Neurophysiological and neuropsychological assessment of recent-onset schizophrenia
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Clinical and neuropsychological correlates of the P300 in schizophrenia

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Abstract

We investigated the relationship between the P300, neuropsychological test performance and symptomatology in recent-onset schizophrenic patients (n = 45) to gain insight into underlying mechanisms of abnormal P300 in schizophrenia. The P300 was recorded in two sessions with an intermission of five minutes, at the midline frontal, central and parietal electrode site. P300 amplitude and latency were compared with those obtained in 25 controls. Twenty patients were treated with olanzapine and 19 patients with risperidone. P300 amplitude was smaller and latency longer in patients than in controls. In the patient group, parietal P300 amplitude reduction was related to poorer performance on neuropsychological tests of memory. Frontal P300 amplitude reduction was related to impaired selective attention. In patients with negative symptomatology, P300 amplitude was reduced in the second P300 session compared with the first session. Patients on risperidone demonstrated a smaller parietal P300 amplitude than patients using olanzapine. Reduced parietal P300 amplitude could signify a dysfunction in the continuous memory updating of current events. Negative symptomatology may be associated with a time dependent decrease in neuronal firing, as indicated by reduced P300 amplitude in the second P300 session.
Introduction

Event-related potentials (ERPs) are studied in schizophrenia to gain insight into information processing abnormalities that may constitute the core deficit of this disease (Braff, 1993). Amplitude reduction of the P300 component of the ERP is the most replicable biological marker of schizophrenia (Ford, 1999; Hirayasu et al., 1998). The P300 has been associated with a number of cognitive processes, including orientation, attention, stimulus evaluation and memory (Knight and Scabini, 1998). Despite the large volume of work on the P300, however, it has been difficult to elaborate its specific functional role, or to characterize the underlying neural machinery (Pineda et al., 1993).

Cognitive abnormalities reported in schizophrenia include dysfunctions in memory, attention, learning, goal directed problem solving and motor speed (Grant and Adams, 1996). There are few data available on whether attention, memory or other cognitive functions assessed with a comprehensive neuropsychological test battery, are related to P300 amplitude and latency in recent-onset schizophrenia. Investigating this relationship may be helpful for gaining insight in underlying mechanisms of abnormal P300 in young schizophrenic patients.

P300 amplitude reduction has been reported to be related to an increase in severity of disorganization symptoms (Higashima et al., 1998), positive symptoms (Egan et al., 1994) and negative symptoms (Strik et al., 1993) as well. These previous studies included patients with various ages and medications. The subject group in the present study consists of only young recent-onset schizophrenic patients using mainly atypical antipsychotic medication. The homogeneity of our subject group may help in the clarification of the relation between the P300 and symptomatology in recent-onset schizophrenia.

The P300 has usually been recorded in one session. Recording the P300 in two sessions (with an intermission of five minutes) may give insight into time dependent changes in P300 amplitude and latency. Negative symptoms have been found to relate to a time dependent decrease in performance on neuropsychological tests (Everett et al., 1989). We investigated if negative symptomatology is also related to a time dependent reduction in P300 amplitude.

The effect of antipsychotic medication on the P300 is still unclear. In our study, 39 patients were treated with either olanzapine or risperidone. Since olanzapine has a
different receptor binding profile than risperidone, differential effects of olanzapine and risperidone may give insight into the effect of blocking certain receptors on the P300 in schizophrenia.

The first aim of the present study was to elucidate pathophysiological mechanisms involved in abnormal P300 in early schizophrenia by investigating a possible relationship between P300 and neuropsychological test results and clinical features in a group of young patients with recent-onset schizophrenia. The second aim was to compare the effects of olanzapine and risperidone on the P300 in young schizophrenic patients.

