Sensory prediction errors in the continuum of psychosis

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Abstract

Sensory prediction errors are fundamental brain responses that signal a violation of expectation in either the internal or external sensory environment, and are therefore crucial for survival and adaptive behaviour. Patients with schizophrenia show deficits in these internal and external sensory prediction errors, which can be measured using electroencephalography (EEG) components such as N1 and mismatch negativity (MMN), respectively. New evidence suggests that these deficits in sensory prediction errors are more widely distributed on a continuum of psychosis, whereas psychotic experiences exist to varying degrees throughout the general population. In this paper, we review recent findings in sensory prediction errors in the auditory domain across the continuum of psychosis, and discuss these in light of the predictive coding hypothesis.

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1. Introduction

The brain, once viewed as a passive recipient of sensory information is now thought to actively predict sensations (Picard and Friston, 2014). It manages an onslaught of incoming stimuli by amplifying relevant information and suppressing irrelevant or predictable information (Lakatos et al., 2013). An inability to accurately predict forthcoming sensations which are internal, self-generated or sensations that are externally-generated in the environment results in sensory prediction errors, which is a failure to suppress neuronal activity.

Sensory prediction errors have been studied extensively in the context of externally-generated stimuli, with mismatch negativity (MMN) being a key component of auditory or visual change detection in the environment (Fisher et al., 2012; Stefanics et al., 2014a; Todd et al., 2013). Self-generated sensory prediction errors have been studied in the tactile (Martinelli et al., 2016; Shergill et al., 2005; Wolpert et al., 1995), auditory (Aliu et al., 2009; Baess et al., 2011; Martikainen et al., 2005; Timm et al., 2013) and visual domains (Mifsud et al., 2016). Patients with schizophrenia demonstrate deficits in prediction of both external stimuli (Erickson et al., 2016; Fisher et al., 2012; Todd et al., 2008) and self-generated stimuli (Ford et al., 2007a; Ford and Mathalon, 2012; Ford et al., 2014). These deficits can also be seen in individuals at high-risk for psychosis (Erickson et al., 2016; Ford and Mathalon, 2012; Umbricht et al., 2006).

Schizophrenia is a psychiatric disorder characterized by negative symptoms, such as blunted affect, poverty of speech, apathy and anhedonia as well as positive, psychotic symptoms, such as delusions and hallucinations (Andreasen and Flaum, 1991; Meehl, 1962). The current method of diagnosing schizophrenia is based on the categorical symptom specification according to standardised classification systems such as the Diagnostic and Statistical Manual (DSM-V; American Psychiatric Association (2013)) or the International Classification of Diseases (ICD-10; World Health Organization (1993)). This traditional categorical approach of diagnosing mental disorders views the general population as being composed of two simple categories of individuals i.e. healthy or unhealthy (Linscott and van Os, 2010). In psychotic disorders, such a binary categorisation has been challenged due to mounting evidence that psychotic experiences can also be present, to certain degrees, in otherwise healthy individuals (Kaymaz and van Os, 2010).

This more recent perspective proposes that psychotic experiences in the general population vary across a continuum (van Os et al., 2009); (see Fig. 1A). A ‘continuum of psychosis’ implies that the same psychotic experiences seen in clinical populations with psychotic disorders can be seen in non-clinical populations, albeit to a lesser degree (van Os et al., 2009). Criticisms of this perspective centre around concerns that viewing psychosis on a continuum may pose a difficulty for clinicians to distinguish between clinical psychoses and healthy populations (Lawrie et al., 2010). A categorical approach is, nevertheless, more valuable for treatment in clinical practice when distinguishing amongst related...
psychotic disorders such as schizophrenia and bipolar disorder (BPD) which show considerable differences in risk factors, pathology and treatment response (Lawrie et al., 2010). Nevertheless, the perspective of a continuum is useful for developing measures of psychosis proneness and for studying the aetiology of schizophrenia (DeRosse and Karlsgodt, 2015).

2. Prediction errors in external sensory stimuli

Responses to externally-generated auditory stimuli have been studied in detail using event-related potentials (ERPs) with the use of electroencephalography (EEG) and magnetoencephalography (MEG). Patients with schizophrenia show significant reductions in N1, P1, N2, P50, P300 and P3a components compared to healthy controls (for an overview of ERP components see (O’Donnell et al., 2017; Sur and Sinha, 2009)). The mismatch negativity (MMN) component is a hallmark of sensory prediction errors (Garrido et al., 2009), arguably a highly robust neurophysiological signature of schizophrenia (Michie, 2001; Nagai et al., 2013a), and a potential biomarker for prediction of conversion to psychosis in high-risk individuals (Bodatsch et al., 2011; Näätänen et al., 2016).

2.1. Mismatch negativity (MMN)

MMN is elicited by a violation to a regularity or pattern of auditory or visual stimuli (see Fig. 1D for examples of auditory regularity violations). In order to elicit an MMN response, the sensory system must recognize a stimulus as being different (deviant) to, or unexpected, given a learnt pattern of stimuli (standards). MMN is the negative component obtained by subtracting an ERP to a standard from the ERP to a deviant, typically peaking at about 100-250 ms from change onset. It exhibits the highest intensity at fronto-temporal scalp regions. While attending to auditory stimuli has been shown to result in larger MMN amplitudes (Auksztulewicz and Friston, 2015; Oades and Dittmann-Balcar, 1995; Woldorff et al., 1991), MMN can be captured even when the participant’s attention is deployed to an unrelated task (Garrido et al., 2008; Sams et al., 1985). The elicitation of MMN appears to reorient attention towards salient events and the deficiency in this process may lead to a disconnection of individuals with schizophrenia with the external environment and/or their own sensations (Javitt and Sweet, 2015).

