomatic remission does not correlate with functional remission in CHR samples (Addington et al., 2011; Oorschot et al., 2012; Wunderink, Nieboer, Wiersma, Sytema, & Nienhuis, 2013).

One of the strengths of the chapter 5 was the operationalisation of remission by incorporating symptomatic and functional remission (T. Y. Lee, Kim, et al., 2014). On the other hand, the symptomatic and functional outcome of UHR individuals was defined based on one-off cross-sectional measure at 12 months. Since we did not have information about potential fluctuations in APS between baseline and follow-up, it could be that some of the individuals classified as remitters were already in recovery, namely remission maintained for > 6 months, and that some of the individuals classified as non-remitters were in relapse, namely presence of UHR status after recovery. Although defining an outcome based on a single-data point is a common approach in the literature, Polari and collagues (2018) recently proposed standardised definitions for identifying more refined longitudinal trajectories of CHR individuals based on multiple assessment points to capture the unstable and changeable pattern of symptoms in the early stages of psychosis. Hence, future studies examining the predictive value of MMN, as well as other measures, should adopt more refined and standardised definitions of outcomes to be able to better replicate and generalise findings.

It is worth noting the relatively high percentage (39 %) of CHR individuals without 12-month follow-up data in chapter 5. A group comparison of CHR participants with and without 12-month follow-up data in Appendix B.1 showed that CHR individuals participating at a 12-month follow-up visit had better global functioning and lower prevalence of suicidal ideation but higher APS severity at baseline than CHR individuals with no follow-up data. This is similar to a recent longitudinal study that also found CHR individuals with follow-up data to have a higher global functioning than those who did not complete the follow-up assessment (M. Kim et al., 2018). Similarly Atkinson and colleagues (2017) found that CHR individuals lost prior to the 12-month follow-up visit had lower baseline functional status than participating CHR individuals. Importantly, because these

differing characteristics were used as outcome measures in chapter 5, CHR groups with and without follow-up data might differ in terms of the outcome at 12 months and potentially the reported rate of symptomatic remitters is underestimated as the current findings showed higher baseline severity of APS to predict APS at 12 months. Most importantly, however, the two groups did not differ in MMNm amplitude.

6.3 **Strengths and limitations of the thesis**

Several results of the present thesis, namely those related to the effects of recruitment pathway in chapter 3 and transition to psychosis in chapter 5, are limited as they relied on small sample sizes of 12 and 5 participants that are considered small for neuroimaging studies and might result in an increased risk of false positive results. Thus these results should be treated with caution until replicated using sample sizes minimum of 20 participants as recommended in the neuroimaging literature (Poldrack et al., 2017; Simmons et al., 2011)

In the current thesis, similar to the majority of past CHR studies, global functioning was based on the GAF instrument that takes into account both functioning and positive symptoms and thus might confound these two variables. Indeed the use of GAF to assess functionality has been heavily criticised in CHR research (Roy-Byrne, Dagadakis, Unutzer, & Ries, 1996) (but see Startup, Mike, & Bendix, 2010). Nonetheless, one strength of our study is that we also employed two other measures of functioning, namely role and social functioning, that are independent of symptoms and have been developed specifically to provide a short and easy to use ratings on prodromal functioning and to disentangle role and social functioning profiles (Cornblatt et al., 2007).

Not all first episode patients and CHR individuals were naïve to antipsychotic treatment at the study entry and thus we cannot rule out the possibility that antipsychotic medication affected MMNm amplitudes and underlying connectivity. However, this is unlikely considering previous studies showing that antipsychotics do not improve MMN in schizophrenia patients (D. Umbricht et al., 1998; D. Umbricht, Kane, et al., 2002). On the other hand, other studies have reported contradicting results and found antipsychotics to significantly increase the amplitude of MMN and P300 in schizophrenia patients, suggesting

antipsychotic medication to normalise some of the electrophysiological abnormalities associated with psychosis (Su, Cai, Shi, & Wang, 2012; Zhou, Zhu, & Chen, 2013). In fact, the high heterogeneity of exclusion and inclusion criteria in terms of use of previous/current anti-psychotic medication in the CHR field overall has been criticised for resulting in non-comparable CHR samples (Os & Guloksuz, 2017) and hence it is important for future studies to obtain detailed medication profiles of participants. Furthermore, previous studies have shown that nicotine increases MMN amplitude in controls (Baldeweg, Wong, & Stephan, 2006; Martin, Davalos, & Kisley, 2009) and schizophrenia patients (Dulude, Labelle, & Knott, 2010). As we did not ask participants to refrain from smoking prior to the MEG recording, we cannot rule out the potential impact of nicotine on MMNm amplitudes.

We employed MEG as a tool to assess MMNm in the current study and the imaging method has some noteworthy characteristics. Firstly, it is a non-invasive and safe method with a high temporal resolution, which makes it suitable for studying early auditory processing on the order of milliseconds in the high risk and early psychosis participants. Secondly, MEG has an advantage in terms of spatial resolution over EEG as magnetic fields are less distorted by the skull and scalp than electric fields resulting in more accurate source localisation of the signal (Hämäläinen et al., 1993). This was important in order to be able to investigate group differences in ROIs in chapter 3 and effective connectivity underlying the generation of the MMNm response in chapter 4. However, while scalp EEG can detect activity in the sulci and gyri, MEG is limited to detecting activity from neurons in the sulci. Thus, when comparing studies using different imaging methods, it is important to keep in mind that the chosen method is likely to have an effect especially on identifying generators of the MMNm signal. For instance, as discussed in the introduction chapter, previous MMN studies using EEG have reported frontal MMN sources more frequently than MMN studies using MEG, which might be due to the source location being radially orientated to which MEG is blind (Hämäläinen et al., 1993).

There are some common methodological limitations in the early psychosis literature, which contribute to a problematic large degree of clinical and methodological heterogeneity between CHR and first episode studies. Firstly,

the lack of standardized recruitment methods results in high clinical heterogeneity as demonstrated by a recent meta-analysis (Paolo Fusar-Poli, Schultze-Lutter, et al., 2016; Oliver et al., 2019). Our preliminary results from chapter 3 are in line with the notion that CHR samples recruited from the community might not be directly comparable to clinically recruited CHR samples. On the other hand, while it has been suggested that individuals recruited through clinical pathways have a higher risk for psychosis (15 % at 3 years) compared to those from the community (0.43 % at 3 years) (Paolo Fusar-Poli, Rutigliano, et al., 2016), this was not the case in our study. Nonetheless, while the exact factors contributing to the psychosis risk enrichment remain unknown, assessing well-established factors for psychosis in future studies could help understanding and controlling for factors that may contribute to pre-test risk (Paolo Fusar-Poli, Tantardini, et al., 2017).

