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Schizotypy and auditory mismatch negativity in a non-clinical sample of young adults

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ABSTRACT

Schizophrenia may be conceptualised using a dimensional approach to examine trait-like expression such as schizotypy within non-clinical populations to better understand pathophysiology. A candidate psychosis-risk marker, the auditory mismatch negativity (MMN) is thought to index the functionality of glutamatergic NMDA receptor mediated neurotransmission. Although the MMN is robustly reduced in patients with schizophrenia, the association between MMN and schizotypy in the general population is under-investigated. Thirty-five healthy participants completed the Schizotypal Personality Questionnaire (SPQ) and a multi-feature MMN paradigm (standards 82%, 50 ms, 1000 Hz, 80 dB) with duration (100 ms), frequency (1200 Hz) and intensity (90 dB) deviants (6% each). Spearman's correlations were used to explore the association between schizotypal personality traits and MMN amplitude. Few associations were identified between schizotypal traits and MMN. Higher Suspiciousness subscale scores tended to be correlated with larger frequency MMN amplitude. A median-split comparison of the sample on Suspiciousness scores showed larger MMN (irrespective of deviant condition) in the High compared to the Low Suspiciousness group. The trend-level association between MMN and Suspiciousness is in contrast to the robustly attenuated MMN amplitude observed in schizophrenia. Reductions in MMN may reflect a schizophrenia-disease state, whereas non-clinical schizotypy may not be subserved by similar neuropathology.

1. Introduction

Schizophrenia is a psychiatric illness characterised by positive symptoms including hallucinations and delusions, negative symptoms such as avolition and alogia, and disorganised symptoms including bizarre behaviour and speech (APA, 2013). Whilst current antipsychotic treatments have moderate efficacy (Leucht et al., 2009), up to one third of patients remain symptomatic (van Os and Kapur, 2009). The aetiology of schizophrenia remains poorly understood, and the importance of moving from a categorical diagnosis to a dimensional approach is increasingly advocated by researchers within this field (David, 2010; Ettinger et al., 2014; Nelson et al., 2013).

One way in which this continuum might be understood is in terms of trait-like expressions of schizophrenia that are also present in varying degrees in the general population (Ettinger et al., 2014; Johns and van Os, 2001). For example, schizotypy describes a cluster of personality traits which include unusual perceptual experiences, odd beliefs or magical thinking, odd or eccentric behaviour, social anxiety and isolation, constricted affect, suspiciousness and paranoia (Raine, 1991). Each of these is argued to map broadly onto the positive, negative and disorganised dimensions of schizophrenia (Fonseca-Pedrero et al., 2011; Nelson et al., 2013). Nelson et al. (2013) review competing models of schizotypy, including the *quasi-dimensional* approach which suggests that a small group of people, approximately 10% of the population known as "schizotypes", are vulnerable to schizophrenia (Lenzenweger, 2006; Meehl, 1990) and the *fully dimensional* approach (Claridge and Beech, 1995; Rawlings et al., 2008) in which schizotypy is conceptualised as existing along a continuum within the general population. The latter model is well supported in the literature (Johns and van Os, 2001; Van Os et al., 2009), and is consistent with models describing continuity in clinical versus

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non-clinical symptoms of schizophrenia in the population (Linscott and Van Os, 2013; Linscott and Van Os, 2010). Neither model assumes that schizotypal traits are sufficient indicators of psychosis-risk, but rather that schizotypal traits interact with other environmental and genetic factors to confer risk (Nelson et al., 2013; Rawlings et al., 2008). Given the complexities of investigations into schizophrenia, including medication history, lifestyle factors such as substance use and smoking, and disease chronicity, research exploring schizotypy in the general population may provide information pertinent to the aetiology and risk factors associated with psychotic disorders (Nelson et al., 2013).

While there is a plethora of evidence from genetic studies in particular supporting the existence of schizotypy on a continuum with schizophrenia, increasing evidence also comes from neuropsychological and neurobiological research (for comprehensive reviews see, Ettinger et al., 2014; Nelson et al., 2013). For example, recent structural MRI work has indicated that high schizotypy is associated with reduced grey matter in the frontal and temporal lobes (DeRosse et al., 2014), reduced grey matter volume in medial prefrontal, orbitofrontal, and temporal cortical regions (Ettinger et al., 2012), and an aberrant neural prediction error signal (Corlett and Fletcher, 2012). Patients with schizotypal personality disorder showed altered auditory evoked potential N1, P2, N2 and P3 components intermediate between schizophrenia patients and healthy controls (Trestman et al., 1996). Schizotypy traits in a non-clinical population have also been associated with reduced P3 amplitude (Kimble et al., 2000), altered power within the electroencephalography (EEG) gamma frequency band (Kornmayer et al., 2015), sleep spindle density (Lustenberger et al., 2014), altered neural oscillations during a working memory task (Koychev et al., 2011), and impaired sensory gating as indicated by reduced P50 suppression (Croft et al., 2004; Croft et al., 2001; Evans et al., 2007). However, others have found a less clear pattern of findings; for example, Lagioia et al. (2010) did not find an association between default-mode activity and schizotypy in an adolescent sample. Modinos et al. (2010) also reported larger regional volumes in the medial posterior cingulate cortex (PCC) and the precuneus in individuals with high psychosis proneness as measured by the Community Assessment of Psychic Experiences (CAPE), which is contrary to findings in patients.

