



## Sensory gating deficits in the attenuated psychosis syndrome



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### ABSTRACT

**Background:** Individuals with an “Attenuated Psychosis Syndrome” (APS) have a 20–40% chance of developing a psychotic disorder within two years; however it is difficult to predict which of them will become ill on the basis of their clinical symptoms alone. We examined whether P50 gating deficits could help to discriminate individuals with APS and also those who are particularly likely to make a transition to psychosis.

**Method:** 36 cases meeting PACE (Personal Assessment and Crisis Evaluation) criteria for the APS, all free of anti-psychotics, and 60 controls performed an auditory conditioning–testing experiment while their electroencephalogram was recorded. The P50 ratio and its C–T difference were compared between groups. Subjects received follow-up for up to 2 years to determine their clinical outcome.

**Results:** The P50 ratio was significantly higher and C–T difference lower in the APS group compared to controls. Of the individuals with APS who completed the follow-up ( $n = 36$ ), nine (25%) developed psychosis. P50 ratio and the C–T difference did not significantly differ between those individuals who developed psychosis and those who did not within the APS group.

**Conclusion:** P50 deficits appear to be associated with the pre-clinical phase of psychosis. However, due to the limitations of the study and its sample size, replication in an independent cohort is necessary, to clarify the role of P50 deficits in illness progression and whether this inexpensive and non-invasive EEG marker could be of clinical value in the prediction of psychosis outcomes amongst populations at risk.

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### 1. Introduction

The P50 auditory evoked potential has been used to reflect the brain's gating mechanism, which is the individual's ability to filter out repetitive or trivial stimuli in order to minimize information overload (Freedman et al., 1996). P50 auditory event-related potential (ERP) waves are generated by identical pairs of clicks 500 ms apart in what is commonly referred to as the conditioning–testing paradigm. The first stimulus (condition P50; C) activates or conditions the inhibition phenomenon, while the second (test P50; T) tests its strength. Normally, individuals exhibit more than a 70% reduction of the second wave relative to the first. This diminished T wave is thought to be the product

of inhibitory neural circuitry by the C stimuli (Adler et al., 1982; Freedman et al., 1997).

Compared to controls, patients with schizophrenia show a relatively larger P50 response to the second stimulus in a paired-click auditory evoked response paradigm, resulting in only 20%–50% suppression (Freedman et al., 1983, 1987; Nagamoto et al., 1989; Judd et al., 1992; Ward et al., 1996; Clementz et al., 1997, 1998; Shaikh et al., 2010). Unaffected first-degree biological relatives of schizophrenia patients also have poor P50 suppression, suggesting that this effect may be familial, indeed relating to the genetic liability for this illness (Siegel et al., 1984; Waldo et al., 1988, 1995, 2000; Stevens et al., 1996; Clementz et al., 1998; Shaikh et al., 2010). Diminished P50 suppression has also been found in bipolar disorder patients with psychotic features and their unaffected relatives (Franks et al., 1983; Baker et al., 1990; Olincy and Martin, 2005; Schulze et al., 2007; Hall et al., 2008; Sanchez-Morla et al., 2008).

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There is some controversy regarding whether or not the schizophrenia-related deficit represents a 'gating' phenomenon. Some studies have reported that the amplitude from the second stimulus is the same in patients and controls, while the amplitude and/or latency for the first stimulus is altered in patients, perhaps accounting for the decreased ratio (Jin and Potkin, 1996; Jin et al., 1997). As such, the reduced P50 amplitude to the second of paired clicks (C, T) might be more reliably measured as the difference between P50 amplitudes (C–T) rather than its ratio (T/C) (Dalecki et al., 2011). Generally, the utility of P50 paired-click measures has been limited by their unestablished reliability, unknown effects of time differences in peak selection methodology and rater blinding, poor signal-to-noise ratio, sound intensity, seating position and long protocol (de Wilde et al., 2007a, 2007b; Dalecki et al., 2011). In spite of controversies surrounding the P50 ERP, reduced P50 ratio in schizophrenia has been confirmed meta-analytically (Bramon et al., 2004; de Wilde et al., 2007a, 2007b).