Secondly, there is a number of symptom criteria developed to assess psychosis risk, in fact one review listed 22 different instruments designed to assess the risk for psychosis, and different criteria and instruments are combined to increase the detection of at risk individuals which again increases clinical heterogeneity (Daneault et al., 2013). Similarly there is also a lack of consensus regarding the operational definition of first episode of psychosis (Breitborde, Srihari, & Woods, 2009). In terms of assessing and predicting longitudinal clinical trajectories and outcomes of CHR individuals, a lack of standardised definition for remission, recovery, relapse and transition to psychosis further complicates replicating findings as recently underlined by Polari and collagues (2018).

Lastly, MMNm is especially suitable for clinical research compared to other electrophysiological measures as it is has a good test-retest reliability ranging from 0.81 to 0.90 (Recasens & Uhlhaas, 2017) and is elicited optimally in the absence of attention (Paavilainen, Tiitinen, Alho, & Näätänen, 1993), which is vital in clinical studies. However, while eliciting MMN is relatively easy and straight-forward, some of the inconsistent findings in the literature maybe due to methodological differences in terms of quantifying the MMN amplitude. While guidelines for quantifying MMN are available, there are still different ways adopted to quantify this component, resulting in the inability to fully generalise and replicate outcomes (Duncan et al., 2009). We quantified the MMNm response

as the peak rather than the frequently used mean amplitude, following the guidelines for the use of ERPs in clinical research (Duncan et al., 2009).

6.4 Directions for future

Regardless of advancements in neuroimaging and genetic technology enabling investigations of different electrophysiological, structural and functional imaging measures and genetic variants as potential biomarkers for psychosis over the past five decades, currently there are no clinically meaningful biomarkers for psychosis available. Moreover, only a few of the potential biomarkers have been rigorously assessed in the literature and overall the field has been suggested to be limited by small samples, unclear biomarker terminology and lack of replications (P. Fusar-Poli & Meyer-Lindenberg, 2016). Furthermore, a systematic review of psychosis-related biomarkers found evidence for a publication bias in the literature (Prata et al., 2014), highlighting the importance of systematically reporting all study findings, including the null findings, to promote progress in the field.

In addition to utilising neuroimaging methods to elucidate the underlying pathophysiology of emerging psychosis, EEG/MEG parameters would make ideal markers because they are easy to elicit, inexpensive and fast to obtain in a non-invasive manner even in a clinical setting. In fact, a recent study demonstrated the feasibility of recording MMN and P3 using a simple 2-channel EEG system in a large scale multi-site study, supporting the introduction of these two ERP components into clinical, non-expert, practice (Light et al., 2015). However, even if the implementation of ERP/ERF based biomarkers to clinical practice would be supported by empirical evidence, studies are based on group means and it is difficult to interpret evoked responses on an individual level because of individual differences (Luck, Mathalon, Donnell, Hämäläinen, & Spencer, 2012). For instance, the key challenge for using MMN in clinical practice would be the lack of a normative reference point against which to assess an individual's MMN amplitude (Näätänen, Todd, & Schall, 2016), as even healthy controls show high inter-individual variability in MMN amplitudes (Koelsch, Schröger, & Tervaniemi, 1999; Lang et al., 1995; Sanju & Kumar, 2016). However, considering the current lack of evidence for using MMNm as a marker for emerging psychosis and the possibility of rather using it for indexing illness progression and related ongoing

pathological process, a repeated measures design would allow observing changes in MMN over multiple time points which could possible provide information about the trajectory of chronic illness progression at an individual level as suggested by Näätänen and colleagues (2016).

Although the lack of specificity would prevent the hypothetical use of MMN (Hermens, Chitty, & Kaur, 2018), as well as other ERPs, as a predictive or diagnostic marker in clinical practice, its specificity could be improved by using multivariate data by obtaining data related to well-known environmental (Paolo Fusar-Poli, Tantardini, et al., 2017), clinical and neuropsychological risk factors for psychosis. In addition to using MMN adjunctively to non-imaging measures, it could be combined with other potential neurophysiological markers, for instance, to improve sensitivity and specificity for psychosis prediction in CHR individuals. For example, as discussed in the introduction chapter, some neural correlates of early sensory processing (P50 and P300) have shown potential as markers for psychosis prediction in CHR individuals (Bodatsch et al., 2015). Also gamma-band auditory steady-state response, possibly reflecting GABAergic interneuron dysfunction, has been found to be abnormal in CHR individuals, although its utility as predicting psychosis remains unknown (Koshiyama, Kirihara, Tada, Nagai, Fujioka, Ichikawa, et al., 2018; Tada et al., 2016). By adopting a sequential testing approach starting with easily obtained clinical, environmental and neurocognitive measures and finally obtaining imaging data could keep the procedure feasible. Overall, if supported by empirical research, the use of neurophysiological ERP/ERF markers as a part of multivariate and multi-sequential testing could potentially be used, for instance, by early psychosis detection and intervention services for risk prediction.

Recent work has revealed that psychotic disorders emerge from non-psychotic high risk states in addition to the CHR state for psychosis (T. Y. Lee, Lee, Kim, Choe, & Kwon, 2018) and about 30 % of first episode patients do not report APS prior to their first psychotic episode (Shah et al., 2017). This line of evidence questions whether the current CHR state captured by the clinical CHR criteria represents a good prototypical phase of risk for developing psychosis (Paolo Fusar-Poli, 2018) and if not, it could complicate finding replicable and reliable markers for early psychosis. Moreover, the high number of false positives captured by the CHR criteria, as reflected by the low number of CHR-Ts in the

present as well as previous studies, is problematic as in addition to potentially provoking stigmatization and anxiety in mislabelled individuals (Corcoran et al., 2005; Yang, Wonpat-Borja, Opler, & Corcoran, 2010), it results in insufficient power to examine the utility of candidate markers for improving psychosis prediction in CHR individuals.

Refining the detection strategy of CHR individuals might address the limitation of the insufficient statistical power in future longitudinal studies aiming to determine the predictive value of candidate measures for psychosis in CHR individuals. It could be valuable to adopt a wider identification approach incorporating psychotic and non-psychotic symptoms to also detect individuals with heterogeneous pathways to psychosis outside of the UHR framework. In fact, there is an ongoing debate in the literature whether staging models for mental disorders should be conceptualised as disorder-specific or transdiagnostic (Scott & Henry, 2017). Interestingly, the developers of the disorder-specific UHR paradigm have recently started to make a move towards a broader at risk mental state framework and have introduced a novel approach called the Clinical High At Risk Mental State (Mcgorry et al., 2018). The aim of the approach is to identify a broader range of subthreshold at risk states and outcome disorders instead of only focusing on psychosis (Hartmann et al., 2017; Mcgorry et al., 2018).

