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P300 deficits are present in young first-episode patients with schizophrenia and not in their healthy young siblings

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ABSTRACT

Objective: To evaluated P300 (P3b) abnormalities in young first episode patients with schizophrenia and their healthy young siblings.
Methods: An auditory oddball paradigm was used to assess P300 in 53 patients, 27 unaffected siblings and 28 healthy controls. Amplitude and latency of the three midline sites (Fz, Cz, and Pz) were compared between patients, siblings, and controls by a mixed-effects regression model.
Results: P300 amplitude was significantly reduced in patients with schizophrenia but not in healthy siblings, when compared to healthy controls. P300 latency did not significantly differ between the three groups.
Conclusions: P300 amplitude but not latency was found to be affected in young patients with recent onset schizophrenia. However, P300 amplitude and latency were found not to be affected in healthy unaffected young siblings and, therefore, did not qualify as an endophenotype for schizophrenia.
Significance: The failure to find the P300 (P3b) abnormality in healthy siblings of patients with schizophrenia is an important finding and should be added to P300 literature.

1. Introduction

Deficits in the P300 event-related potential (ERP) have been reported in schizophrenia, including the early stages of the illness (Brown et al., 2002; Demiralp et al., 2002; Hirayasu et al., 1998; McCarley et al., 2002; Salisbury et al., 1998; Wang et al., 2003, 2005) and have been studied as promising candidate endophenotype of schizophrenia (Duncan et al., 1987; Mathalon et al., 2000; Saitoh et al., 1984; St. Clair et al., 1989; van der Stelt et al., 2005; Turetsky et al., 1998).That is: a genetically influenced biobehavioral characteristic that will enhance the likelihood of identifying schizophrenia susceptibility (Gottesman and Gould, 2003). If the presence of such a characteristic increases the risk to develop schizophrenia it could also be present in excess of general population levels in the biological relatives of individuals with schizophrenia.

Different studies on P300 in relatives of patients with schizophrenia have shown conflicting results. Some find clear differences (Frangou et al., 1997; Karoumi et al., 2000; Kidogami et al., 1992; Kimble et al., 2000; Roxborough et al., 1993; Schreiber et al., 1992; Turetsky et al., 2000; Weisbrod et al., 1999), and others do not (Blackwood et al., 1991; Friedman et al., 1988; Winterer et al., 2003).

Bramon et al. (2005) performed meta-analysis on P300 studies in relatives of patients with schizophrenia and found heterogeneity in outcome and a small to moderate effect size across the included studies.

In their own relative study Bramon et al. (2005) confirmed the existence of delayed latency in family members but not reduced amplitude. Even though they could not detect it in their own study Bramon et al. (2005) suggested that a bimodal distribution in the relatives of schizophrenia offspring may explain the heterogeneity in outcome. This was also reported by Blackwood et al. (1991) and Frangou et al. (1997) for P300 latency. The history of mental illness of the family members may also have been a confounder since some studies included healthy relatives as well as relatives with a history of mental illness (Bramon et al., 2005; Frangou et al., 1997; Winterer et al., 2003; Weisbrod et al., 1999; Kimble et al., 2000).

All patient and relative studies to date included relatively older relatives (mean age range is 31.38–61.8), except for Friedman and others (1988) and Schreiber and others (1992) who studied children of patients with schizophrenia, who were at high risk for developing schizophrenia (mean age was 15.1 and 12.1, respectively).

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An aging effect has been hypothesized for P300 (Frodl et al., 2002; Polich, 1996; Araki et al., 2006) as it has been for other evoked related potentials: first-episode patients appear to have normal MMNs (Salisbury et al., 2002; Umbricht and Krljes, 2005; Umbricht et al., 2006) and P50 ratios (de Wilde et al., 2007) in contrast to chronic patients with schizophrenia. These findings are suggested to reflect ongoing neuropathological changes.

Considering the findings from previous studies and the possible effect of age and the history of mental illness on P300 we examined group differences between young, predominantly first-episode, patients with schizophrenia, and thoroughly screened young physically and mentally healthy siblings and controls – closely matched for age – to investigate whether P300 amplitude and/or latency deficits are also present in a young group of patients and siblings.

2. Methods

2.1. Subjects

Subjects were 53 inpatients of which 44 patients had a first episode of schizophrenia (8 patients had 2 episodes and 1 had 3 episodes). All patients were admitted to the Adolescent Clinic of the Academic Medical Center of the University of Amsterdam. Two patients were medication naïve, 48 were treated with atypical (including 6 patients who were treated with Clozapine) and 5 treated with typical anti-psychotics (4 patients on Haloperidol and 1 patient on Pimozide). In addition, 27 unaffected siblings were recruited through written correspondence followed up by phone contact. Twenty families were represented by one sibling, 2 families by 2 siblings and one family by three siblings. They were screened and considered psychiatrically healthy if they met the same inclusion criteria as nonpsychiatric controls. In particular, they did not have a DSM-IV mood disorder, any psychotic symptom or a substance abuse diagnosis now or in the past. In addition, they were between the ages of 16–35, spoke Dutch fluently, had neither history of neurological disease, a systemic disease known to involve CNS functioning, clinically significant head injury, nor mental retardation.