MMN is most commonly evoked using auditory stimuli, however MMN has also been investigated in the visual domain (vMMN) and is described as the electrophysiological response to the automatic detection of unpredicted changes in the visual environment (Stefanics et al., 2014b). vMMN has been studied in relation to a number of features including colour (Czigler et al., 2006; Stefanics et al., 2011), and orientation (Kimura et al., 2009), often using gabor and also more complex visual objects such as faces arranged within oddball paradigms. For the purposes of this review we focus on auditory prediction errors (but see Kremlacek et al. (2016), for a review of vMMN in psychiatric and neurological disorders and Stefanics et al. (2014b), for a predictive coding account of vMMN).
2.2. Eliciting MMN: Oddball paradigms in schizophrenia

MMN attenuation in schizophrenia was first described using a simple two-tone duration deviant paradigm (Shelley et al., 1991). Since then, MMN amplitude, particularly in duration oddball paradigms, has been consistently shown to be attenuated in schizophrenia compared to healthy controls (Light et al., 2015; Nagai et al., 2013b; Todd et al., 2008). Subsequently, MMN studies in schizophrenia expanded to explore other physical properties of tones in the form of frequency and intensity deviants (Todd et al., 2008) as well as gap deviants (Fisher et al., 2008, 2012). While EEG is most commonly used in MMN studies, duration MMN attenuation in schizophrenia has also been shown using MEG (Shin et al., 2012; Suga et al., 2016; Thonnessen et al., 2008).

MMN paradigms have increased in complexity over time. The Roving paradigm (Cowan et al., 1993), presents a train of repeated sounds followed by a second set of sounds with different properties (e.g., new frequency or duration), the first tone in this second stimulus train serves as the deviant. Using this paradigm, Balderweg and Hirsch (2015) suggested that frequency and duration MMN attenuation are specific to schizophrenia when compared to Alzheimer’s patients and patients with BPD. However, this study may lack sufficient power to make such conclusion as the Alzheimer’s disease group had a relatively small sample size \( (n = 15) \) compared to the BPD group \( (n = 25) \) and the group of schizophrenia patients \( (n = 49) \). The ‘optimal’ multi-feature paradigm by Näätänen et al. (2004), which includes multiple deviant types in the same stimulus train such as duration, frequency, intensity and gap, has provided important insights into MMN generation in individuals with schizophrenia. For example, Thonnessen et al. (2008) compared the ‘traditional oddball’ paradigm with the ‘optimal’ paradigm using both EEG and MEG, and concluded that using MEG in combination with the ‘optimal’ paradigm improved sensitivity in detecting MMN attenuation in schizophrenia. Using the ‘optimal’ paradigm, Fisher et al. (2012) found significant negative correlations between gap MMN amplitude and trait and state severity ratings of auditory hallucinations in patients with schizophrenia, indicating that the presence of auditory hallucinations may make a significant contribution to the widely reported MMN deficits in schizophrenia. This study is however limited by its relatively small sample size \( (n = 12) \) and further research is needed to corroborate this finding. Another study by van Lutterveld et al. (2010) using an ‘active’ frequency oddball paradigm (where participants are asked to detect oddballs), found no significant differences in frequency MMN in non-psychotic individuals with auditory verbal hallucinations (AVH; \( n = 18 \)), compared to individuals without AVH \( (n = 18) \). Simple variations of the basic oddball paradigm such as the inclusion of a third ‘novelty’ stimulus, for example a baby’s cry (termed novelty MMN) have been shown to elicit smaller MMN amplitudes in schizophrenia patients compared to healthy controls. This novelty MMN has also been shown to be significantly positively correlated with auditory hallucinatory traits (Fisher et al., 2014), however this finding may also be limited by it’s small sample size \( (n = 10) \). In a systematic review of studies investigating AVH using oddball paradigms, Upthegrove et al. (2016) reported that MMN alone cannot explain AVH and further studies in non-clinical populations with AVH would be beneficial in verifying the underlying manifestations of AVH. Jarkiewicz and Wichniak (2015), provide a detailed review of oddball paradigms beyond frequency and duration deviants used in studying MMN in schizophrenia.

2.3. Do different deviant types represent trait or state of psychosis?

Evidence from a meta-analysis of 32 studies suggests that MMN attenuation in schizophrenia elicited by frequency deviants is significantly correlated with duration of illness (Umbricht and Krijes, 2005). Duration MMN attenuation on the other hand has been suggested to be more closely related to the genetic predisposition to develop schizophrenia (McGorry et al., 2014). This is supported by an attenuation in duration MMN in the early stages of disease, but attenuation of frequency MMN with increasing disease stage (Todd et al., 2008). Jahshan et al. (2012a) also found significant attenuation of duration MMN in at-risk, recent-onset, and chronic schizophrenia patient groups when compared with healthy controls. They also found that MMN amplitude reflected disease progression (Fig. 1B). Furthermore, positive symptoms in schizophrenia have been associated with reduced duration MMN amplitudes (Kärgel et al., 2014). Kim et al. (2014) found duration MMN attenuation in schizophrenia patients when compared to genetically high-risk relatives and healthy controls, and that reduced duration MMN amplitudes were associated with reduced state of functioning as measured by the Global Assessment of Functioning Scale (American Psychiatric Association, 2000). These findings suggest that duration MMN is a marker of state of functioning rather than a genetic marker of disease. However, based on a meta-analysis, which included relatives of patients with schizophrenia (Fig. 1C), Erickson et al. (2016) suggests that duration MMN may represent a genetic trait marker, but cautions on drawing this conclusion due to the small sample size in the relative group. Thus, it is not yet clear whether MMN impairment represents an index of an emerging illness or is better conceptualized as an endophenotype marker of genetic vulnerability (Erickson et al., 2016).