6.5 **Conclusions**

In conclusion, based on the current thesis it appears that neither the peak amplitude nor the DCM extracted effective connectivity measures of MMNm response are associated with the clinical high risk state for psychosis and thus are unlikely to be potential MEG-based markers of psychosis risk. Moreover, we did not find evidence for reduced MMNm amplitude in first episode patients either, the current data suggesting MMNm deficiency not to be a marker for early stages of psychosis. Lastly, in contrast to our expectations, findings from this thesis do not provide evidence for MMNm as a potential marker for predicting psychosis, although this result has to be considered limited due to the small sample size of CHR-Ts, or as a tool that might improve outcome prediction when combined with non-imaging measures in CHR individuals. Given the robustness of a large MMNm impairment in chronic schizophrenia reported in the

literature and the current lack of support for the presence of a reduced MMNm amplitude in high risk and first episode stages of psychosis, MMNm deficits may represent a marker for illness progression. The current preliminary finding suggesting a difference in MMNm, clinical and cognitive measures between community and clinical CHR samples highlights the importance of controlling for recruitment strategies in future studies. Further sufficiently powered longitudinal studies with multiple recordings are necessary to determine what contribution MMNm can make to identification of early stages of psychosis and prediction of outcome in CHR individuals.

Appendices

APPENDIX A: Supplementary Material Chapter 3

A.1 Interviewer-rated psychiatric conditions for HC and CHR groups

Supplementary 1 Interviewer-rated psychiatric conditions for HC and CHR groups.

		HC (n = 49)		CHR (n = 106)			
Measure	Sub-Measure	Frequency	Percent	Frequency	Percent	Statistics	Significance
MDE current	No	49	100	67	63.8	x^2 (1) = 23.11	p < .001
	Yes	0	0	38	36.2		
MDE past	No	49	100	78	76.7	x^2 (1) = 13.96	p < .001
	Yes	0	0	23	23.3		
Panic disorder (lifetime)	No	49	100	67	63.8	x^2 (1) = 20.60	p < .001
	Yes	0	0	38	36.2		
Panic disorder (current)	No	49	100	96	91.4	x^2 (1) = 4.46	p = .028
	Yes	0	0	9	8.6		
Social phobia (current)	No	49	100	75	71.4	x^2 (1) = 17.39	p < .001
	Yes	0	0	30	28.6		
OCD (current)	No	49	100	91	88.3	x^2 (1) = 6.08	n.s. (.08)
	Yes	0	0	12	11.7		
Anorexia nervosa	No	49	100	103	99	x^2 (1) = .47	n.s. (.68)
	Yes	0	0	1	1		
Bulimia nervosa	No	49	100	98	93.3	x^2 (1) = 2.42	n.s. (.084)
	Yes	0	0	7	6.7		
GAD (current)	No	49	100	51	49	x^2 (1) = 38.21	p < .001
	Yes	0	0	53	51		

HC, healthy control; CHR, clinical high risk; MDE, major depressive episode; OCD, obsessive-compulsive disorder; GAD, generalised anxiety disorder; n.s., non-significant. P > 0.05 listed as non-significant.

A.2 CHR subgroup analyses

A.2.1 Baseline demographic information

Supplementary 2 provides key baseline variables for the three CHR subgroups (BS only, UHR only and BS + UHR) and controls. All three subgroups were significantly different from controls in medication, treated mental health problems, drug dependence, social, role and global functioning. Post hoc pairwise comparisons showed that the UHR group was less likely to have received psychological treatment than the BS + UHR group and the BS + UHR group had a significantly lower GAF score compared to the BS only and UHR only group.

Supplementary 2 Baseline demographic and clinical characteristics of CHR subgroups.

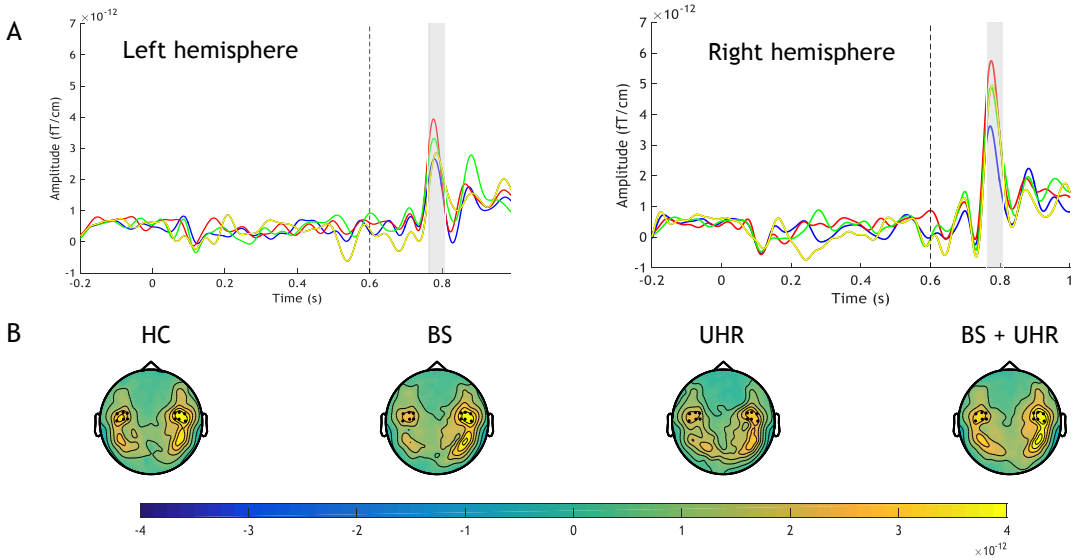
Measure	Sub-Measure	HC (n = 49)	UHR (n = 34)	BS (n = 29)	BS + UHR (n = 42)	Statistics	Significance	Post Hoc
Age (mean & SD)		22.5 (3.57)	20.97 (4.30)	21.38 (4.00)	22.62 (5.00)	H (3) = 5.80[a]	n.s. (.122)	
Gender	Male	16	7	9	12	x^2 (3) = 1.55	n.s. (.671)	
	Female	33	27	20	30			
Handedness	Left	4	3	1	0	x^2 (6) = 4.40	n.s. (.623)	
	Right	37	20	19	24			
	Amdidextrous	8	3	5	6			
Employment	Full time paid	3	1	0	1	x^2 (15) = 10.96	n.s. (.755)	
	Part time paid	2	3	0	3			
	Voluntary	1	1	0	0			
	Student	41	27	26	34			
	Unemployed	2	2	1	4			
Years of Education (mean & SD)		16.6 (3.03)				H (3) = 11.74[a]	n.s. (.008)	
Medication	Any medication	0	15	16	18	x^2 (3) = 38.10	p < 0.001	HC < BS, UHR, BS & UHR
	None	49	19	13	24			
Treated Mental Health Problems	None	46	17	11	10	x^2 (6) =54.07	p < 0.001	HC < BS, UHR, BS & UHR, UHR < BS & UHR
	Current	0	7	3	7			
	Past	3	10	15	25			
Family History (1st Degree)	No	49	29	27	39	x^2 (3) = 7.22	n.s. (.065)	
	Yes	0	5	2	3			
Drug (non alcohol) dependence	No	49	30	24	37	x^2 (3) = 7.93	p = .048	HC < BS, UHR, BS & UHR
	Yes	0	4	5	5			
Drug (non alcohol) abuse	No	48	30	25	35	x^2 (3) = 4.24	n.s. (.237)	
	Yes	0	3	2	3			
GF: Role scale (mean & SD)		8.57 (.764)	7.59 (.892)	7.83 (.889)	7.19 (1.30)	x^2 (15) = 60.52[a]	p < 0.001	HC < BS, UHR, BS & UHR
GF: Social scale (mean & SD)		8.82 (.391)	7.50 (.992)	7.90 (.976)	7.33 (1.162)	x^2 (15) = 79.83[a]	p < 0.001	HC < BS, UHR, BS & UHR
GAF (mean & SD)		87.6 (6.44)	59.18 (13.67)	65.80 (11.64)	54.07 (11.87)	H (3) = 92.91[a]	p < 0.001	HC > BS, UHR, BS & UHR and UHR & BS < BS, UHR