Methods

Subjects
Forty-five schizophrenic patients were assessed with the P300 (six women), mean age was 21 years ± 2.9, SD. All patients attended the adolescent psychiatric clinic of the Academic Medical Center, Amsterdam, The Netherlands for inpatient and outpatient treatments and all satisfied the criteria in the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1994) for the diagnosis of schizophrenia. The diagnosis at admission was made in a clinical consensus meeting of three experienced psychiatrists, a research psychologist and two residents with the use of all possible information, such as medical records, interviews with patients and parents. Clinical diagnosis was confirmed in all included patients at discharge and follow up. Exclusion criteria were mental retardation, epilepsy, endocrine disease, diagnosis of a primary alcohol- or drug related psychosis, hearing disorders and known neuropsychological impairment due to factors other than schizophrenia (e.g., closed head injury). Mean number of previous psychotic episodes was 0.2 ± 0.5. Mean illness duration, including the prodromal phase was 19.3 ± 15.1 months.

All 45 patients were assessed at intake and at the time of ERP recording with the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987) for the evaluation of symptoms in schizophrenia. The scale is composed of 30 items, each of which is given a score of one through seven according to defined criteria. The negative symptom dimension was composed of the PANSS items for blunted affect, emotional withdrawal, passive/apathetic withdrawal, lack of spontaneity and stereotyped thinking. The
disorganization symptom dimension comprised conceptual disorganization, difficulty in abstract thinking and disorientation. The positive symptom dimension was composed of delusions, grandiosity, suspiciousness and unusual thought content. Forty-one of these 45 patients were assessed with a neuropsychological test battery (four patients refused).

The patients were semi-randomized for medication; if patients were admitted with olanzapine or risperidone and responded well, then medication was continued. Otherwise, patients were randomly allocated to olanzapine or risperidone. Twenty patients were treated with olanzapine (mean dosage 15.5 ± 6.9 mg) and 19 patients with risperidone (mean dosage 4.7 ± 1.9 mg). Of the remaining six patients, one patient was receiving pimozide, one sertindole and one flufenazine, whereas three patients were non-compliant with taking their prescribed medication at the time of testing. Three patients given olanzapine and two given risperidone used an antidepressant (paroxetine) and one patient given olanzapine and two patients given risperidone used antiparkinsonian medication. All 39 patients who received either olanzapine or risperidone were assessed with the neuropsychological test battery.

Twenty-five healthy controls (six women) with a mean age of 22.5 ± 4.2 years with no psychiatric history, served as control group for the P300. They were matched as a group on age and estimated intelligence. Sample characteristics of the patient and control group are summarized in Table 5.1.

<table>
<thead>
<tr>
<th>Table 5.1: Sample characteristics</th>
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<tr>
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<tr>
<td>Schizophrenic patients (n=45)</td>
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<tr>
<td>Patients medication study (n=39)</td>
</tr>
<tr>
<td>Control subjects (n=25)</td>
</tr>
<tr>
<td>Age 21 (2.9)</td>
</tr>
<tr>
<td>Gender m/f 39/6</td>
</tr>
<tr>
<td>Olanzapine 20</td>
</tr>
<tr>
<td>Risperidone 19</td>
</tr>
<tr>
<td>Other antipsychotics 3</td>
</tr>
<tr>
<td>No antipsychotics 3</td>
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</table>

The study was approved by the research and ethics committee of the Academic Medical Center and all patients and controls gave written informed consent after the procedures had been fully explained.
Event-related potential recording

In two sessions, separated by an intermission of 5 minutes, target stimuli with a frequency of 2000 Hz and standard, nontarget stimuli with a frequency of 1000 Hz were presented binaurally through headphones at an intensity of 75 dB above hearing threshold. In the first session, lasting about 15 minutes, 60 targets were presented randomly amidst 465 nontargets. In the second session, that lasted about 10 minutes, 60 targets amidst 341 nontargets were presented. The subjects were instructed to count the targets and respond to them with a button press. The total number of counted targets was asked at the end of each session. To familiarize the subjects with the task, three practice trials were presented. The stimuli were generated with a stimulation frequency of 0.67/sec.