The healthy control group consisted of medically and psychiatrically healthy participants who were recruited from the community via advertisement posters placed in the hospital and schools. Inclusion criteria for controls were identical as for relatives, except that potential controls were excluded if they had a first-degree biological relative who had ever received psychiatric treatment.

Psychiatric history relevant to these criteria for both relatives and controls was determined by the Mini International Neuropsychiatric Interview Plus (M.I.N.I. Plus) for DSM-IV (Sheehan et al., 1998).

All subjects had normal hearing.

Demographic data for patients, siblings and control subjects included in the final data analysis are summarized in Table 1.

After complete description of the study to the participants, written informed consent was obtained.

2.2. P300 procedure

The electrophysiological examination was performed at the Department of Clinical Neurophysiology of the AMC of the University in Amsterdam. Stimuli were 300 75-dB tones (absolute dB), with a 2-s inter-stimulus interval presented binaurally through earphones. Of the tones 80% were 'non-targets' of 1000 Hz and 20% 'targets' of 2000 Hz with a duration of 100 ms in a random sequence. Subjects were instructed to press a button in response to targets only. The stimuli were generated with an inter-stimulus interval of 1480 ms, i.e. a stimulation frequency of 0.67 Hz.

EEG was recorded with 21 surface Ag–AgCl disc electrodes applied with adhesive paste according to the international 10/20-system and referenced to linked mastoids. Additionally four electrodes were attached at the outer canthi of both eyes and above and below the left eye for the registration of eye movements and blinks. Electrode resistance was kept below 5 kΩ at all electrode sites. The EEG was recorded with a band-pass filter of 0.04–300 Hz, with a sampling rate of 1000 Hz. Digitized data for each subject were stored in a database for subsequent off line analysis using Brainvision Analyzer (Brainproducts; http//:www.brainproducts.com). After baseline correction, the signals were digitally filtered with a low-pass filter of 30 Hz and a high-pass filter of 0.10 Hz (24 dB/oct) and were epoched at 50 ms pre-stimulus and 450 ms post-stimulus. The maximum allowed absolute difference between two values in one segment was 200 μV and the maximum allowed voltage step was 50 μV. Segments in which these values were exceeded were removed. Epochs were averaged separately for non-target and target tones. The P300 was defined as a positive waveform generated by the target tones and peaking between 250 and 450 ms post-stimulus. Both its peak amplitude as well as its peak latency were calculated using a computer algorithm. The P300 can be divided into a frontocentral P3a and a parietocentral P3b. The P3a has been regarded as an index of the novelty of information and may be the neurophysiological correlate of the orienting response, whereas the P3b is elicited by expected (but rare) task-relevant stimuli. P300s elicited in a standard oddball target detection task are likely to reflect both P3a and P3b subcomponents, with frontocentral and parietal distributions, respectively (Turetsky et al., 1998).We report on both the frontocentral as the parietocentral electrodes but only used an expected odd-ball task, therefore when in this article the P300 naming is used this only reverse to the P3b component.

2.3. Statistical analysis

Peak amplitude (measured with respect to the baseline) and peak latency of the three midline sites (Fz, Cz, and Pz) were compared between patients, sibs, and unrelated controls by a mixed-effects regression model. We used this model to account for the family-relationship between the patient and his/her siblings. In order to do this we used family-number as a random-effect in the mixed-effects model. The fixed-effect in the model was the group-indicator (patient/sib/unrelated control). With this model we estimated the average differences between the groups of patients, groups of sibs, and groups of unrelated controls, but also the within- and between family-variances of the P300 parameters. The ratio of the between-family variance over the sum of the within- and between-family variances is called the intraclass correlation (icc), which we used as a measure of similarity between the patients and their siblings. This might be due to the effect of shared environmental and genetic influences on the P300 parameters.

Cohen's δ effect-size was also reported. Correlation coefficients (Pearson's r) were calculated between P300 and medication dosage (cpz equivalents) and WAIS-III IQ-scores.

3. Results

The mean of usable trials was 58.49 (patients: mean = 58.42, SD = 2.48, range 51–60; siblings: mean = 58.11, SD = 3.19, range = 48–60; controls: mean = 59, SD = 1.33, range = 55–60).