HC, healthy control group; UHR, Ultra High Risk; BS, Basic Symptoms; n.s., non-significant; GAF, Global Assessment of Functioning, [a] Non-normal distribution in the sample (Kolmogorov–Smirnov test; $p < .05$). Frequencies are reported for categorical variables, group means and standard deviations (in parenthesis) are reported for continuous variables, $p > 0.05$ listed as non-significant, + medication and 1st degree family history of schizophrenia was an exclusion criteria for controls.

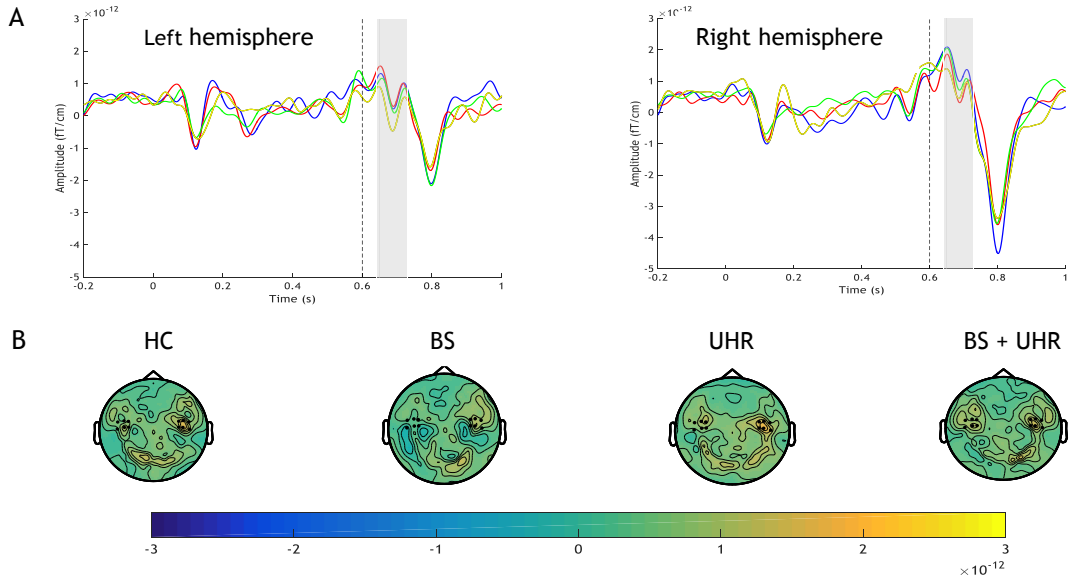
A.2.2 MMNm analyses

A.2.2.1 Sensor level analysis

For durMMNm analysis, a 2 x 4 mixed-design ANOVA revealed a main effect of hemisphere (F (1, 150) = 21.29, p < .01) but no significant main effect of CHR subgroup (F (3, 150) = 1.69, p = .17) or group by hemisphere interaction (F (3, 150) = .38, p = .77) (Supplementary 3). Similarly for omiMMNm, a 2 x 4 ANOVA revealed a main effect of hemisphere (F (1, 150) = 40.76, p < .01) but in contrast to our hypothesis there was no significant main effect of CHR subgroup (F (3, 150) = .50, p = .68) or group by hemisphere interaction (F (3, 150) = .56, p = .64).



Supplementary 3 Sensor level durMMNm for HC and CHR subgroups. (A) Grand average durMMNm waveforms for the HC (green line), BS (yellow line), UHR (blue line) and BS + UHR (red line) group extracted from the six left and right sensors as indicated by the black dots in the topographic plots. (B) Topographic maps of the durMMNm response for each group in the 160 to 210 ms interval (grey shaded area), which was used to extract individual durMMNm peak amplitudes.



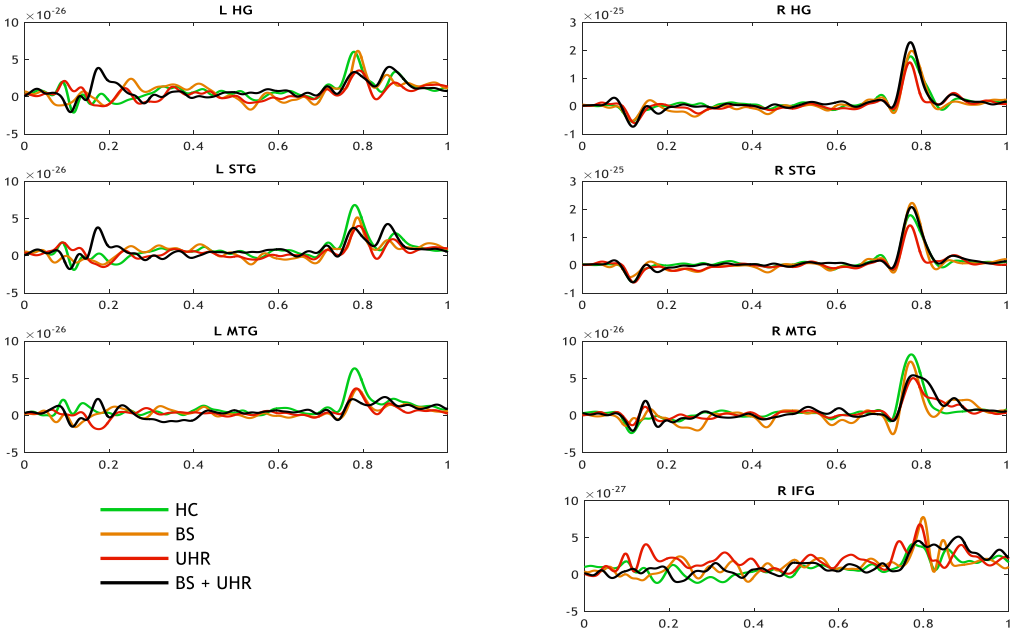
Supplementary 4 Sensor level omiMMNm for HC and CHR subgroups. (A) Grand average planar transformed omiMMNm difference waveforms for HC (green line), BS (yellow line), UHR (blue line) and BS + UHR (red line) group derived from the six left and right SOIs. Grey shaded areas mark the time interval of 40 to 130 ms post stimulus which was used to extract the individual omiMMNm peak amplitudes. (B) Topographic maps of the omiMMNm response for each group.

