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Reduced mismatch negativity predates the onset of psychosis

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ABSTRACT

Background: Individuals with an "At Risk Mental State" have a 20–30% chance of developing a psychotic disorder within two years; however it is difficult to predict which individuals will become ill on the basis of their clinical symptoms alone. We examined whether mismatch negativity (MMN) could help to identify those who are particularly likely to make a transition to psychosis.
Method: 41 cases meeting PACE criteria for the At Risk Mental State (ARMS) and 50 controls performed a duration-deviant passive auditory oddball task whilst their electroencephalogram was recorded. The amplitude of the MMN wave was compared between groups using linear regression. The ARMS subjects were then followed for 2 years to determine their clinical outcome.
Results: The MMN amplitude was significantly reduced in the ARMS group compared to controls. Of the at-risk subjects who completed followed up (n = 41), ten (24% of baseline sample) subsequently developed psychosis. The MMN amplitude in this subgroup was significantly smaller across all three recording sites (FZ, F3 and F4) than in the ARMS individuals who did not become psychotic. Conclusion: Among those with the ARMS, MMN amplitude reduction is associated with an increased likelihood of developing frank psychosis.

1. Introduction

The prodrome is a critical stage in the development of psychosis in which initial symptoms first arise. The basis of the vulnerability to psychosis in this group is not clearly known, and whilst evidence shows that psychological and pharmacological interventions may improve outcomes (Bechdolf et al., 2005; McGorry et al., 2002; Morrison et al., 2007; Politi et al., n.d.; Yung et al., n.d.), treating high-risk subjects remains controversial since most of them are not destined to develop psychosis (Simon et al., n.d.). Indicated prevention is currently regarded as the most promising strategy to attenuate, delay, or even avert psychosis. Studies have found significant specificity regarding prediction of conversion using clinical and other variables (Cannon et al., 2008; Velthorst et al., 2009), but only at the cost of sensitivity and vice versa. However a recent study by Ruhrmann et al (2010) introduced a risk modelling procedure with the use of prognostic indexes for a multivariate clinical staging approach to improve specificity and individual risk assessment to allow for better targeted and earlier interventions. The multivariate clinical staging approach of at-risk symptoms further demands neurobiological markers for early detection, and researchers have tried to find trait markers using several imaging techniques (Bramon et al., 2008; Fusar-Poli et al., 2011a; Howes et al., 2007; Pantelis et al., 2003). Indeed, the better characterisation of the prodrome of psychosis by means of biological investigations is a prerequisite for both prevention and intervention (Broome et al., 2005b; Ruhrmann et al.; Ruhrmann et al., 2010; Yung et al., 2003; Yung et al., 2004).

Direct in-vivo measures of cortical activity observed in the human EEG are useful markers of brain dysfunction in psychosis (Schulze et al., 2007, 2008; Shaikh et al., 2010; Turetsky et al., 2007) and provide high temporal resolution (Bramon et al., 2005). The MMN, in particular, is a change in the EEG (an event related potential) that emerges when a novel stimulus infringes the regularity of the preceding ones. Auditory MMN can be elicited by different qualitative and quantitative types of deviance, including intensity, location, frequency, duration or pattern of auditory stimuli. The deviant type as well as the attentional condition may have substantial effects on the stability and replicability of MMN potentials. Duration deviants, similar to the ones used in this study, generally produce MMN amplitudes of better intraindividual stability and a task demanding focused attention minimizes measurement error (Kathmann et al., 1999). The MMN waveform is an early phenomenon, thought to reflect cortical activation in basic, pre-attentive stages of auditory information processing and perception (Näätänen et al., 1989). It is thought that the

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MMN signal originates in primary and secondary auditory cortex (Kreitschmann-Andermahr et al., 1999; Molholm et al., 2005; Sams et al., 1991).

From the work of Shelley et al. (1991) and subsequent replications (Baldeweg et al., 2002; Javitt et al., 1995; Michie et al., 2002; Umbricht and Krljes, 2005) it is well-established that MMN amplitude, especially duration-MMN, is reduced amongst patients with chronic schizophrenia and first episode psychosis (Hermens et al., 2010) A meta-analysis in established schizophrenia produced a large effect size (0.99), showing that these MMN amplitude deficits are severe and MMN to stimuli differing in duration appeared more impaired in schizophrenia than MMN to frequency deviants. Additional correlation analyses indicated that the frequency MMN performance may worsen with illness duration (Umbricht and Krljes, 2005). It has also been suggested that the unaffected relatives of patients display similar deficits and that therefore MMN may be a potential marker of genetic risk to develop psychosis (Jessen et al., 2001; Michie et al., 2002). However, in our family study we were only able to find duration MMN reductions in our chronic patients while their symptom-free first-degree relatives had a normal MMN wave (Bramon et al., 2004). A recent study has also found that the unaffected first-degree relatives of schizophrenia patients do not show duration or pitch MMN deficits (Magno et al., 2008). It is thus unclear whether or not MMN deficit reflects liability for psychosis or clinical state related changes. Investigations in an at-risk sample with prodromal symptoms will clarify whether duration MMN is related to the disease itself (trait) and can distinguish at-risk subjects that subsequently develop psychosis. With regard to targeted prevention, a state marker would be helpful to the estimation of the individual stage and transition to psychosis.

