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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 antipsychotics, 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.

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 μV 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

Table 1
Sample demographics and baseline clinical symptomatology.

		APS (n = 36)	Healthy controls (n = 60)	Statistics
Age (years)	Mean (+/−1 SD)	24.7 (5.0)	24.9 (4.8)	$t = 0.2$, $p = 0.86$
Sex	% females	33%	47%	$\chi^2 = 1.65$, $p = 0.20$
Nicotine use[a]	% smoker	59%	41%	$\chi^2 = 9.53$, $p = 0.002$
No. of cigarettes per day[a]	Mean (+/−1 SD)	6.5 (7.3)	1.6 (3.8)	$t = -3.5$, $p = 0.001$
P50 ratio	Mean (+/−1 SD)	65.62 (30.07)	50.11 (34.02)	$t(85) = -2.2$, $p = 0.03$
C–T difference	Mean (+/−1 SD)	1.96 (1.12)	3.61 (4.13)	$t(61) = 2.70$, $p = 0.009$
PANSS total score	Mean (+/−1 SD)	56.7 (11.8)		
PANSS positive	Mean (+/−1 SD)	205 (395.5)		
PANSS negative	Mean (+/−1 SD)	170.2 (369.5)		
PANSS general	Mean (+/−1 SD)	187.5 (361.9)		
Treatment during follow-up	Antipsychotics	2 (1 converter)		$\chi^2 = 6.24$, $p = .51$
	Antipsychotics and CBT	14 (4 converters)		
	Antidepressants	1		
	Antidepressants and CBT	4		
	CBT	9 (2 converters)		
	Declined intervention	2		
	Referred back with advice	1		
	Monitored only	3 (2 converters)		

[a] Data for nicotine use and number of cigarettes smoked per day is for a subset of the overall sample (APS n = 32, HC n = 51).

with a zero phase shift 10-Hz high-pass filter (24 dB/octave) and smoothed with a 7-point moving average applied twice.

The P50 ratio was evaluated at Cz. The averaged waveforms for C and T responses in each block were presented simultaneously on a computer monitor for visual inspection. For the C response, the most prominent peak 40–75 ms post-stimulus was selected as the P50 peak. Peak detection was done manually by a trained rater who was blind to group status and to any other clinical characteristic of the sample. The preceding negative trough was used to calculate P50 amplitude (Nagamoto et al., 1989). The trough could have a latency of less than 30 ms with a minimum of 20 ms. If there was no clear trough on Cz, we used at least one other site (Fz or Pz) to help identify the trough. For the T response, the positive peak closest in latency to the C peak was selected as P50 response. Testing wave amplitude was determined in the same way as for the conditioning response.

Blocks without identifiable P50 response or C amplitude less than 0.4 μV, with electro-oculographic activity 40–75 ms post-stimulus exceeding the P50 wave or with a large negative–positive P30 complex (>1.5 times bigger than the P50 wave) were identified by the rater and excluded from the grand average. Grand averages for the C and T responses were compiled separately, and P50 responses were determined as previously described. P50 suppression was quantified in two ways; 1) The P50 ratio was calculated as the ratio of T amplitude to C amplitude, expressed as percentage (T/C * 100), and 2) the difference between the click 1 amplitude and the click 2 amplitude (difference score resulting from click 1 minus click 2) (Smith et al., 1994; Clementz et al., 1997, 1998).

2.4. Statistical analysis

SPSS (Version 21.0, SPSS Inc. Chicago, USA) was used for all statistical analysis. Boxplots were used to examine departures from normality. Differences between groups on demographic and clinical variables were analysed using t-tests and Chi square test as appropriate (Table 1). Separate variance estimates were used when homogeneity of variance assumptions were not met. Between subjects (independent) t-test was used to compare P50 indices between healthy controls and APS subjects as well as converters and non-converters. The area under the receiver-operating characteristic (ROC) curve was used to assess the predictive capacity of P50 ratio and C–T difference scores to discriminate between APS and controls and converters and non-converters. The P50 ratio or C–T difference were not correlated with symptom severity scores measured by the PANSS (positive, negative, general subscales or total score).