Supplementary 5 Means and standard deviations of MMNm peak amplitudes for HC and CHR subgroups and effect sizes of group differences over the left and right hemisphere.

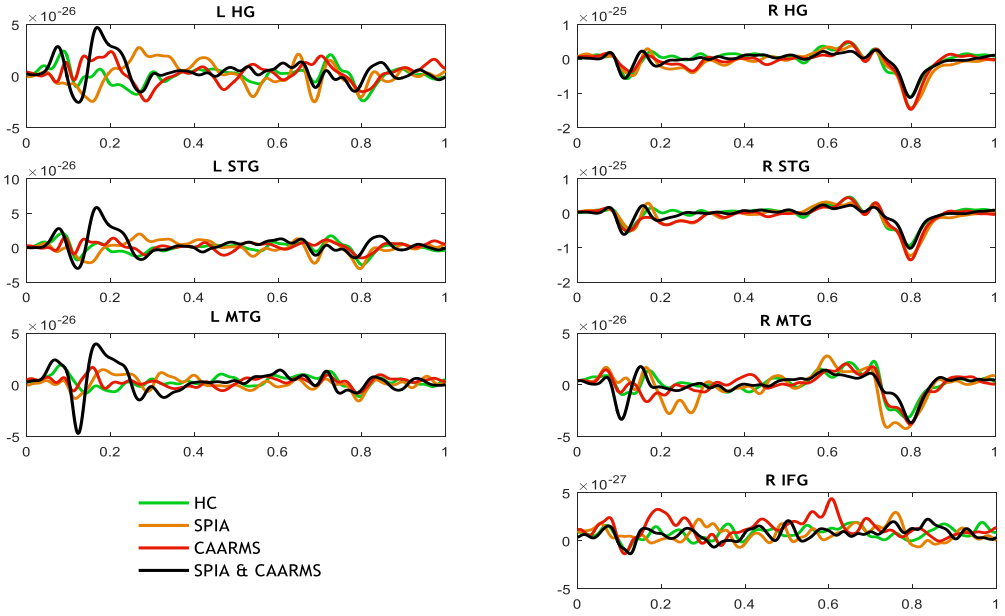
	Group						
Hemisphere	HC (n = 49)	BS (*n* = 29)	UHR (n = 34)	BS + UHR (n = 42)	HC vs BS *d*	HC vs UHR *d*	HC vs BS + UHR *d*
durMMNm							
Left	4.57 (4.65)	3.92 (4.02)	3.50 (3.34)	4.86 (3.27)	0.15	0.26	0.07
Right	6.12 (4.49)	5.99 (4.48)	4.54 (4.18)	6.78 (4.54)	0.02	0.36	0.15
omiMMNm							
Left	2.79 (1.69)	2.38 (1.53)	2.50 (1.56)	2.99 (1.72)	0.26	0.18	0.03
Right	3.57 (2.52)	2.43 (1.49)	2.62 (1.81)	2.87 (1.63)	0.55	0.43	0.33

A.2.2.2 Virtual channel analysis

The Kruskal-Wallis tests revealed no significant group differences in durMMNm or omiMMNm peak amplitudes in any of the ROIs.



Supplementary 6 Virtual channel durMMNm time-courses for HC and CHR subgroups. Grand averaged durMMNm virtual channel time courses for the HC (green), BS (orange), UHR (red) and BS + UHR (black) group plotted separately for each ROI.



Supplementary 7 Virtual channel omiMMNm time-courses for HC and CHR subgroups. Grand averaged omiMMNm virtual channel time courses for the HC (green), BS (orange), UHR (red) and BS + UHR (black) group in seven ROIs.

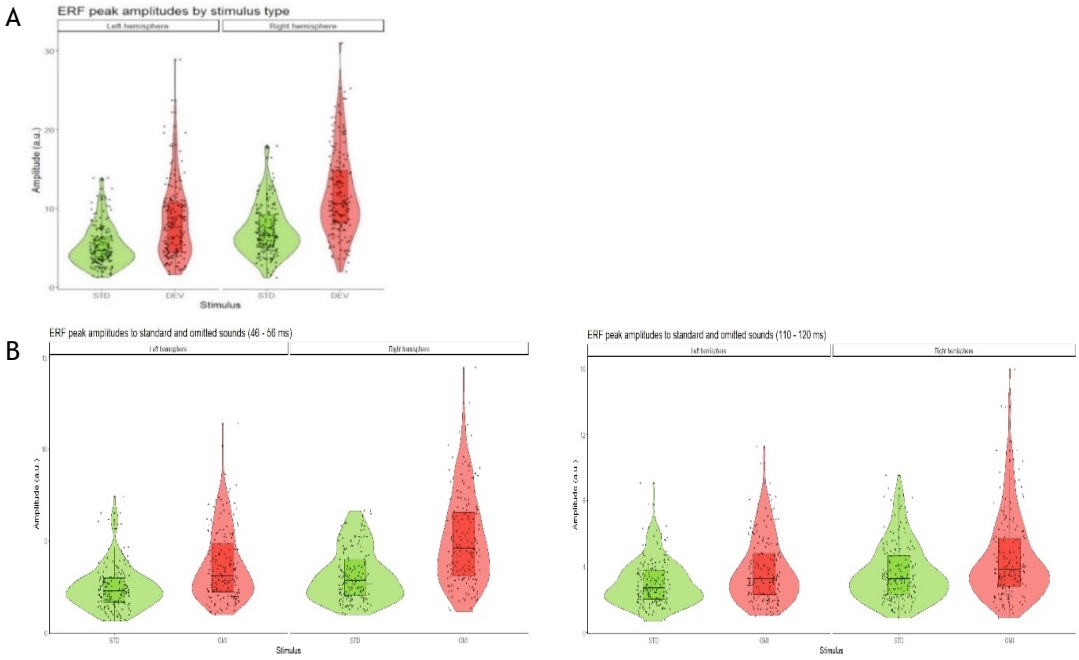
Supplementary 8 Virtual channel results of group differences in MMNm amplitudes between HC and CHR subgroups. Means and standard deviations of MMNm peak amplitudes for each group, effect sizes of group differences and statistical results for each ROI.

