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Mismatch field latency, but not power, may mark a shared autistic and schizotypal trait phenotype

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ABSTRACT

The auditory mismatch negativity (MMN), a preattentive processing potential, and its magnetic counterpart (MMF) are consistently reported as reduced in schizophrenia and autism spectrum disorders. This study investigates whether MMF characteristics differ between subclinically high and low scorers on the recently discovered shared autism and schizophrenia phenotype, Social Disorganisation.

A total of 18 low (10 females) and 19 high (9 females) Social Disorganisation scorers underwent magnetoencephalography (MEG) during a MMF paradigm of 50ms standard (1000Hz, 85%) and 100ms duration deviant tones. MMF was measured from the strongest active magnetometer over the right and left hemispheres (consistent across groups) after 100ms.

No differences in MMF power were found, however there was a significant delay in the MMF peak ($p=0.007$). The P3am (following the MMF) was significantly reduced across both hemispheres for the high Social Disorganisation group ($p=0.025$), there were no specific hemispheric differences in P3am power or latency. Right MMF peak latency increased with higher scores on the schizotypal subscales Odd Speech, Odd Behaviour and Constricted Affect.

Findings suggest that MMF peak latency delay marks a convergence of the autism and schizophrenia spectra at a subclinical. These findings have significant implications for future research methodology, as well as clinical practice.

1. Introduction

Autism and schizophrenia are spectrum disorders with symptom phenotypes readily identified as traits in the non-clinical population. There is increasing evidence for substantial phenotypic overlap between the two disorders, particularly in the negative symptom domain of schizophrenia, and social and communication deficit domain of autism (Dinsdale et al., 2013; Kanai et al., 2011; Spek and Wouters, 2010; Wakabayashi et al., 2012; Ford and Crewther, 2014). At a trait level, a shared autistic and schizotypal phenotype has been identified through factor analysis of the autism spectrum quotient (AQ: (Baron-Cohen et al., 2001)) and schizotypal personality questionnaire (SPQ: (Raine, 1991)). The shared factor, Social Disorganisation (Ford and Crewther, 2014), was in line with a previous study demonstrating a general social-communicative disinterest, impairments and abnormalities component following principal component analysis of the AQ and SPQ-brief (Dinsdale et al., 2013). Similar neurophysiological abnormalities, such as a reduced amplitude of the mismatch negativity (MMN), and its magnetic counterpart (MMF), have also been reported in autism and schizophrenia spectrum disorders (Catts et al., 1995; Shelley et al., 1991; Michie et al., 2000; Ferri et al., 2003; Kemner et al., 1995), and may therefore be characteristic of the shared phenotype (Pinkham et al., 2008; Sugranyes et al., 2011). This study investigated the relationship between MMF characteristics and the shared Social Disorganisation phenotype.

The MMN/F is a preattentive, change-detection, event related potential (ERP). This potential is a function of the difference between the ERP to a consistently presented standard stimulus and the ERP to a rare deviant (such as in duration, frequency or intensity), occurring between 100 ms and 250 ms post stimulus onset (Näätänen, 1990; Michie, 2001; Näätänen et al., 1978). The auditory MMN/F originates in the superior temporal gyrus (STG), specifically the primary auditory cortex, which is responsible for the reception and processing of auditory stimuli, as well as auditory perception and working memory

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functions (Alho et al., 1998; Shelley et al., 1991; Brockhaus-Dumke et al., 2005; Ferri et al., 2003). The MMN/F also appears at around 200 ms in the posterior STG and planum temporale, which are involved in the analysis of stimulus change (Schonwiesner et al., 2007).

The MMN/F has been extensively explored in psychopathology, particularly in schizophrenia spectrum disorders. In fact, the MMN has been regarded as a vulnerability marker for schizophrenia (Näätänen and Kähkönen, 2008; Nagai et al., 2013), with duration deviants consistently eliciting reduced MMNs amplitudes in chronic schizophrenia (Brockhaus-Dumke et al., 2005; Fulham et al., 2014; Kircher et al., 2000; Lee et al., 2014; Michie et al., 2000; Shelley et al., 1991; Todd et al., 2000; Umbricht et al., 2003; Wynn et al., 2010; Todd et al., 2008) and first episode psychosis patients (Nagai et al., 2013; Atkinson et al., 2012; Fulham et al., 2014; Hermens et al., 2010; Hsieh et al., 2012; Kaur et al., 2013; Todd et al., 2008), as well as individuals at high-risk and with prodromal symptoms (Brockhaus-Dumke et al., 2005; Atkinson et al., 2012; Hsieh et al., 2012; Murphy et al., 2013; Nagai et al., 2013), individuals with high trait schizotypy (Hong et al., 2012), and first degree relatives (Michie et al., 2002).

In schizophrenia patients, reduced MMN/F amplitude has been related to poorer social functioning (Wynn et al., 2010; Fulham et al., 2014; Lee et al., 2014; Rasser et al., 2011), poorer performance on proverb interpretation and short term memory (Kiang et al., 2007), as well as poorer global (Fulham et al., 2014; Kiang et al., 2007; Lee et al., 2014; Light and Braff, 2005; Wynn et al., 2010) and workplace functioning (Kaur et al., 2013; Wynn et al., 2010). Reduced MMN amplitude has also been associated with both increased positive and increased negative symptoms of schizophrenia (Lee et al., 2014; Fulham et al., 2014; Kargel et al., 2014; Thonnessen et al., 2008).