Intriguingly, despite a large body of research investigating alterations to the mismatch negativity (MMN) in patients with schizophrenia, a brain marker sensitive to N-methyl-D-aspartate (NMDA) receptor function (for a review see, Todd et al., 2013), very few studies have investigated the association between MMN alterations and schizotypy. MMN is a frontocentrally maximal event-related potential (ERP) component, defined as the point of greatest deviance following infrequent auditory (or visual) stimuli termed deviants, presented within a predictable pattern of frequent tones (or stimuli) (termed standard stimuli) (Kujala et al., 2007; Näätänen, 1995). The 'deviant' may differ from the 'standard' on a number of possible perceptual features including stimulus duration, frequency (pitch), intensity and location. The MMN is a component of the ERP visible within a difference waveform, computed by subtracting the brain response to the standard stimulus from the brain response elicited by the deviant (Picton et al., 2000), and is argued to reflect the evaluation of new auditory sensory input against current models of the acoustic environment (Garrido et al., 2009; Winkler, 2007). The two known generators of MMN, the superior temporal gyrus (STG) and inferior frontal gyrus (IFG; see Michie et al., 2016 for a review) are represented as a sum by mastoid-referenced MMN data recorded at frontal sites and may only be accurately dissociated with source localisation or computational approaches such as direct causal modelling (Garrido et al., 2009). Research in patients with schizophrenia, have consistently focused on MMN recorded at the frontocentral site electrode site 'Fz', noting robust reductions (Umbricht and Krljes, 2005).

Robust reductions in MMN amplitude have been noted in patients with schizophrenia (Erickson et al., 2015; Näätänen and Kahkonen, 2009; Umbricht and Krljes, 2005), as well as their first degree relatives (Jessen et al., 2001; Michie et al., 2002; Sevik et al., 2011). These findings highlight the potential utility of MMN as a candidate endophenotype for the disorder (for a review of MMN as a marker of conferring vulnerability to schizophrenia, see Todd et al., 2013), although the evidence is mixed, (see, Bramon et al., 2004; Magno et al., 2008) and alterations to MMN have been noted in other disorders (for a review see, Näätänen et al., 2011). In patients, reductions in MMN have been linked with greater impairments in social and cognitive function (Näätänen et al., 2011), however evidence for an association between MMN and positive or negative symptoms of schizophrenia remains unclear (Todd et al., 2013; Umbricht and Krljes, 2005). MMN elicited by duration deviants (and to a lesser extent intensity deviants) has been linked in particular with the prodromal phase of illness (Todd et al., 2008), and is reduced in individuals at ultra-high risk of developing the disorder and patients with first episode psychosis (Atkinson et al., 2012; Bodatsch et al., 2011; Hermens et al., 2010; Hsieh et al., 2012; Kaur et al., 2011; Nagai et al. 2013; Perez et al., 2014; Shaikh et al., 2012; Solis-Vivanco et al., 2014). Patients with chronic schizophrenia exhibit significant reductions in frequency MMN, with group differences for duration deviants less apparent at the later stages of illness (Todd et al., 2008). Grey matter loss in left and right Heschl's gyrus has been linked with attenuated frequency (Rasser et al., 2011; Salisbury et al., 2007) and duration MMN (Rasser et al., 2011) respectively in patients with schizophrenia. There is mounting evidence therefore that MMN may be sensitive to stage of illness in schizophrenia (i.e. attenuated duration MMN with the early stages of illness and reductions in frequency MMN with the later stages of illness) and indeed, that (duration) MMN deficits may identify at risk individuals who go on to develop psychosis (Atkinson et al., 2012; Bodatsch et al., 2011; Higuchi et al., 2013; Jahshan et al., 2012; Murphy et al., 2013; Perez et al., 2014). Therefore, MMN is argued to be of particular interest with regard to future work targeting biomarkers of psychosis risk in vulnerable populations (Belger et al., 2012; Bodatsch et al., 2013; Light and Naatanen, 2013; Todd et al., 2013).

This work is already underway in individuals with schizotypal personality disorder features (Hong et al., 2012; Liu et al., 2007; Niznikiewicz et al., 2009), children at risk of developing schizophrenia (Bruggemann et al., 2013; Schreiber et al., 1992) and chronic cannabis users (e.g., Greenwood et al., 2014). Reduced MMN in a normative sample with high positive (schizotypal) symptom scores on the Personality Syndrome Questionnaire was reported in an abstract (Baldeweg et al., 1999), although the type of MMN was not reported. Fernandes et al. (1999) found no effect on frequency MMN amplitude of schizotypal symptoms, family history of psychosis, or group classification based on Chapman scales, in a normative sample. Although they did not measure MMN, Bates (2005) reported an association between auditory imprecision and higher schizotypal scores (measured using the Schizotypal Personality Questionnaire; SPQ) in a normative sample, reflecting reduced fidelity of primary sensory representations measured using a choice-reaction time task. Surprisingly, however, MMN has not been specifically investigated with respect to schizotypal personality traits in the general population as measured by the widely used SPQ, which has robust psychometric properties (Raine, 1991).

Therefore, the aim of the current study was to explore whether higher scores on the SPQ in a non-clinical sample were associated with attenuated MMN amplitude, consistent with the status of MMN as a biomarker for psychosis-proneness.