2.4. Theories of MMN generation

Two early theories have provided explanations on how MMN might be generated. The model adjustment theory suggests that the human brain forms a memory trace to standard events and constantly detects deviations to such sensory memory (Näätänen and Winkler, 1999). An alternative theory, the adaptation hypothesis, proposes that the neuronal populations tuned to the standards become less responsive to repeated stimuli, due to habituation, thus producing a suppression effect (Jääskeläinen et al., 2004; May et al., 1999). According to this account, when a deviant stimulus occurs, there is a release from adaptation, and a larger response is elicited in neuronal populations more tuned to deviant sounds. The adaptation model suggests that MMN is caused by the same mechanism and neuronal populations as those associated with the N1 component, which is limited to the primary auditory cortex; the model adjustment hypothesis argues against this model and states that MMN is caused by a neuronal population that is distinct from the neuronal population which causes the N1 component (Garrido et al., 2009).

A third and more recent perspective – predictive coding, can be viewed as a combination of the two hypotheses (Garrido et al., 2008; Garrido et al., 2009). Predictive coding theories suggest that the brain is constantly trying to minimize the discrepancy between actual sensory input and internal representations of the environment (Friston, 2005; Rauss and Pourtois, 2013). It views the brain as a hierarchical system in which each level is trying to achieve a compromise between the inputs from other levels (Friston, 2005), whereby sensory input is received at lower levels, and predictions are made at higher levels. According to this theory MMN is caused by prediction errors which arise during comparison between an incoming stimulus (and are conveyed through bottom-up connections) and a prediction based on a memory of previous standards (carried by top-down connections) ((Garrido et al., 2009); see Fig. 2A). The continuous interaction between top-down flow of predictions and bottom-up flow of prediction errors keeps our internal model of reality up-to-date (Stefanics et al., 2014a). Effective connectivity studies (Garrido et al., 2008) provide support for the predictive coding view of MMN, which gracefully marries the model adjustment and the adaptation hypotheses, in the sense that it predicts the generation of a model of current stimuli through plastic changes in synaptic connections akin to adaptation-like mechanisms.

2.5. Does auditory MMN represent prediction deficits in schizophrenia?

Despite the mounting evidence supporting the predictive coding view of MMN generation in healthy individuals, there are still some concerns as to whether MMN represents sensory adaptation deficits as opposed to
prediction deficits in schizophrenia (Michie et al., 2016). In other words, does attenuated MMN represent stimulus-specific adaptation effects in schizophrenia patients? To explore this further, more sophisticated paradigms that avoid stimulus-specific adaptation have been employed to elicit a ‘complex MMN’, which represents predictive deficits more specifically (Salisbury, 2012). These paradigms require sensory memory of standards that form a pattern (number of tones grouped temporally), while deviants are a variation in the structure, or violation of such patterns (such as a missing tone). If an individual remembers the grouping structure, or regularity, they learn to expect a particular tone and will be surprised if there is a discrepancy from that predicted tone. Importantly, studies of complex MMN have shown prediction deficits in chronic schizophrenia patients (Salisbury and McCathern, 2016) as well as early episode psychosis patients (Rudolph et al., 2015). Rentzsch et al. (2015) found a significant correlation between suppression measures and both frequency and duration MMN in healthy populations but not in patients with schizophrenia, suggesting a disruption in predictive coding mechanisms which can be distinguished from stimulus-specific adaptation.

2.6. Is MMN attenuation specific to schizophrenia?

MMN attenuation is present in both medicated and unmedicated patients with schizophrenia (Catts et al., 1995) and suggested to be specific to schizophrenia and not deficient in other psychiatric disorders such as major depression or obsessive-compulsive disorder (McGorry et al., 2014). It has since been demonstrated that patients with depression show context-specific attenuation of MMN elicited by oddball paradigms with sad speech syllables as stimuli (Pang et al., 2014). A review by Onitsuka et al. (2013), highlights several ERP abnormalities, including MMN deficits, in bipolar disorder with psychotic features. A recent meta-analysis found that while patients with bipolar disorder did show MMN attenuation compared to healthy controls, it was not as large as the effect size observed in schizophrenia, but more comparable to at-risk of psychosis states (Erickson et al., 2016); see Fig. 1C. This is supported through a study by Kaur et al. (2011), in which first-episode psychosis subgroups (see Table 1) show impairments in the fronto-central MMN consistent with findings in chronic schizophrenia patients, whereas,
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the affective subgroup (patients with mood disorders) showed an ‘intermediate’ frontal response. In a study by Jahshan et al. (2012b), patients with bipolar disorder I and II have both shown attenuation in duration deviant MMN compared to healthy controls. These findings suggest that MMN reduction may be associated more generally with psychosis than schizophrenia specifically. However, findings show that duration MMN amplitude decreases as illness progresses and is nearly abolished in chronic schizophrenia (Baldeweg et al., 2004).

2.7. MMN in the continuum of psychosis

MMN has been studied across various populations in the continuum of psychosis. The studies in Table 1 were selected with the aim of providing an overview of the most recent MMN findings across the continuum of psychosis. For a review of MMN findings specific to schizophrenia and before 2014, see Näätänen et al. (2015) and Todd et al. (2014).

2.7.1. MMN in schizotypy

Schizotypy is a term that was first introduced in 1962 to refer to a vulnerability to schizophrenia spectrum disorders (Meehl, 1962). Schizotypy is a personality dimension, which refers to healthy individuals with psychotic-like experiences, such as delusions and/or hallucinations and is thought to be the sub-clinical manifestation of schizophrenia in the general population (Ettlinger et al., 2015). It has also been suggested to be a specific predictor of schizophrenia spectrum disorders (Poulton et al., 2000). Schizotypy individuals differ from high-risk individuals in that the latter are by definition help-seeking and therefore considered at a higher risk for psychosis. Individuals who score highly on schizotypy and hallucinatory proneness, however, are difficult to differentiate from high-risk individuals and show similarities in distress and metacognitive abnormalities (Barkus et al., 2010).