	Group									
ROI	HC (n = 48)	BS (n = 28)	UHR (n = 32)	BS + UHR (n = 42)	HC vs BS *d*	HC vs UHR *d*	HC vs BS + UHR *d*	x^2	df	*p*
durMMNm										
L HG	8.88 (12.78)	10.55 (14.98)	6.50 (8.54)	8.15 (8.56)	0.11	0.22	0.07	2.56	3	0.46
R HG	25.72 (28.42)	26.94 (31.77)	21.16 (30.27)	29.53 (37.51)	0.04	0.16	0.11	1.40	3	0.71
L STG	9.93 (14.51)	8.84 (13.63)	6.20 (8.81)	8.19 (8.17)	0.08	0.31	0.15	2.75	3	0.43
R STG	25.40 (29.98)	27.63 (32.10)	18.84 (24.78)	26.99 (32.71)	0.07	0.24	0.05	1.71	3	0.63
L MTG	9.08 (13.40)	5.51 (7.43)	4.94 (7.33)	5.65 (6.92)	0.33	0.38	0.32	3.58	3	0.31
R MTG	12.10 (13.36)	10.67 (12.30)	8.36 (12.08)	9.68 (8.37)	0.11	0.3	0.22	3.36	3	0.34
R IFG	.88 (.78)	1.14 (1.26)	1.05 (2.72)	.97 (1.43)	0.25	0.08	0.08	3.64	3	0.30
omiMMNm										
L HG	4.30 (5.03)	4.08 (4.31)	4.83 (5.20)	3.53 (4.15)	0.05	0.1	0.17	2.485	3	.478
R HG	9.03 (9.30)	8.8 (11.30)	9.55 (11.82)	7.34 (7.18)	0.02	0.05	0.2	.718	3	.869
L STG	3.92 (4.53)	2.8 (2.97)	3.44 (3.41)	2.98 (3.40)	0.29	0.12	0.23	1.794	3	.616
R STG	8.42 (8.10)	7.26 (8.00)	8.36 (9.76)	6.74 (7.92)	0.14	0.01	0.21	2.750	3	.432
L MTG	3.81 (5.05)	2.01 (2.46)	2.23 (2.52)	3.57 (4.62)	0.45	0.4	0.05	6.204	3	.102
R MTG	5.71 (7.32)	4.03 (4.75)	4.58 (4.15)	4.13 (7.02)	0.27	0.19	0.22	4.733	3	.192
R IFG	0.49 (.52)	0.66 (.74)	0.58 (.62)	0.47 (.51)	0.27	0.16	0.04	1.126	3	.771