3. Results

Mean P50 ratios and C–T differences are shown in Fig. 1. Fig. 2 illustrates that grand average waveform for the P50 ERP. The mean P50 ratio is lower ($t(85) = -2.2$, $p = 0.03$) and C–T difference higher ($t(61) = 2.70$, $p = 0.009$) in the controls, when compared to those with APS. To elucidate further whether P50 ratio or C–T difference could identify the risk of developing psychosis we compared individuals with APS who made a transition to psychosis to those who did not within the follow-up period. There were no statistically significant differences between the non-converters and converters on P50 indices (P50 ratio: $t(34) = -0.64$, $p = 0.53$; C–T difference: $t(31) = 0.04$, $p = 0.97$). However, as can be seen in Fig. 1, cases that made a conversion to psychosis display higher P50 ratios and the non-converters are intermediate between healthy controls and the conversion group. C–T difference also shows a similar pattern with mean C–T difference highest in the control group and the non-converters and converters performing similarly. This might be suggestive of a possible linear relationship between P50 ratio and conversion to psychosis; however this hypothesis needs to be confirmed in a much larger sample.

The area under the ROC curve for discriminating individuals with APS from controls using the P50 ratio was 0.65 ($p = 0.023$) and C–T difference 0.64 ($p = 0.036$). To discriminate between converters and non-converters the area under the ROC curve was 0.69 for both P50 ratio ($p = 0.11$) and C–T difference ($p = 0.11$). These results indicate that individuals with APS have a more abnormal P50 test result than 64–65% of the controls and converters have a more abnormal P50 test result than 69% of non-converters.

4. Discussion

Our study demonstrated deficits in P50 suppression indexed by higher P50 ratios and smaller C–T differences in the antipsychotic-free cases with APS compared to controls, indicating an association between this well established neurophysiological marker and early clinical symptomatology. However, P50 deficits were not found to be greater in the subgroup of APS participants who subsequently developed psychosis than in those who did not. In addition, ROC curve analysis indicated that P50 indexes have low accuracy in identifying individuals with APS and also conversion to psychosis. Nine individuals (25%) at the time of analysis in this relatively small sample developed psychosis, which is broadly consistent with published transition rates (Fusar-Poli et al., 2013). However, the analysis comparing only nine individuals who transitioned to psychosis to those who did not lacked statistical power as the required sample size to detect a difference in P50 ratio

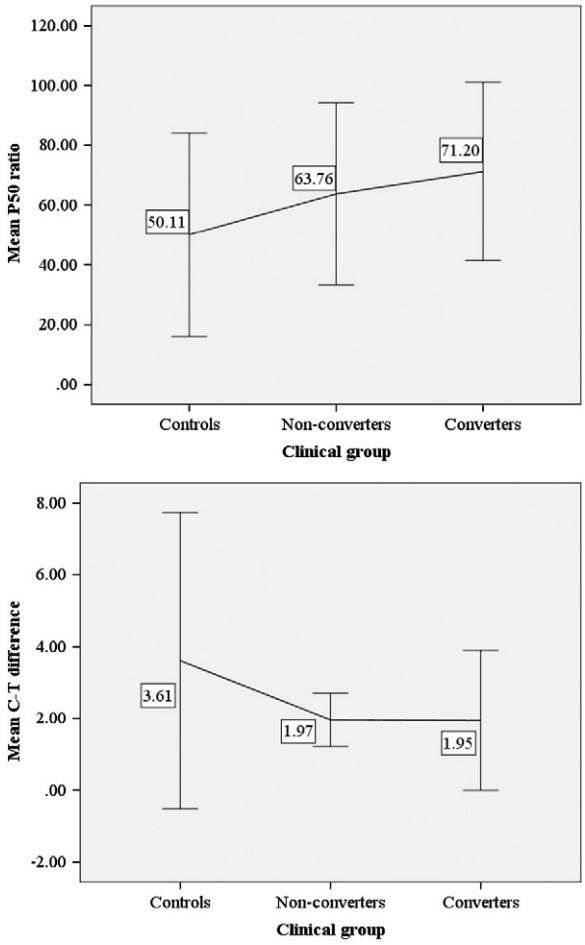

Fig. 1. Relationship between P50 indices and conversion to psychosis (mean & +/−1 SD).

between converters and non-converters with 80% power is at least 540 for small effect sizes (0.12) observed for P50 indexes. Therefore, these results should be taken as preliminary.

Our findings are in line with previous reports of diminished P50 suppression in the clinical high-risk sample (Myles-Worsley et al., 2004; Brockhaus-Dumke et al., 2008), first episode psychosis (Myles-Worsley et al., 2004; Brockhaus-Dumke et al., 2008) and in schizophrenia and psychotic bipolar disorder (Freedman et al., 1996; Olincy et al., 2000; Olincy and Martin, 2005; Schulze et al., 2007; Shaikh et al., 2010) and support the suggestion that P50 gating deficits are not specific to schizophrenia or bipolar disorder, but might be associated with psychosis in general.