One study investigating frequency MMN in schizotypy showed no differences in MMN between low and high schizotypal groups (Broyd et al., 2016). However, trend level differences of frequency MMN were reported when categorizing groups based on a suspiciousness subscale. Contrary to expectation, duration, frequency, and intensity MMN were enhanced (instead of reduced) in the high suspiciousness group compared to the low suspiciousness group. This suggests that attenuation of duration MMN may be an important tool in the differentiation of healthy individuals and individuals at actual risk of psychosis as opposed to individuals with personality traits of psychotic-like experiences as defined by schizotypy. Longitudinal studies of schizotypal individuals would provide a better understanding regarding the putative association of MMN and psychotic experiences, as well as an indication of whether MMN can be used as an early biomarker for conversion from schizotypy to florid psychosis.

2.7.2. MMN in people at risk for psychosis

Clinically high-risk (CHR) for psychosis, also known as “ultra-high risk (UHR),” “at-risk mental state (ARMS),” and “prodromal” (Pusar-Poli et al., 2013), is an important construct in studying the transition to psychosis. Several MMN studies have focused on ARMS populations, as defined by the comprehensive risk assessment of at-risk mental states (CараRMS) scale, and include individuals i) experiencing sub-threshold psychotic symptoms ii) having experienced brief episodes of psychotic symptoms such as hallucinations or delusions iii) having a close biological relative with a psychotic disorder and having a significant loss of ability to carry out typical daily activities in a period of 12 months (Yung et al., 2005).

Studies using long duration deviants have consistently shown an MMN attenuation in ARMS/UHR individuals (Atkinson et al., 2012; Nagai et al., 2013b; Perez et al., 2014; Shaikh et al., 2012; Solis-Vivanco et al., 2014). The findings are less robust with frequency MMN, with some studies showing attenuation (Perez et al., 2014) and others reporting no difference (Nagai et al., 2013b). Longitudinal studies in schizophrenia patients and ARMS have shown that individuals who converted to schizophrenia had baseline reductions in duration MMN compared to non-converters (Bodatsch et al., 2015; Higuchi et al., 2014). Perez et al. (2014) further showed that a paradigm with two deviants in the same block (frequency and duration) could significantly predict the time to psychosis onset in clinically high-risk participants, while two-tone paradigms with duration or frequency deviants could not. This is a remarkable finding as it demonstrates the potential for using duration MMN as a biomarker for detecting psychosis proneness (Bodatsch et al., 2015) as well as using double duration paradigms for predicting psychosis onset.

2.7.3. MMN in Schizotypal Personality Disorder (SPD)

Schizotypal Personality Disorder (SPD) is a personality disorder characterized by unusual perceptual experiences, odd or eccentric behaviour, magical and/or paranoid beliefs and few, if any, close relationships (Esterberg et al., 2010). SPD is more common in relatives of patients with schizophrenia, supporting the genetic diathesis for psychotic disorders (Kendler and Diehl, 1993) and the notion of a continuum of psychosis (Krabbendam et al., 2004).

A study by Niznikiewicz et al. (2009) reported that SPD individuals exhibited significantly reduced frequency MMN compared to healthy controls.

2.7.4. MMN in First Episode Psychosis (FEP)

FEP is a broad category which has traditionally been demarcated into three subgroups: (i) ‘schizophrenia spectrum psychoses’ (schizophrenia, schizoaffective disorder, and schizophreniform disorder); (ii) ‘affective spectrum psychoses’ (bipolar disorder with psychotic features and major depressive disorder with psychotic features); and (iii) ‘other psychoses’ (e.g. brief psychotic disorder and substance-induced psychotic disorder) (Kaur et al., 2011), usually including individuals no more than 5 years after onset of a psychotic episode (For a review on definitions of FEP see Breitborde et al., 2009).

MMN amplitude findings in FEP have been variable across studies, with some finding significant MMN attenuation compared to healthy controls (Atkinson et al., 2012; Hermens et al., 2010; Kaur et al., 2011; Solis-Vivanco et al., 2014) and others finding no differences (Kaur et al., 2013). Haigh et al. (2016) conducted a meta-analysis of frequency and duration MMN findings in 14 studies that included patients within 12 months of their first episode of psychosis. It was found that the overall effect size showed no MMN reduction in FEP patients to frequency deviants, and a small-to-medium reduction to duration deviants. The authors suggest that frequency MMN is not a candidate biomarker for schizophrenia prediction, while duration MMN may hold some promise. Salisbury et al. (2016) confirmed these findings in a meta-analysis of frequency and duration MMN in the first-episode schizophrenia-spectrum and FEP (mixed schizophrenia-spectrum and affective-spectrum).

2.8. Cognitive and pharmacologic modulators of MMN

An early meta-analysis by Umbricht and Krjes (2005) found that there were no significant effects of duration of illness, gender ratio, age of patients, and test paradigm on the effect sizes of MMN amplitudes in schizophrenia patients. However, in a meta-analysis of 9 studies (182 young and 165 elderly subjects), age has been shown to negatively correlate with both duration and frequency MMN amplitudes (Cheng et al., 2013) and more specifically found to alter significant findings of MMN attenuation in schizophrenia studies when included as a covariate (Kiang et al., 2009). Nicotine use is also an important consideration in MMN studies, as schizophrenia patients who smoke have been shown to have lower MMN amplitudes than non-smoking patients (Light et al., 2015).

MMN attenuation in schizophrenia has been correlated with impaired working memory (Kiang et al., 2007), and larger duration MMN amplitudes in patients have been found to be correlated with...
better social cognition and with better work and independent living (Wynn et al., 2010). Moreover, MMN attenuation appears to index cognitive impairment in neuropsychiatric and neurological diseases in ageing (for a review see Nättänen et al., 2011). However, Baldeeweg and Hirsch (2015) found that working memory impairments correlated with MMN attenuation only in patients with schizophrenia but not in patients with Alzheimer’s disease. Further studies have found MMN attenuation to be associated with impairment in psychosocial functioning in patients with schizophrenia (Kim et al., 2014; Light and Braff, 2005; Light et al., 2015). These findings suggest that MMN may represent a decline of social and cognitive functioning in schizophrenia.