Alterated MMN is of particular interest in relation to psychosis, as this appears to be a marker of brain glutamate dysfunction (Javitt, 2000), which is a key pathophysiological feature of psychotic disorders (Kantrowitz and Javitt; Lin et al.; Marsman et al.). Moreover, recent research using MR spectroscopy indicates that brain glutamate levels are altered in ARMS subjects (Stone et al., 2009), and that this is associated with changes in the structure and function of the medial temporal and prefrontal cortex (Fusar-Poli et al.; Stone et al., 2009; Valli et al.), and a change in the relationship with striatal dopamine function (Stone et al.). Furthermore, the later onset of psychosis in ARMS subjects may be linked to progression of these glutamatergic abnormalities (Stone et al.).

Brockhaus-Dumke et al (2005) reported that 43 cases with at-risk symptoms of psychosis displayed a trend for small reductions in MMN, with values intermediate between those in healthy controls and patients with schizophrenia. They did not examine the relationship between MMN and the subsequent onset of psychosis. However, a more recent study reported that the subgroup of ARMS subjects who went on to develop psychosis had reduced MMN amplitudes at presentation relative to the rest of the sample (Bodatsch et al., 2010). We set out to attempt to replicate this finding in an independent sample, using similar methods. Our first prediction, was that MMN would be reduced in the ARMS group as a whole, relative to controls. We then tested the hypothesis that, within the ARMS sample, the reduction in MMN would be greater in the subgroup of subjects who subsequently developed psychosis than in those who did not.

2. Materials and methods

Subjects were 41 individuals with an 'at risk mental states (ARMS)' according to criteria established by Yung et al (2003) and 50 healthy volunteers with no family or personal history of psychotic disorders. At risk people were recruited by referrals from general practice professionals, university and other health care facilities and occasionally by self-referrals to a clinical team operating in a deprived inner-city area of London (OASIS 'Out-reach and Support in South London'). For further details on the overall clinical sample and service see Broome et al (2005a). Controls were recruited by advertisements in the local press and lived in the same area as the patients. Participants were excluded if they had neurological disorders, or head injury with loss of consciousness longer than five minutes. Substance abuse and occasional use did not constitute exclusion criteria since this is a well known risk factor for psychosis (Arseneault et al., 2004). All participants gave written informed consent to enter the study. This research was approved by the Ethical Committee at the Institute of Psychiatry.

2.1. Clinical assessments

All participants underwent a clinical assessment to collect information on socio-demographic, physical and mental health data and the timing and nature of any symptoms. The instrument used to identify at risk cases was the Comprehensive Assessment of At-Risk Mental States (Yung et al., 2003). In addition, in order to examine current psychopathology, all participants completed the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997). Family history of mental illness, in particular psychosis, was assessed during the psychiatric interview for all participants. Having a family history of psychosis constituted an exclusion criteria for controls and was one of the inclusion criteria for at risk cases. Where there was a possible relevant family history the participant was invited to give full details using the Family Interview for Genetic Studies (FIGS) (Nurnberger et al., 1994). Due to the nature of our recruitment and ascertainment only a small subset of participants had an additional FIGS carried out with a relative of theirs. Transition to psychosis was defined according to the criteria in the CAARMS (i.e., presence of at least 1 positive psychotic symptom at high severity for more than 1 week). The type of psychotic disorder was defined using the SCID (First et al., 1997), performed by an experienced psychiatrist approximately 12 months after the point of transition. The sample was followed up clinically by OASIS for a minimum period of 2 years. The mean observation period was 750 days (sd = 330.87) and mean months to conversion were 26.5 (sd = 22.63). The sample of patients at risk for psychosis received standard clinical management (psychosocial support, CBT, monitoring only and antipsychotic medication) through OASIS, irrespective of participation in this study. Of the 41 cases at-risk, none of them were taking antipsychotics at the time of EEG testing. During the 2 year follow up, 2 received antipsychotics (1 converter), 15 received a combination of antipsychotics and CBT (4 converters), 1 received antidepressant, 4 received antidepressants combined with CBT and 11 received CBT only (3 converters). None of the controls were on any psychotropic medication at the time of EEG testing.

2.2. Auditory duration-deviant MMN paradigm

Stimuli were twelve hundred 80 dB, 1000 Hz tones, with a 0.3 s inter-stimulus interval. These were presented as three blocks of 400 stimuli through bilateral intra-aural earphones. 85% of the tones were 'standards' (25 ms duration, 5 ms rise/fall time) and 15% were 'deviants' (50 ms duration, 5 ms rise/fall time). Further details can be found in Bramon et al. (2004).

2.3. Data acquisition

EEG data were collected from 64 scalp sites according to the 10/20 International System (Jasper, 1958) and were grounded at Fpz using syntered electrodes in a cap. Bilateral mastoids served as reference and vertical and horizontal electro-oculographs monitored eye movements. Data were continuously digitised at 500 Hz with a 0.05 to 200 Hz band-pass filter (24 dB/octave roll-off). Impedances were kept below 5 kΩ.