A study by Brockhaus-Dumke et al. (2008) included a considerable number of subjects in different stages of schizophrenia and at-risk states including 18 at-risk subjects who did not develop a full psychosis within the follow-up period of two years, 21 truly prodromal subjects who developed frank psychosis within the follow-up period, 46 antipsychotic-naïve subjects with first-episode schizophrenia, 20 antipsychotic-free subjects with chronic schizophrenia, and 46 healthy control subjects to assess P50 suppression. They found differences between healthy controls and all patient groups with respect to P50 suppression. Our findings together with those of Brockhaus-Dumke et al. show that P50 deficits are present early in the disease even in individuals at clinical high risk who did not develop a full blown psychotic episode within the follow-up period of two years. These authors were also able to show that these deficits are most prominent in chronic stages. However, as found in the current study, APS participants with and without conversion to psychosis did not significantly differ on P50 impairment (Brockhaus-Dumke et al., 2008), thus future studies would need to clarify the role of illness progression and its impact on sensory gating disturbances and the predictive value of P50 deficits.

There are several limitations to this study. Casual or intermittent heavy use of a number of illicit substances and tobacco may have long-term effects on electrophysiological measures and thus be a potential confounding factor. 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 was not. Information on use of a number of illicit substances and tobacco use was collected by self-report and is available only for a subset of the sample therefore comprehensive analysis addressing the role of nicotine or substance use as a possible confounder was not feasible. Thus, future studies should investigate the role of current and lifetime substance use as a potential mediator and/or confounder of P50 deficits in the APS.

As for clinical outcomes after an average of two years follow-up, the rate of transition in our sample was lower than in some early studies of the APS (Klosterkotter et al., 2001; Miller et al., 2002; Yung et al., 2003a, 2004, 2007; Broome et al., 2005; Addington et al., 2007; Schultze-Lutter et al., 2010), but there is considerable variation across centres, reflecting different populations and ascertainment methods, and a rate of 25% is in line with that reported in recent work from European centres (Morrison et al., 2002; Ruhrmann et al., 2010; Simon and Umbricht, 2010; Ziermans et al., 2011). The average duration of the prodromal phase is 5 to 6 years (Hafner et al., 1998; Schultze-Lutter et al., 2010) and this takes account of the early and late prodrome definitions. Our study uses a 'late' definition of prodrome (Broome et al., 2005; Fusar-Poli et al., 2012); however, it remains a possibility that our observation period of two years may still be insufficient to determine the true final outcome of some non-converters.

The APS construct is a more heterogeneous concept than either schizophrenia or first episode psychosis and it is likely to include a mixture of true prodromal schizophrenia, affective psychosis and other psychotic disorders, individuals who are in psychotic spectrum but have a favourable outcome, and a majority of individuals who will never develop the illness. Therefore future studies should be large and long enough to follow sufficiently large numbers of patients who can be characterised into subgroups of psychotic disorders and outcome trajectories. It is likely that the reduction in the heterogeneity of the prediction endpoint will yield a greater possibility to identify specific predictors and biomarkers with clinically sufficient predictive power (Yung et al., 2004). In this regard, the recent development toward large, multi-centric studies is clearly beneficial to detect potential deficits and characterise the differences in neurophysiological function and developmental trajectory of psychosis leading to the development and testing of markers that are predictive of conversion and readily measureable during APS. Furthermore, a multivariate marker based on a weighted combination of electrophysiological features, provides greater diagnostic classification power than any single marker, therefore, future studies should adopt this approach.

As a result of heterogeneity in APS, it is expected that a lesser percentage of APS individuals would for example, have P50 deficits leading to small/modest effect sizes. Consequently, as in almost all current early detection studies, conclusions about the predictive validity are limited to the respective investigated period. Nevertheless, like other early anomalies predisposing to psychosis, any potential neurophysiological deficits are likely to be subtle and will require large samples for convincing replication and longitudinal designs to establish whether P50 can contribute to the prediction of conversion to psychosis.