Salisbury et al. (2016) found that MMN amplitude attenuation in frequency and duration paradigms were associated with lower estimates of premorbid intelligence in both healthy and first hospitalized schizophrenic patients and that MMN was associated with a higher quantity of positive symptoms in first hospitalized patients with schizophrenia. In another study, first-episode schizophrenia patients who had not attended college had smaller MMNs than healthy controls and FEP patients who attended college (Umbricht et al., 2006). Therefore, it was suggested that academic achievement and premorbid IQ might be important variables associated with duration-MMN findings.

Early work indicated that long duration MMN amplitude in patients who were taking antipsychotics was not significantly different from MMN recorded in patients free of antipsychotic medication in the prior 3-6 month period (Catts et al., 1995). Similarly, no differences were seen in frequency MMN amplitudes and latencies in patients medicated with Olanzapine (Korostenskaja et al., 2005). This finding is supported by subsequent studies that used other atypical antipsychotics such as amisulpride (a dopamine receptor antagonist), which also reported no significant change in duration MMN amplitudes in first-episode schizophrenia patients between baseline and after 6 weeks of treatment (Düring et al., 2015). However, a study investigating the atypical antipsychotic Aripiprazole (a partial dopamine receptor antagonist), showed improvement in both frequency and duration MMN amplitudes of schizophrenia patients 8 weeks after treatment (Zhou et al., 2013). Clozapine doses were positively associated with frequency MMN amplitudes but negatively associated with the amplitude and latency of duration MMNs in patients with schizophrenia (Horton et al., 2011). These findings highlight the importance of differentiating between specific antipsychotics when studying effects of MMN in chronic patients (who are typically treated with antipsychotics).

### 2.9. The functional anatomy of MMN

Identifying the functional neuroanatomy of MMN generation is not trivial as the precise anatomical location of the MMN generation may depend on the physical characteristics of the stimuli used to elicit the MMN. In healthy populations, generation of auditory frequency MMN has been attributed to neural populations in the primary auditory cortex (A1), superior temporal gyrus (STG), and the inferior temporal gyrus (IFG) (Garrido et al., 2008; Opitz et al., 2002); (see Fig. 2C). Using fMRI, dura-perior temporal gyrus (STG) and the inferior temporal gyrus (IFG) attributed to neural populations in the primary auditory cortex (A1), such as anterior cingulate cortex), areas of the visual system, and the dorsal attention network.

Investigating the auditory system with fMRI poses some limitations due to the acoustic noise which is intrinsic to the technique (Ravicz et al., 2000) as well as poorer temporal resolution. Nevertheless, it is worth mentioning a number of elucidating findings. Mathiak et al. (2002) employed a frequency and duration MMN paradigm which mimicked the gradient switching noise as reflected in fMRI and investigated the elicited MMN using MEG. It was found that duration MMN was right lateralized in the secondary auditory cortex in healthy participants. Further imaging studies in patients with schizophrenia have shown contrasting activation patterns in intensity and duration deviant MMN. Kircher et al. (2004) employed a tone sequence constituting fMRI tones, which mimicked the gradient switching noise, as the auditory stimuli in both an experiment using both fMRI and MEG. The MEG experiment revealed an attenuation of MMN in patients, and the fMRI study showed a strong left lateralization for intensity deviants in patients. Such lateralization was not apparent for duration deviants in the patients, which is often seen over the right hemisphere in healthy individuals.

Using EEG source reconstruction methods, Fulham et al. (2014) found duration MMN generation within a temporal, parietal and frontal network, which was right hemisphere dominant only in healthy controls. Reduced frontal MMN amplitude was found in both recent-onset and chronic schizophrenia patient groups, which involved reduced hemispheric asymmetry, and was correlated with Global Assessment of Functioning (GAF) and negative symptom ratings. During the early phase of the MMN (110–160 ms), schizophrenia patients showed reduced bilateral temporal and parietal responses and no lateralization in frontal regions, whereas controls showed larger activity in the right hemisphere. For late MMN (160–210 ms), patients showed reduced bilateral parietal response but larger temporal activity in the right compared to the left hemisphere.

Overall, evidence from structural and functional neuroimaging suggest right lateralized structural deficits in both frequency and duration MMN in patients with schizophrenia. Further studies are needed to understand if such deficits exist in other populations along the continuum of psychosis.

### 2.10. Taking MMN forward

While the findings in MMN and sensory prediction errors in schizophrenia have expanded vastly with the development of complex paradigms, there is a lack of standardization and lack of sufficient normative data to move MMN to the clinic (Schall, 2016). Despite duration MMN paradigms showing reliability, there is still limited evidence for the best paradigm to be used in large multi-scale studies. However, a recent study from our group found that the left gap and duration MMN paradigm best predicts diagnosis with up to 80% accuracy (Taylor et al., 2017).
Promising attempts of taking MMN forward into the clinic include work by Light et al. (2015) who investigated duration MMN and P3a in multi-site studies of schizophrenia. The study recruited 966 schizophrenia patients and 824 healthy controls, across 5 tests sites in the USA as part of the Consortium on the Genetics of Schizophrenia (COGS). Critically, this study replicated typical duration MMN attenuation in patients, demonstrating the feasibility of conducting multi-site clinical studies for the advancement of findings in MMN.