Ag-AgCl disc electrodes were attached to the midline frontal (Fz), central (Cz) and parietal (Pz) sites according to the international 10-20 system with a reference electrode on linked ears and a ground electrode on the forehead. The electro-oculogram (EOG) was recorded from an electrode located laterally at the supraorbital ridge of the right eye referenced to an electrode located laterally below the left eye. Trials with eye movement artifacts were excluded from analysis. The inter-electrode impedances were always less than 5 kΩ in each subject investigated. The subjects were seated in a comfortable chair with eyes open.

The EEG was recorded with a band-pass filter of 0.03-160 Hz (-3 dB). Analysis time was 750 ms, including a 75 ms prestimulus baseline interval and sampling rate was 700 Hz. Epochs that contained voltage exceeding 50 μV were rejected. The P300 component was identified as the most positive peak in the averaged response to the target stimuli between 250 and 500 msec. Sixty trials were entered into the P300 measures. The P300 was recorded in patients when they had been on the same medication for six weeks, when they were no longer in an acute, psychotic phase of the disease.

Neuropsychological test battery

A neuropsychological test battery was administered that included tests to assess psychomotor speed and attention: Finger Tapping, Continuous Performance Test, Trail Making, Stroop (Lezak, 1995). Intelligence: four subtests of the Wechsler Adult Intelligence Scale (Lezak, 1995). Working memory: Subjective Ordering Task (Hijman et al., 1998; Nieman et al., 2000). Verbal and spatial memory: Verbal Fluency, the
Dutch version of the California Verbal Learning Test, Complex Figure of Rey (Lezak, 1995).

In most patients, the neuropsychological test sessions were divided over two days and in a few patients over three days. Patients were tested within two weeks after P300 recording.

Data-analysis
The P300 amplitude and latency means of the patient and control group were compared by two-tailed t-tests after separate multivariate analyses of variance (MANOVAs) for P300 amplitude and latency, including interindividual variability of the group and intra-individual variability in electrode site. Correlations between the first session of the P300 and the neuropsychological test battery were examined with Pearson correlation coefficients. Using a Bonferroni correction, only two-tailed p-values below 0.03 were considered significant for correlation coefficients. Mean P300 amplitude and latency in the risperidone and olanzapine group were compared with two-tailed independent samples t-tests. Patients were categorized in two negative symptom categories, divided by the mean of the score on the negative symptom dimension at the time of testing of the whole patient group. Mean P300 amplitude and latency in the group with above and below mean negative symptomatology in the first and second P300 session were compared with two-tailed paired samples t-tests. The data were analyzed with a statistical computer program (SPSS 9.0 for Windows, Chicago, IL).

Results
Multivariate analysis of variance indicated differences between both groups for P300 amplitude (F=3.77, p<0.02) and P300 latency (F=4.54, p<0.006). P300 amplitude was significantly reduced at the parietal (t=-3.36, p<0.001) and central (t=-2.57, p<0.01) electrode sites in the schizophrenic group compared to the control group (Fig. 5.1A). P300 latency was prolonged in the patients compared to the controls at all electrode sites (parietal t=2.19, p<0.03; central t=2.99, p<0.004; frontal t=3.56 p<0.001).

There were no significant correlations between P300 latency and amplitude with estimated intelligence. In the patient group, reduced performance on the California
Fig. 5.1A: Grand average ERPs in the control group (n = 25; black line) and the patient group (n = 45; grey line) in response to the relevant, high tones. The arrow indicates stimulus presentation.

Fig 5.1B: Grand average ERPs in the control and patient group in response to the low, irrelevant tones.
Verbal Learning Test, assessing verbal learning and memory, was related to reduced amplitude at the central and parietal electrode site and not at the frontal site (Table 5.2).