Our findings support the hypothesis that the P50 ratio and C–T amplitude difference, which reflect disturbances in sensory registration and gating, are already present in people with APS and are potential risk indicators of psychosis liability (Brockhaus-Dumke et al., 2008; Hsieh et al., 2012). However, longitudinal assessments of P50 sensory gating in larger samples will be needed to establish to what extent early

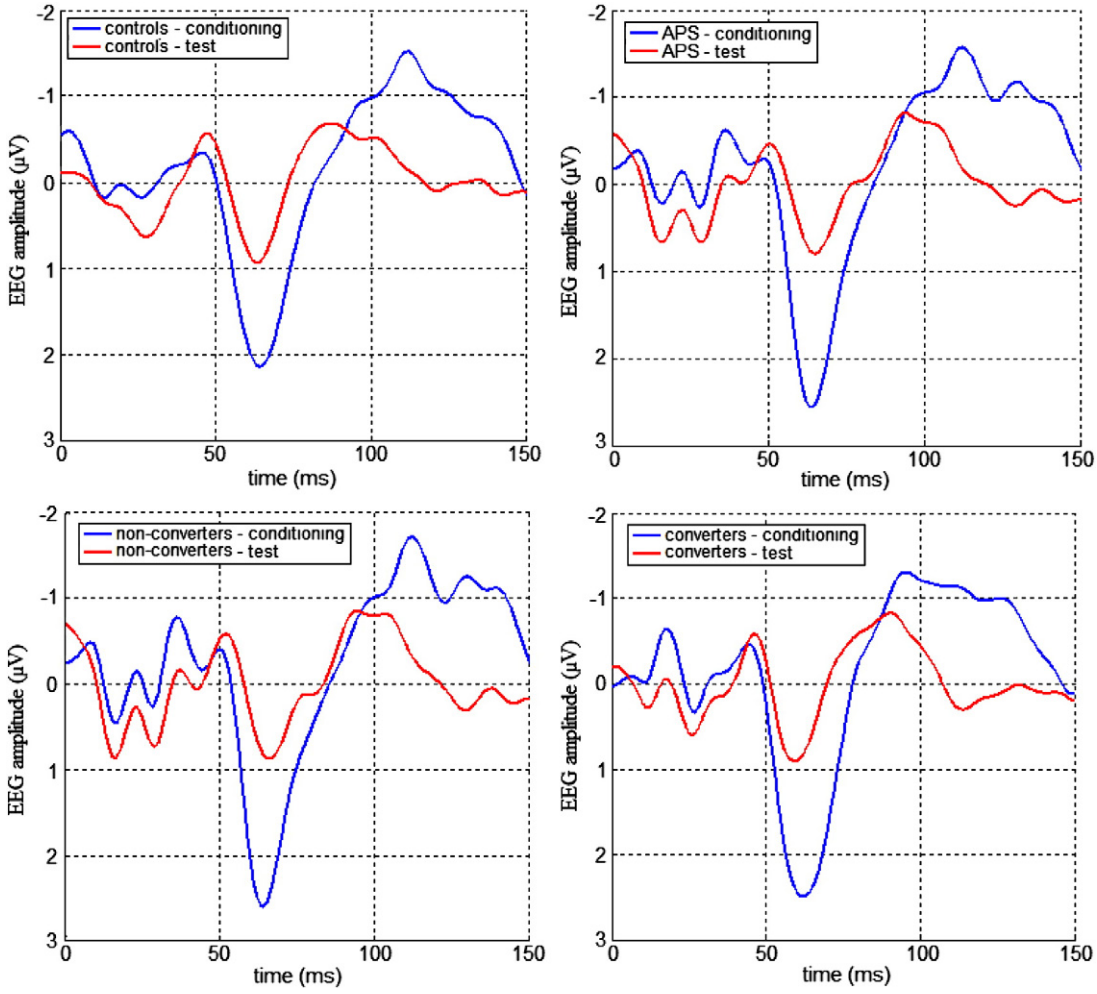

Fig. 2. Grand average waveforms for the P50 ERP at the CZ electrode.

impairment in this ERP increases risk for subsequent transition to psychosis; and cross sectional designs comparing healthy controls, APS, first episode and schizophrenia groups can help to understand whether P50 deficits fluctuate with clinical symptomatology and treatment in a way that could be useful in clinical practice.

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Contributors

Dr. Bramon designed the study, collected the data and from inception reviewed the manuscript, statistics and literature review. Dr. Shaikh conducted the EEG data processing and statistical analyses, interpreted the analysis, carried out the literature review and wrote the manuscript. Ms Amankwa and Drs. Dutt, Vozmediano, Diez, Ranlund, Hall and Caseiro contributed to EEG data processing. Prof. McGuire assisted in planning the study, and Drs. Valmaggia, Broome, Dutt, Lappin, Carletti, Walshe, Fusar-Poli, Howes, Ellett, Ranlund, Diez and Sir Prof. Murray either facilitated the recruitment of participants, data collection and/or reviewed the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no financial interests or potential conflicts of interest.

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