The findings in MMN across the continuum do not show a clear linear trajectory and suggest that further longitudinal studies will be valuable for assessing whether MMN can be used in the early detection and treatment of psychosis. While there is evidence for a continuum of MMN deficits within the spectrum of clinically diagnosed psychosis, there is little evidence to confirm whether such continuity encompasses the healthy population. Deficiencies in self-generated sensory prediction errors, on the other hand have been found to be aligned on a continuum of psychosis within the schizophrenia spectrum that also extends to non-clinical individuals, such as individuals who score highly on schizotypy.

3. Prediction errors in self-generated stimuli

Sensory self-suppression refers to the phenomenon that sensations initiated by our own actions are typically less salient, and elicit an attenuated neural response, compared to sensations resulting from changes in the external world (Wolpert et al., 1995). The sensory consequence of a self-generated action is predicted and thereby attenuated in healthy individuals, allowing for salience enhancement of sensations that have external sources or are conflicting with the predicted sensation (Baess et al., 2011; Palmer et al., 2016; Wolpert et al., 1995). Schizophrenia patients however, show a deficiency in this process, manifest in an inability to attribute self-generated sensations to an internal source and an abnormal sense of agency (Fletcher and Frith, 2009; Ford, 2016; Franck et al., 2001; Martikainen et al., 2005; Martinelli et al., 2016).

3.1. Theories of sensory self-suppression

Sensory self-suppression has been explained in the context of the Forward Model (Fig. 3A): When we initiate a movement, a motor command of that movement is sent to the motor system. At the same time, an ‘effference copy’ of that action is sent to the sensory cortex, generating a ‘corollary discharge’ of the expected sensory consequence of the motor act (Wolpert et al., 1995). The expected sensation is then compared to the actual sensation, and the discrepancy between the two is the so-called prediction error. In the absence of a discrepancy, the sensation is experienced to be internally rather than externally generated.

Self-generated sensory prediction errors have been studied in the tactile, visual and auditory domains. In the tactile domain, suppression of self-generated sensations has been investigated mainly with force-matching paradigms in which participants receive an external pressure on their hand and are required to match the force received by pressing down on a button (Shergill et al., 2005). These studies show that self-generated tactile sensations are not attenuated in schizophrenia, suggesting a dysfunction in the ability to predict the sensory consequences of one’s own actions (Martinelli et al., 2016; Shergill et al., 2005). Similarly, self-generated eye movements elicit an effference copy, which is sent to the visual cortex (Sperry, 1950), therefore, rather than perceiving the room to be moving, we recognize that the changes in visual field input are due to our eye movements. In the auditory domain, speech production areas in the frontal lobes send an effference copy of
self-generated speech sounds to the auditory cortex (Creutzfeldt et al., 1989). The corollary discharge then predicts the onset of our own speech (and arguably also thought) and thereby reduces the auditory cortical responsiveness. This enables the recognition of speech sounds (and thought) to be self-generated (Feinberg, 1978; Ford et al., 2007a). A failure of this system in producing a corollary discharge has been suggested as a possible cause for auditory verbal hallucinations (AVH), commonly experienced by schizophrenia patients (Blakemore et al., 2000; Ford and Mathalon, 2004; Frith, 1995).

Specifically, during speech production, patients with schizophrenia (particularly those experiencing AVH) show increased activity in temporal lobe structures, instead of suppression as observed in healthy individuals (Frith, 1991). Further speech production tasks have also suggested that reduced fronto-temporal functional connectivity may contribute to the misattribution of internal to external voices in schizophrenia (Ford et al., 2002). These findings are in line with forward models of sensory self-suppression, and suggest that the corollary discharge from speech areas in the frontal cortex fail to inform the temporal regions of the intention to speak (Ford and Mathalon, 2004).

While the forward model has strength in explaining passivity experiences, such as delusions of control, it has received criticism due to its limitations of studying AVH in schizophrenia directly. Specifically, Gallagher (2004) argues that there are no actual vs. predicted internal speech comparisons in AVH and that the ‘comparator mechanism’ fails to explain why all thoughts are not perceived as hallucinations. Brown et al. (2013) also draw attention to limitations of the forward model stating that it relates the intensity of the prediction error to the attenuation effects and that it overlooks the multidimensional nature of sensory attributes; they instead suggest a mechanism under the predictive coding view. Brown et al. (2013) suggest that sensory suppression is not a by-product of an initiating motor command, but a process based on active inference in which the precision of sensory evidence is attenuated during movement to allow proprioceptive predictions (that incite movement) to be fulfilled rather than being corrected by sensory prediction errors. This explanation is potentially important because a failure of sensory attenuation may result in false inference about the cause of self-generated events, which can explain known characteristics of the positive symptoms of schizophrenia such as delusions of self-control.

3.2 N1-suppression

The suppression of self-generated auditory sensations has been studied in healthy individuals and schizophrenia patients focusing on the N1 component of an ERP. N1-suppression is a measurable prediction error of self-generated auditory stimuli which is deficient (i.e., less suppressed) in patients with schizophrenia (Ford et al., 2007a; Ford and Mathalon, 2012; Ford et al., 2013). N1-suppression for self-generated tones also appears to occur independently of attention (like MMN) and indicates the operation of an internal predictive mechanism (Timm et al., 2013). In healthy individuals, it has been shown that the N1 amplitude can be reduced with training of temporal expectation, thus suggesting that training might potentially be used to alleviate subnormal sensory attenuation in patients with schizophrenia (Elijah et al., 2016).

N1-suppression is commonly studied using paradigms in which participants passively listen to a stimulus (control condition), compared with when they listen to a sound generated by their own actions. The most commonly employed tasks include Talk—Listen conditions in which participants self-generate speech and listen to a recording of their own voice played back to them (Ford et al., 2007a; Ford and Mathalon, 2004; Ford et al., 2001a), as well as conditions in which participants either passively listen to a tone or press a button to generate the same tone (Ford et al., 2010). N1-suppression has also been studied using pitch-shifted voices, to identify if participants could differentiate between their own voice and an altered voice. In healthy controls, N1 to unaltered self-voice feedback was dampened relative to N1 to altered self-voice or alien auditory feedback. This pattern was not seen in hallucinating patients, and showed a correlation between the severity of hallucinations and the percentage of misattribution errors (Heinik-Maldonado et al., 2007).