Table 5.2: Pearson correlation coefficients of P300 amplitude with neuropsychological tests

<table>
<thead>
<tr>
<th>Site</th>
<th>Amplitude</th>
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<tbody>
<tr>
<td>CVLT</td>
<td>Pz</td>
<td>Cz</td>
<td>Fz</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>r = 0.41*</td>
<td>r = 0.34 #</td>
<td>ns</td>
</tr>
<tr>
<td>Stroop</td>
<td>ns</td>
<td>r = 0.40*</td>
<td>ns</td>
</tr>
<tr>
<td>CFR ola. group (n = 20)</td>
<td>r = 0.56*</td>
<td>ns</td>
<td>ns</td>
</tr>
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*p < 0.01; # p < 0.03
CVLT = California Verbal Learning Test. CFR = Complex Figure of Rey. ola. group = patient group receiving olanzapine.

Poorer performance on Verbal Fluency, assessing memory retrieval, was also related to reduced central and parietal amplitude. Poorer Stroop performance (selective attention) was related to amplitude reduction at the frontal electrode site. In the olanzapine patient group, reduced performance in the memory session of the Complex Figure of Rey was related to P300 parietal amplitude reduction.

In the category of patients with above mean negative symptoms, P300 amplitude was significantly smaller in the second P300 session compared with the first session at all electrodes (parietal t=3.47, p<0.002; central t=4.45, p<0.001; frontal t=3.01, p<0.007), whereas this was not the case in the group with below mean negative symptoms (Fig. 5.2) nor in the group with positive and disorganization symptoms.

Increased severity of disorganization symptoms at the time of intake was related to P300 amplitude reduction at the central (r=-0.41, p<0.006) and parietal (r=-0.44, p<0.003) electrode site. The total score of the PANSS items of the disorganization symptom dimension at intake correlated with the total score of these PANSS items at the time of testing (r=0.57, p<0.001). Thus, the patients with disorganization symptoms at intake had disorganization symptoms at the time of testing but the severity of disorganization symptoms was reduced. Negative and positive symptoms at the time of intake were not related to P300 amplitude.
Fig. 5.2: Mean P300 amplitude and standard error in the group with below mean (A) and above mean (B) negative symptomatology. The filled circles represent P300 amplitude in the first P300 session, the open squares represent the P300 amplitude in the second P300 session. In the second session, P300 amplitude was significantly reduced compared to the first session in the group with above mean negative symptoms at all electrode sites whereas this was not the case in patients with below mean negative symptoms.

Figure 5.3: Grand average ERPs in the patient group with olanzapine (n = 20; black line) and risperidone (n = 19; grey line).
Mean P300 amplitude in the risperidone group was significantly smaller than in the olanzapine group at the parietal electrode site ($t=2.88, p<0.007$). The PANSS total score at the time of P300 recording was not significantly different between the olanzapine and risperidone group. No significant differences in latency were present (Fig. 5.3). The PANSS total score at the time of P300 recording was not significantly different between the olanzapine and risperidone group. No significant differences in latency were present.

**Discussion**

The present study showed a relationship in the patient group of P300 amplitude reduction at the midline parietal and central electrode sites with a poorer performance on neuropsychological tests of memory and learning. P300 amplitude reduction at the frontal electrode site was related to reduced Stroop performance, reflecting disturbed selective attention. Furthermore, amplitude reduction at all three electrode sites in the second P300 session related to increased negative symptomatology at the time of testing. Increased disorganization symptomatology at intake was related to reduced P300 amplitude at the midline central and parietal electrode site. Finally, risperidone was associated with a smaller P300 amplitude than olanzapine only at the parietal electrode site.