In high functioning autism spectrum disorders, reduced MMN amplitude to duration deviants has also been reported (Andersson et al., 2013; Kujala et al., 2010; Lepisto et al., 2005, 2006). However, there is inconsistency in the autism MMN/F literature, which may be due to the vast heterogeneity of samples in autism studies, such as in age, intelligence, medication use, and degree of symptomology (Gomot et al., 2000). In fact, clinical studies of the MMN/F are limited in general by disorder heterogeneity and the effects of medication.

Behavioural correlates of the MMN are largely unstudied in autism; one study reports no relationship between MMN and autistic trait symptoms (Andersson et al., 2013), while reduced MMN to emotional stimuli has been related to higher AQ score (Fan and Cheng, 2014). Nevertheless, the association between MMN/F and social cognitive (Wynn et al., 2010; Fulham et al., 2014; Lee et al., 2014; Rasser et al., 2011; Kiang et al., 2007) and global functioning (Fulham et al., 2014; Kiang et al., 2007; Lee et al., 2014; Light and Braff, 2005; Wynn et al., 2010), which are compromised in autism and schizophrenia spectrum disorders, and central to the Social Disorganisation phenotype, indicates the potential for a relationship between Social Disorganisation and MMN/F characteristics.

The latency of the MMN/F peak reflects the efficiency of the systems involved in auditory change processing (Fulham et al., 2014), and delays have been reported in adults with autism (Kasai et al., 2002) and schizophrenia (Fulham et al., 2014). Many clinical studies report no differences in MMN/F latency (Lepistö et al., 2007; Andersson et al., 2013; Kujala et al., 2007; Lepisto et al., 2005, 2006; Murphy et al., 2013; Brockhaus-Dumke et al., 2005; Hermens et al., 2010; Todd et al., 2000; Kircher et al., 2000; Michie et al., 2000; Umbricht et al., 2003; Atkinson et al., 2012; Hsieh et al., 2012; Hong et al., 2012).

Following the MMF is the magnetic P3am component between 200 ms and 300 ms (Alho et al., 1998). The electrophysiological P3a is suggested to mark involuntary attention switching (Lepisto et al., 2006; Kujala et al., 2007). Reduced P3a amplitude to duration deviants has been reported in those at high-risk of psychosis and first episode psychosis patients (Nagai et al., 2013; Atkinson et al., 2012; Hermens et al., 2010), as well as children with ASD, which suggests poor involuntary reorienting to auditory environmental changes for these groups (Dunn et al., 2008).

A reduction in MMN/F amplitude has been thought to result from: 1) a deficient memory trace formation as a result of *N*-methyl-D-aspartate receptor (NMDAr) dysfunction, 2) a reduced frontal attention switch, or 3) grey matter loss in the temporal lobe (Näätänen and Kähkönen, 2008). NMDArs regulate excitation and inhibition of neuronal circuits. Excitatory glutamatergic neurotransmission facilitates short-term synaptic plasticity, and this activation is necessary for memory and learning (Javitt et al., 1996; Naatanen et al., 2012). Excitatory glutamatergic neurotransmission is also integral to the integration of the multiple systems that process stimulus duration information (Kompus et al., 2015). Inhibitory GABAergic interneurons regulate this cortical excitation, and are in turn regulated by NMDArs. Recently, increased glutamate, decreased GABA and subsequently increased glutamate/GABA ratio has been found in the superior temporal region of those with high levels of Social Disorganisation (Ford et al., under review). Altogether, these processes are suggested to be involved in the memory trace formation, which leads to the MMN/F when violated (Javitt et al., 1996; Umbricht et al., 2003).

Magnetoencephalography (MEG) is a superior method for localising group and hemispheric differences in MMN/F and P3a/m over electroencephalography (EEG) for several reasons. First, magnetic fields are unimpeded by cortical matter, thus allowing for direct response measurement from the auditory cortices. Second, MEG optimally records superficial, tangential cortical response such as those from the auditory cortices. Finally, EEG recording of the MMN and P3a from frontal and central electrodes likely includes additional regions of cortical activity (Alho et al., 1998; Thonnessen et al., 2008; Hillebrand and Barnes, 2002; Naatanen et al., 2012). Altogether, MEG is a superior tool for the assessment of auditory MMF and P3am generators at a sensor space level.

Overall, differences in age (Gomot et al., 2000), psychopharmacological treatment (Javitt et al., 1996; Oranje et al., 2008), clinical and non-clinical group heterogeneity (Michie et al., 2000), and/or the lacking trait data for control groups may contribute noise to clinical studies. The multi-dimensional nature of the autism and schizophrenia spectra, as well as then above-mentioned differences across studies, are likely to contribute to the inconsistencies in the MMN/F literature. Given that psychosocial functioning has been related to the MMN (Wynn et al., 2010; Fulham et al., 2014; Lee et al., 2014; Rasser et al., 2011; Kiang et al., 2007), and the shared Social Disorganisation phenotype of the autism and schizophrenia spectra, and in particular their respective traits, is centred around psychosocial functioning, this study investigated the relationship between Social Disorganisation and the MMF in a non-clinical, unmedicated, adult population. It was predicted that those with a high degree of Social Disorganisation would elicit a significantly less MMF power to a duration increment than those with a low degree of Social Disorganisation. Furthermore, trait subscales within Social Disorganisation were expected to increase with reducing MMF power.

2. Methods

The Swinburne University Human Research Ethics Committee approved the study in accordance with the 1964 Declaration of Helsinki. All participants provided informed consent to participate in the study. MMF data were acquired within a larger experimental battery; only the MMF-related methodology is reported below.

2.1. Participants

Participant recruitment is detailed elsewhere (Ford et al., 2017a). In brief, a total 428 males and 1250 females aged 18 to 40 years completed an autism schizotypy questionnaire (ASQ) via the Opinio software interface (ObjectPlanet, 1998-2016). The ASQ was a combined