3.3 N1-suppression in the continuum of psychosis

Patients with schizophrenia and schizoaffective disorders have reduced N1-suppression compared to healthy controls (Ford et al., 2013; Ford et al., 2014); See Fig. 3B, 3C. While significant differences of N1-suppression deficits have also been shown in clinically high-risk (Perez et al., 2012) and in high schizotypal individuals compared to low schizotypal individuals (Oestreich et al., 2015, 2016), no significant differences were observed in first-degree relatives of patients when compared to patients and healthy controls, though an intermediate pattern between healthy controls and patients was observed (Ford et al., 2013). N1-suppression has also been found in bipolar disorder (Ford et al., 2013), implicating that corollary discharge dysfunction may be a common feature across psychotic disorders. Table 2 provides an overview of studies on N1-suppression arising from self-generated auditory stimuli in the continuum of psychosis.

Furthermore, similar to a study by Whitford et al. (2011), whereby a 50 ms delay between a button-press and a tone delivery was found to normalize N1-suppression in patients with schizophrenia, it has been shown that that a 25 ms time delay results in N1-suppression in highly schizotypal participants, which is similar to that of the undelayed condition in individuals with few schizotypal tendencies (Oestreich et al., 2016). This suggests that the predictive processes are still active but are affected by slow connectivity, possibly induced by conduction delays. These findings suggest the possibility of training patients to adjust to the time delay (Elijah et al., 2016).

4. Discussion

In this paper, we review MMN and N1-suppression to self-generated sounds, both of which are hallmarks of sensory prediction errors, which are impaired across the continuum of psychosis. Individuals with schizophrenia display aberrant sensory prediction errors, indexed by MMN attenuation as well as a failure to suppress N1 elicited by self-generated sounds, but current evidence suggests that these deficits may lie more broadly on a continuum, rather than being specific to schizophrenia. While studies using N1-suppression paradigms with self-generated stimuli report deficits in non-clinical individuals with high schizotypal characteristics (see Table 2 for a comprehensive list of references), MMN attenuation is seen more specifically in at risk groups rather than in healthy, high schizotypal individuals (Table 1, Fig. 1C). In other words, sensory prediction errors to internally and externally generated sensations can be observed across a broad spectrum in clinical and non-clinical individuals with psychotic symptoms. Moreover, these findings show that severe self-suppression deficits are characteristic to schizophrenia, possibly as a result of disease progression. However, current evidence does not point to a linear relationship between MMN attenuation and disease progression (Erickson et al., 2016). The current review supports that deficits in auditory prediction processes are an important aspect of studying the aetiology of schizophrenia, and show potential in being used as diagnostic tools and as predictors of disease prior to onset.

Elucidating the underlying mechanisms of sensory prediction error generation and what causes them to go awry in schizophrenia is essential for understanding disease progression, as well as determine their effectiveness as disease biomarkers. Theoretical conjectures inspired by predictive coding suggest that patients with schizophrenia form not only inaccurate but also imprecise predictions about incoming sensory information (via top-down connections), which then leads to the formation and propagation of inaccurate predictions upstream (via
### Table 2
Summary of findings in N1-suppression across the continuum of psychosis.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Sample</th>
<th>Paradigm</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Schizophrenia spectrum</strong></td>
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<tr>
<td>(Ford et al., 2014)</td>
<td>SZ (n = 23), schizoaffective (n = 3), HC (n = 22)</td>
<td>Button press sound generation</td>
<td>N1-suppression larger ↑ in HC than SZ.</td>
</tr>
<tr>
<td>(Whitford et al., 2011)</td>
<td>Chronic SZ (n = 21), HC (n = 25)</td>
<td>Button press initiation of participants pre-recorded voice, including un-delayed, 50 ms delayed and 100 ms delayed conditions</td>
<td>N1 suppression ↑ in HC than in SZ for un-delayed condition.</td>
</tr>
<tr>
<td>(Ford et al., 2007a)</td>
<td>SZ (n = 23), schizoaffective (n = 4), HC (n = 26)</td>
<td>Talk-listen paradigm; agency condition: button-press to deliver speech sound, expectancy: speech sound preceded by visual warning</td>
<td>N1-suppression during talk-listen ↑ in HC than SZ, less N1-suppression during agency and expectancy only in HC, not SZ.</td>
</tr>
<tr>
<td>(Whitford et al., 2011)</td>
<td>S Z (n = 21), HC (n = 25)</td>
<td>Pre-recorded voice, including un-delayed, 50 ms delayed and 100 ms delayed conditions</td>
<td>SZ showed ↑ N1 suppression than HC in 50 ms delayed condition, and no significant difference in the 100 ms delay condition.</td>
</tr>
<tr>
<td>(Ford et al., 2007b)</td>
<td>S Z (n = 24), HC (n = 25)</td>
<td>Talk-listen paradigm</td>
<td>Pre-speech neural synchrony was related to subsequent N1-suppression in HC but not SZ.</td>
</tr>
<tr>
<td>(Heinks-Maldonado et al., 2007)</td>
<td>S Z (n = 20), HC (n = 17), sex- and age-matched</td>
<td>Pitch-shifting voices “self,” “other,” or “unsure.”</td>
<td>In HC, N1 to unaltered self-voice feedback was ↓ relative to N100 to altered self-voice or alien voices, but not in hallucinating patients.</td>
</tr>
<tr>
<td>(Ford et al., 2001a)</td>
<td>S Z (n = 7), HC (n = 7)</td>
<td>Talk-listen paradigm</td>
<td>N1-suppression larger ↑ in HC than SZ.</td>
</tr>
<tr>
<td>(Ford et al., 2001b)</td>
<td>S Z (n = 12), HC (n = 10)</td>
<td>Talk-listen paradigm; visual task</td>
<td>N1-suppression ↑ in HC than SZ; no N1-suppression in visual domain.</td>
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<td><strong>At-risk of psychosis</strong></td>
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<tr>
<td>(Perez et al., 2012)</td>
<td>CHR (n = 40) based on SIPS score, SZ patients (n = 81) including early illness SZ (ESZ) (n = 41) subgroup, healthy controls (n = 89)</td>
<td>Talk-listen paradigm</td>
<td>SZ showed ↓ speech-related N1 suppression relative to HC. This was also observed in ESZ. N1 suppression values in CHR were intermediate to HC and ESZ and not statistically distinguishable from either comparison group.</td>
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<tr>
<td><strong>Psychotic patients and non-psychotic first-degree relatives</strong></td>
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<tr>
<td>(Ford et al., 2013)</td>
<td>SZ (n = 30), schizoaffective (n = 19), bipolar patients with a history of psychosis (BPP; n = 39), nonpsychotic relatives of SZ (n = 30), schizoaffective (n = 23), and BPD (n = 50) patients, and healthy controls (n = 43).</td>
<td>Talk-listen paradigm</td>
<td>N1- suppression was significantly ↓ in SZ and BPD patients, with a similar trend in the schizoaffective group. Patient groups did not differ, and unaffected relatives did not differ from controls or probands.</td>
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<tr>
<td><strong>Schizotypy</strong></td>
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<td>(Oestreich et al., 2016)</td>
<td>High Schizotypy (n = 39), Low Schizotypy (n = 41)</td>
<td>Button press sound generation. Time of tone onset after button press was temporally controlled</td>
<td>Low Schizotypy had ↑ levels of N1-suppression to un-delayed tones compared to High Schizotypy. N1-suppression was found to decrease linearly with increasing delays between the button press and the tone in the Low Schizotypy group, this was not the case in the High Schizotypy group. Low schizotypy group showed significant N1-suppression in the Talk condition relative to the Listen and cued-listen conditions. The low schizotypy group also significant reduction in N1-amplitude in the cued listen condition compared to other conditions, but High schizotypy group did not.</td>
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<tr>
<td>(Oestreich et al., 2015)</td>
<td>High schizotypy (n = 37) and low schizotypy (n = 37)</td>
<td>Talk-listen paradigm with an addition of cued listen condition in which participant listened to a recording of the vocalizations while simultaneously watching a video depicting the sound-wave of the forthcoming vocalizations, allowing them to be temporally predicted</td>
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</table>