Studies have shown that P50 gating is already impaired in the early stages of schizophrenia. Myles-Worsley et al. (2004) compared a genetically defined high-risk group and a clinically defined sample of at-risk adolescents and showed that P50 suppression was impaired in both groups. Yet, in the genetically high-risk group, P50 suppression abnormalities were found only in those with clinically defined prodromal symptoms. Cadenhead et al. (2005) showed that subjects at risk of developing a psychosis with a first-degree relative with schizophrenia had significantly lower levels of P50 suppression relative to control subjects. Furthermore Brockhaus-Dumke et al. (2008) found that P50 gating deficits are present in individuals at clinical high risk and amongst drug-naïve first-episode patients in comparison to control subjects. However, not all studies have shown P50 deficits in high risk individuals (Ziermans et al., 2012), first episode psychosis (de Wilde et al., 2007b; Bachmann et al., 2010) and established schizophrenia (Kathmann and Engel, 1990).

Since the P50 wave has been shown to be both heritable (Young et al., 1996; Hall et al., 2006) and possibly linked to liability for psychotic disorders, we expected to demonstrate and replicate P50 suppression in individuals with APS. Our first prediction was that P50 ratio would be increased and C–T amplitude difference smaller in the APS group relative to controls. As a preliminary analysis we also explored whether P50 suppression could be used to identify those individuals with APS who are likely to make a conversion to psychosis.

## 2. Methods

### 2.1. Sample

Subjects were 36 individuals with 'at risk mental states' (Yung et al., 2003b), all antipsychotic free at the time of testing, and 60 healthy volunteers with a similar demographic background but without any family or personal history of psychotic disorders. At risk people were recruited by referrals from general practice professionals, university health care facilities and occasionally by self-referrals as part of a clinical team operating in a deprived inner-city area of London (OASIS 'Outreach And Support In South London'). For further details on the overall clinical sample and service see Broome et al. (2005). 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 5 min. While substance (except nicotine) and alcohol use meeting criteria for dependence in the last 12 months was an exclusion criterion for all participants, substance and alcohol misuse including occasional (once a month or less) consumption of illicit substances, did not constitute exclusion criteria since this is a well known risk factor for psychosis (Arseneault et al., 2004). After a complete description

of the study, all participants gave written informed consent. The study was approved by the Joint South London and Maudsley and the Institute of Psychiatry NHS Research Ethical Committee.

### 2.2. 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 (CAARMS) (Yung et al., 2003b). In addition, all participants completed the Structured Clinical Interview for DSM-IV (First et al., 1997). Family history of mental illness was assessed during the psychiatric interview for all participants based on self report. Four APS subjects (11%) had a family history of psychosis. 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 based on self report 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 additional FIGS carried out with a relative of theirs. Of the 36 APS subjects, none of them were taking antipsychotics at the time of EEG testing. None of the controls were on any psychotropic medication at the time of EEG testing.

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 Structured Clinical Interview for DSM Disorders (SCID) (First et al., 1997), performed by an experienced psychiatrist approximately 12 months after the point of transition, and the nine individuals in this sample who converted to psychosis during the 2 year follow-up period were diagnosed with Schizophreniform Disorder at the time of transition. Within the follow-up period, seven received a diagnosis of psychosis and two had bipolar disorder. The APS subjects received standard clinical management (psychosocial support, Cognitive Behavioural Therapy (CBT), monitoring only and antipsychotic medication) through OASIS, irrespective of participation in this study (Table 1). During the 2 year follow-up, 2 APS participants received antipsychotics (1 converter), 14 received a combination of antipsychotics and CBT (4 converters), 9 received CBT (2 converters), 1 received antidepressant, 4 received antidepressants combined with CBT, 2 declined an intervention, 1 was referred back to referrer with advice and 3 were monitored only (2 converters).

### 2.3. P50 data acquisition and analysis

P50 suppression was recorded with a conditioning–testing paradigm, as described in Shaikh et al. and Hall et al. (2006). Three blocks of 30 conditioning (C)–testing (T) click pairs were presented. The C and T clicks were of 1-millisecond duration and separated by 500 ms, with 10 s between consecutive conditioning stimuli. Acquisition time was –100 to 400 ms per trial. Participants were instructed to avoid blinks and eye movements during sound presentation and to rest their gaze on a fixed target.

Signal processing was performed using Neuroscan (4.3) software. A 1-Hz high-pass filter was applied to all channels and epoch baseline corrected to pre-stimulus interval. Automatic artefact detection was used to delete any sweeps with activity exceeding 35  $\mu\text{V}$  in the vertex (Cz) or the ocular channel 0–75 ms after stimulus. Accepted sweeps were averaged for C and T separately for each block of 30 trials. Ideally, participants would have an average C and T waveforms from each block. However, if the number of artefact-free sweeps/block was too small (less than 50% of trials), trials from consecutive blocks were combined. Average waveforms containing at least 15 trials were digitally filtered

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