The P300 is composed of two components. The first component is mainly recorded at the frontal electrode site and normally has an earlier peak latency than the second component that is recorded at the parietal electrode site (Frodl-Bauch et al., 1999; Squires et al., 1975; Knight, 1997). Our data support the hypothesis that the frontal P300 component is associated with the initial orienting and selective attention to an important stimulus in the environment (Knight and Scabini, 1998; Polich, 1998). The posterior P300 component may signify the subsequent memory updating of the event. The temporal lobe plays an important role in memory processes (Lezak, 1995). Heidrich and Strik (1997) found a significant correlation between right-sided lateralization of the P300 maximal positivity and neuropsychological evidence for left-hemispheric temporal-hippocampal dysfunction. Furthermore, McCarley et al. (1997) reported that reduced left-hemispheric P300 amplitude related to left temporal lobe dysfunction.
In our young group of patients, the severity of negative symptoms assessed at the time of P300 recording was related to a rapid decline in P300 amplitude over two P300 sessions at all electrode sites. Increased severity of disorganization symptoms at intake was related to reduced posterior P300 amplitude recorded about six weeks after assessment of symptoms. The P300 has been described as both a state and a trait marker (Blackwood, 2000; Mathalon et al., 2000). Our results suggest that both negative and disorganization symptoms affect P300 amplitude. Disorganization symptoms may affect posterior P300 amplitude in a more stable manner. Reduced P300 amplitude has often been found to relate to disorganized thought (Higashima et al., 1998; Juckel et al., 1996; Iwanami et al., 2000). Disorganized thought has been described as a trait marker because of its persistent and stable nature (Marengo and Harrow, 1997) and its presence in subjects with a high risk for schizophrenia (Parnas and Schulinger, 1986). Iwanami et al (2000) hypothesized that the relationship between reduced P300 amplitude and disorganized thought suggests a genetic impairment of information processing in schizophrenia. Laurent and Barilux (1992) reported that schizophrenic patients with thought disorder showed a worsening of ERP abnormalities in the clinical course.

The reduction of P300 amplitude in the second session compared to the first session in patients with negative symptoms may be caused by a time dependent increase in the threshold for neuronal firing. This increase in threshold may reduce the amount of firing neurons, resulting in a reduced P300 amplitude and may reflect the clinical symptom of inhibited responsiveness to external stimuli.

The increased target probability in the second P300 session may have contributed to the amplitude reduction in the second P300 session compared to the first session (Ford, 1999). However, if increased target probability was the main cause of the amplitude reduction in the second session, then the amplitude reduction would have been similar for all patients. In the patient groups with few negative symptoms or other symptomatology, the amplitude reduction was small and not significant. In contrast, in the patient group with increased negative symptomatology the amplitude reduction was significant.

Amplitude of the P300 was reduced in the risperidone group compared to the olanzapine group at the parietal electrode site. Symptomatology assessed with the PANSS was not significantly different between both groups. Compared to the control group, the risperidone group had more reduced P300 amplitudes than the olanzapine group. One of the differences in the receptor binding profile of olanzapine and
Risperidone is the affinity of risperidone for the alpha\textsubscript{2} adrenergic receptor, olanzapine has no affinity for this receptor. In a P300 study performed by Pineda and Westerfield (1993) in primates, P300 amplitude was reduced at the parietal, but not at other electrode sites, after application of an alpha\textsubscript{2} antagonist in primates. Furthermore, alpha\textsubscript{2} adrenergic hyperactivity has been related to enhanced parietal P300 amplitude (Swick et al., 1994). Our data support the notion that the alpha\textsubscript{2} receptor plays a role in the determination of parietal P300 amplitude.

In conclusion, memory appears to be the main cognitive function associated with parietal P300 amplitude whereas selective attention may be related to frontal P300 amplitude in schizophrenic patients. Frontal P300 amplitude may signify the initial orienting and attention directing process whereas parietal P300 amplitude may signify the subsequent updating of memory of the current situation. These memories, that are neither short-term (seconds) nor long-term (years) but 'mediate-term' (minutes), are necessary for the correct interpretation and understanding of the current situation. When the continuous stream of memory updating is deficient, experiences may become fragmented. Furthermore, negative symptoms may be associated with a time dependent decrease in neuronal firing, reflected by reduced P300 amplitude in the second P300 session. Finally, alpha\textsubscript{2} adrenergic receptor blockade in risperidone may have an adverse effect on parietal P300 amplitude in schizophrenia.

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References