All studies were conducted using EEG. Schizophrenia (SZ), clinically high-risk for psychosis (CHR), healthy controls (HC); SIPS – structured interview for prodromal syndromes (Miller et al., 2002).
bottom-up connections), hence posing a difficulty in updating prior beliefs (Fletcher and Frith, 2009). Adams et al. (2016) suggest that if the accuracy of incoming sensory information is believed to be high, along with high uncertainty in the prior prediction, then the inference will be biased towards sensory information and away from the prior. This could explain why people with schizophrenia are less susceptible to optical illusions (Dima et al., 2009). In schizophrenia, this is represented as an imbalance or disruption of hierarchical information flow between top-down and bottom-up brain pathways (Adams et al., 2013), formalised in terms of the dysconnection hypothesis (Friston et al., 2016; Friston and Frith, 1995). This view is supported by resting state fMRI connectivity findings showing thalamic-overconnectivity within bilateral sensory–motor cortices in patients with schizophrenia (compared to controls), and under-connectivity within prefrontal–striatal–cerebellar regions, which predicts positive symptoms (Anticevic et al., 2014). This is interpreted as possibly reflecting sensory gating and top-down control disturbances. Evidence from aberrant internal and external sensory prediction errors, indexed by reduced N1-suppression and MMN amplitudes, fits well with the notion of imprecise belief formation in schizophrenia. Crucially, deficits in formation and encoding of valid predictions may increase as psychotic symptoms increase along the continuum of psychosis, as well as with disease progression. Indeed, false inference has been suggested to go hand-in-hand with positive symptoms, impaired learning, and cognitive difficulties (Friston et al., 2016). While there is strong evidence that psychotic symptoms and sensory prediction errors align on a continuum of psychosis, less is known about the neurobiological underpinnings. Future work is necessary to fill in the gaps of the disconnection hypothesis with regards to the continuum of psychosis as currently we only have very few data points (mostly on the extremes of the spectrum) for what happens in terms of brain (dis)connectivity in psychosis.

Current methods of diagnosing psychiatric disorders show variability between clinicians and researchers (Wilson et al., 2014), demonstrating the qualitative nature of the diagnostic system. The combination of exposure to antipsychotics and the effects of the illness itself have profound impacts on cognitive performance (Fritth et al., 1992) and lead to structural neuroatrophy (Ho et al., 2011). It is therefore of utmost importance to accurately identify the individuals who do need antipsychotic treatment, and predict which individuals will respond best to a particular treatment. Biomarkers are of extreme importance in providing objective diagnosis criteria and also in predicting who will convert to psychosis (Bodatch et al., 2015). Validating which paradigms and parameters can be used to identify early predictors of schizophrenia is increasingly important to study the aetiology of this disorder and to develop prophylactic treatments (Kiehl et al., 2005). The recent studies of prediction errors in the continuum of psychosis and schizophrenia reviewed in this article provide a very promising basis for the development of better diagnostic tools for schizophrenia. Moreover, they suggest that prediction errors may be potential biomarkers for the identification of individuals at high-risk for psychosis who might benefit from prophylactic treatments.

Conflicts of interest
We declare no conflicts of interest and all authors have approved the submission of this manuscript.

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