A.3 MMNm distributions

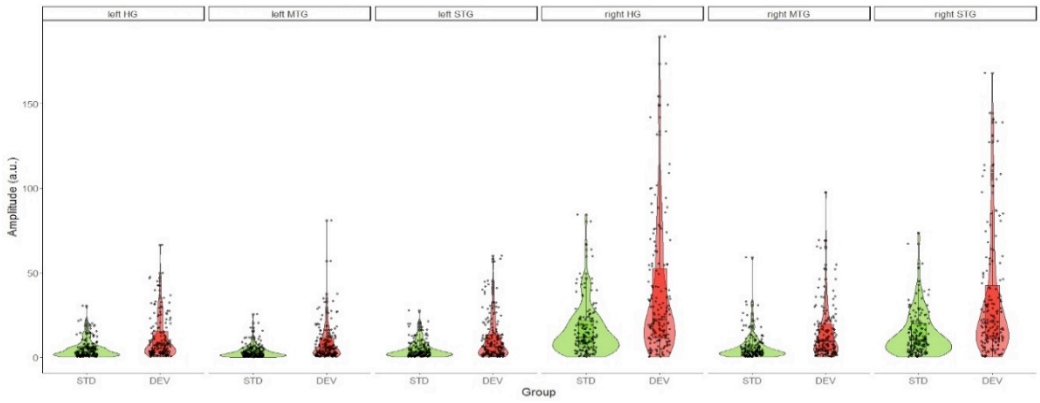
A.3.1 Condition effect

A.3.1.1 Sensor space

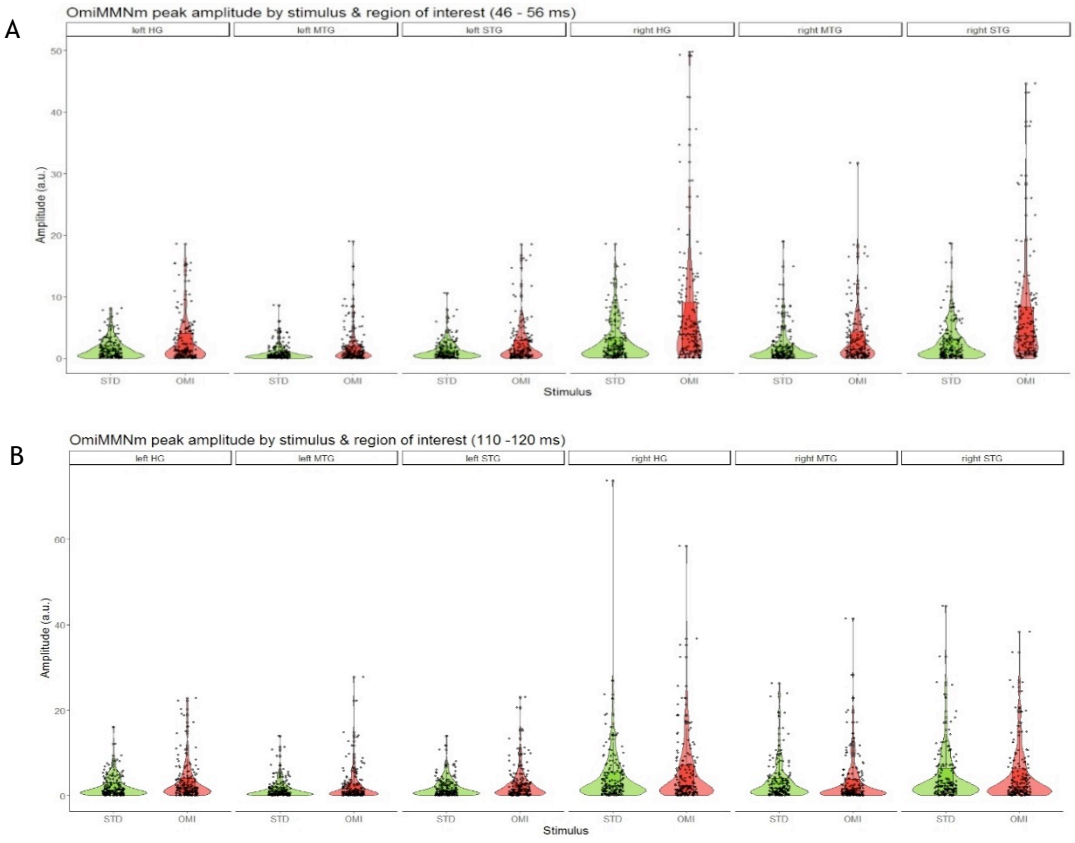


Supplementary 9 Sensor level STD, DEV and OMI peak amplitude distributions. The distributions of individual ERF peak amplitudes in response to deviant (in red) and standard (in green) sounds over the left and right hemisphere. Panel (A) presents the durMMNm effect and (B) omiMMNm effect in the two TOIs. STD, standard; DEV, deviant; OMI, omission.

A.3.1.2. Source space



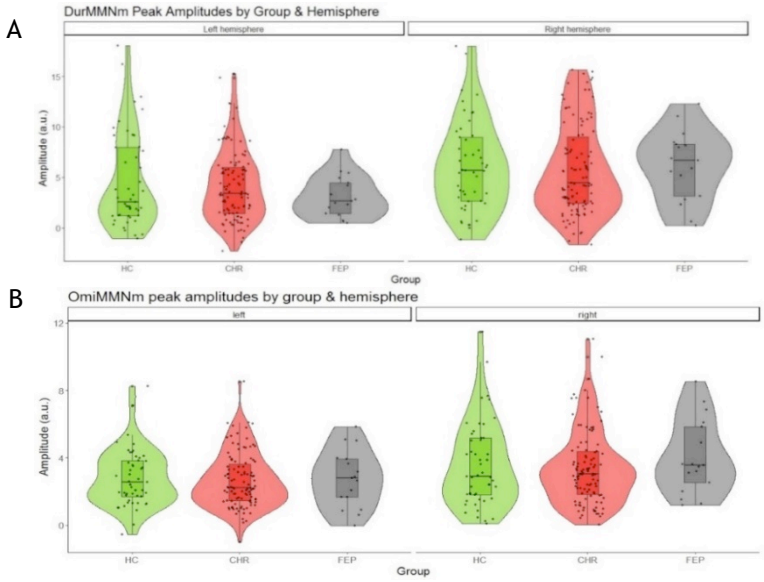
Supplementary 10 Virtual channel STD and DEV peak amplitude distributions in each ROIs. ERF peak amplitudes to standard (green) and duration deviant (red) stimulus for each ROI. HG, Heschl's gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus.



Supplementary 11 Virtual channel STD and OMI peak amplitude distributions. Distributions of individual ERF peak amplitudes to standard (green) and omitted (red) stimulus for each ROI. Panel (A) presents the omiMMNm effect in the 46-56 ms TOI and (B) omiMMNm effect in the 110-120 TOI. HG, Heschl's gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus. HG, Heschl's gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus.

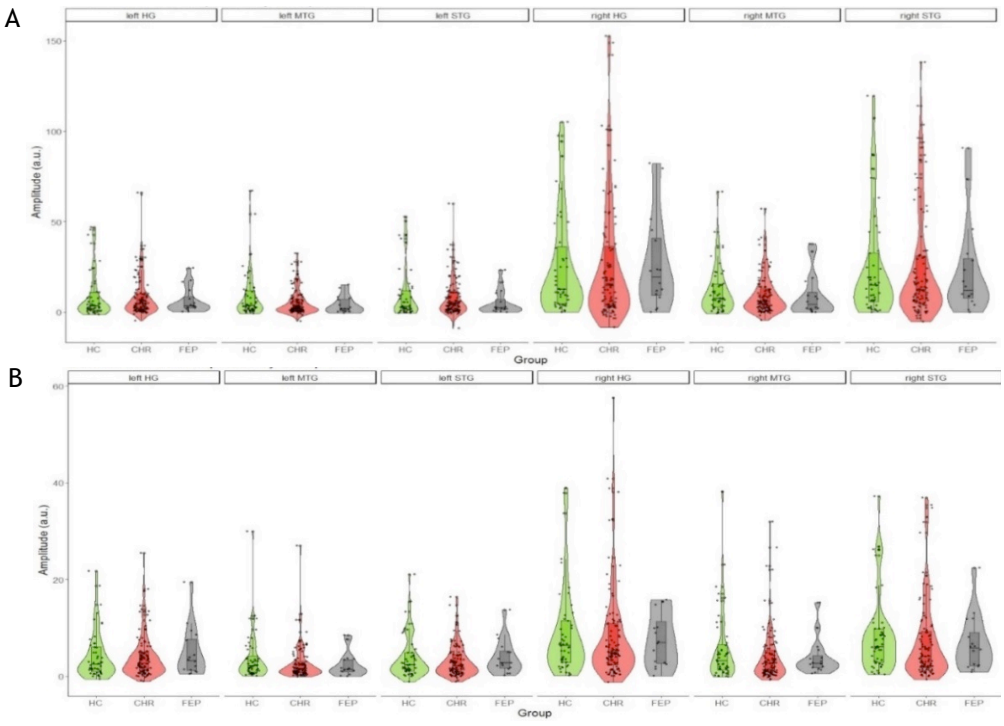
A.3.2 MMNm distributions for the HC, CHR and FEP groups

A.3.2.1 Sensor space



Supplementary 12 Sensor level distributions of individual MMNm peak amplitudes for HC (green), CHR (red) and FEP (grey) groups over the left and right hemisphere. Panel (A) presents the durMMNm effect and (B) omiMMNm effect.

A.3.2.2 Source space



Supplementary 13 Virtual channel distributions of individual MMNm peak amplitudes in six ROIs for the HC (green), CHR (red) and FEP (grey) group. Panel (A) presents the durMMNm effect and (B) omiMMNm effect.

A.4 Associations between the severity of APS and comorbidity and global, role and social functioning in the CHR sample

The results of Spearman's correlations indicate that the CAARMS positive symptom severity correlates with the presence of comorbid anxiety/depressive disorders (r = .20, p =.046) as well as global (r = - .36, p < .01), social (r = -.26, p = .01) and role functioning (r = -.27, p = .01) in the CHR sample.

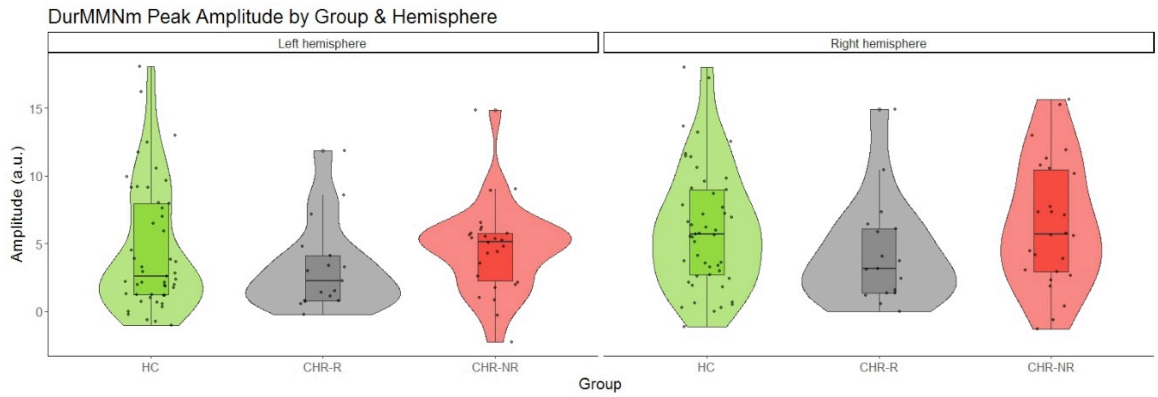
APPENDIX B: Supplementary Material Chapter 5

B.1 CHR individuals with and without follow-up information

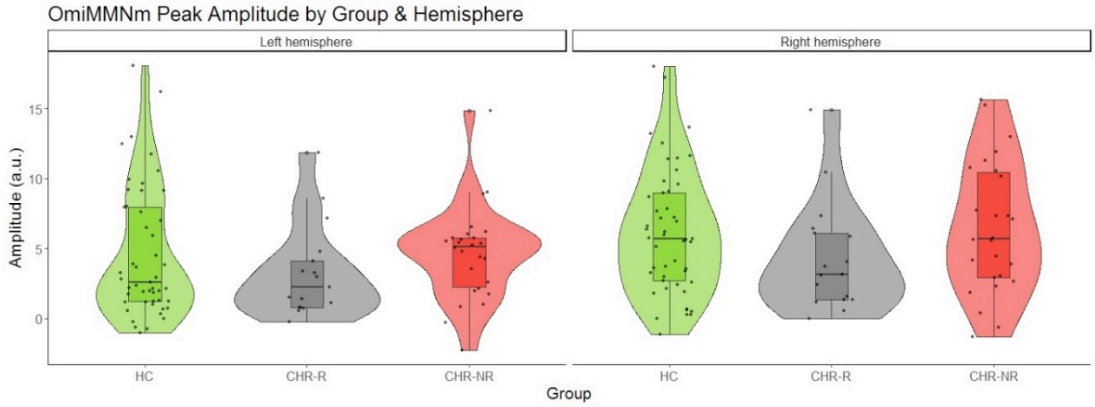
Supplementary 14 Demographic and clinical characteristics of CHR individuals with and without 12 month follow-up data.

Measure	Sub-Measure	Not Followed Up (n = 41)	Followed Up (n = 65)	Statistics	Significance
Age		21.40 (4.59)	21.95 (4.51)	t (103) = - .607	n.s. (.545)
Gender	Male	13	15	x^2 (1) = .963	n.s. (.326)
	Female	28	50		
Employment	Full time paid	1	1	x^2 (5) = 10.70	n.s. (.06)
	Part time paid	3	3		
	Voluntary	0	1		
	Student	28	59		
	Unemployed	6	1		
Years of Education		14.38 (2.53)	15.57 (3.62)	t (103) = -1.93	p = 0.05
Medication +	Any medication	21	34	x^2 (1) = .012	n.s. (.536)
	None	20	31		
Treated Mental Health Problems	None	15	23	x^2 (2) = .192	n.s. (.908)
	Current	7	10		
	Past	18	32		
Family History (1st Degree) +	No	38	58	x^2 (1) = .351	n.s. (.554)
	Yes	3	7		
CAARMS severity		23.78 (16.71)	30.43 (16.38)	t (103) = -2.006	p = 0.047
GAF		55.45 (13.43)	61.12 (12.66)	t (103) = -2.178	p = 0.032
GF: Social scale		7.48 (1.11)	7.58 (1.06)	t (103) = -.506	n.s. (.614)
GF: Role scale		7.25 (1.10)	7.65 (1.07)	t (103) = -1.824	n.s. (.071)
Current Suicide Risk	No	12	37	x^2 (1) = 7.642	p = .006
	Yes	28	27		
Verbal memory		48.33 (10.43)	48.94 (11.74)	t (103) = -.271	n.s. (.787)
Working memory		21.10 (3.70)	20.34 (4.24)	t (103) = .937	n.s. (.351)
Motor speed		73.03 (15.07)	66.98 (15.62)	t (103) = 1.95	n.s. (.006)
Verbal fluency		59.35 (13.43)	55.35 (12.22)	t (103) = 1.57	n.s. (.120)
Processing speed		64.50 (10.44)	67.68 (15.03)	t (103) = -1.173	n.s. (.243)
Executive funtion		17.87 (2.07)	18.38 (2.69)	t (101) = -1.002	n.s. (.319)
BACS composite score		285.08 (37.102)	277.91 (42.739)	t (103) = .860	n.s. (.392)
durMMNm left		4.09 (3.56)	4.18 (3.52)	t (104) = -.125	n.s. (.901)
durMMNm right		5.20 (4.31)	6.18 (4.56)	t (104) = -1.094	n.s. (.277)
omiMMNm left		2.45 (1.39)	2.79 (1.74)	t (104) = -1.036	n.s. (.302)
omiMMNm right		3.20 (2.06)	3.49 (2.27)	t (104) = -.677	n.s. (.500)

B.2 MMNm distributions for the CHR-R, CHR-NR and HC groups



Supplementary 15 Distributions of individual durMMNm peak amplitude values for the HC CHR-R and CHR-NR group.



Supplementary 16 Distributions of individual omiMMNm peak amplitude values for the HC CHR-R and CHR-NR group.

B.3 Association between the severity of APS and comorbidity in CHR individuals

There was a significant difference in the CAARMS positive symptom severity between CHR individuals with a comorbid anxiety/depressive disorder (M = 30.68, SD = 17.04) and without a comorbid disorder (M = 23.80, SD = 15.88) (t (101) = -2.05, p = .04).

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