**BRAIN ERPS IN SCHIZOPHRENIA DURING TONAL AND PHONETIC ODDBALL TASKS: RELATIONS TO DIAGNOSTIC SUBTYPE, SYMPTOM FEATURES AND VERBAL MEMORY**

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**Running title**: Brain ERPs in schizophrenia

**Key Words**: Event-related potentials (ERPs); Schizophrenia; Paranoid Subtype; Symptoms; Verbal Memory

**Abstract**

**Background**: This study compares event-related potentials (ERPs) for paranoid \( n = 13 \) versus matched undifferentiated patients and unmedicated patients \( n = 14 \) versus matched healthy adults. **Methods**: ERPs of right-handed patients and controls were recorded from 30 electrodes during oddball tasks using consonant-vowel syllables or complex tones. Patients were also assessed using the Positive and Negative Syndrome Scale, the Thought Disorder Index, and the Wechsler Memory Scale. **Results**: Paranoid did not differ from undifferentiated patients in N1 or P3 amplitude, but showed larger N2 at frontocentral sites to phonetic stimuli, as well as larger N2 over left than right hemisphere. Unmedicated patients showed reduced N2, but not N1 or P3, compared to controls. **Conclusions**: The N2 findings are consistent with neuropsychological evidence of greater verbal abilities and left hemisphere dominance in paranoid than nonparanoid schizophrenia. The findings also confirm the relationship of P3 to total BPRS, negative symptoms and verbal associative memory.

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Introduction

A recent study measured event-related potentials (ERPs) from 66 schizophrenic patients during oddball tasks (Kayser et al 2001). The present report takes advantage of this large sample of well characterized patients to examine the relation of ERPs in schizophrenia to clinical subtype, symptom severity, verbal memory, and medication status.

The paranoid subtype of schizophrenia is characterized by delusions or hallucinations and absence of flat affect and disorganized speech or behavior, and shows little cognitive impairment (American Psychiatric Association 1994). Seltzer et al (1997) found paranoid patients had better verbal skills, memory for spoken sentences, and problem solving abilities compared to undifferentiated patients. Paranoid patients might therefore show less reductions of cognitive ERPs, particularly in tasks involving verbal processing. Although two studies did not find differences between paranoid and nonparanoid subtypes in the P3 potential, they relied on an oddball paradigm with tones (Boutros et al 1997; St. Clair et al 1989). The use of both phonetic and tonal tasks enabled us to test the following predictions: (1) paranoid patients will have larger cognitive ERPs than undifferentiated patients, particularly in the phonetic task; (2) paranoid will differ from undifferentiated patients in showing greater N2 over left than right temporoparietal sites in the phonetic task.

We also tested specific predictions concerning the relationship between ERP amplitudes in schizophrenia, clinical severity, and memory function. Based on prior findings, it was predicted that symptom severity will negatively correlate with P3 amplitude (Ford et al 1999; Mathalon et al 2000; Turetsky et al 1998). Greater severity of negative symptoms, and to a lesser extent positive symptoms, will be associated with smaller P3 amplitude (Ford et al 1999). Also, greater Thinking Disturbance on the Brief Psychiatric Rating Scale (BPRS) will correlate with smaller N1 amplitude (Ford et al 1999), and greater thought disorder as measured by the Thought Disorder Index (TDI; Johnston & Holzman 1979) and poorer verbal associative memory will correlate with smaller P3 amplitude (McCarley et al 1993; Nagasawa et al 1999).

Methods

Participants and Assessments

A description of the total sample of 66 patients and diagnostic procedures are given in Kayser et al (2001). Symptom ratings of 60 of these patients were obtained using the Positive and Negative Syndrome Scale (PANSS; Kay et al 1992). BPRS items for computing Total and Thinking Disturbance scores (conceptual disorganization, unusual thought content, hallucinations) were derived from the respective PANSS items. Ratings of formal thought disorder were obtained for 42 patients using the TDI, which was administered and scored by trained raters using the procedures described elsewhere (Johnston & Holzman 1979; Shenton et al 1989; Solovay et al 1986).

We used the data for all 13 patients who met DSM-IV criteria (American Psychiatric Association 1994) for paranoid schizophrenia and selected 13 of 27 undifferentiated patients from the total sample who matched these patients in gender, age, education and response hand (Table 1). Four paranoid and 4 undifferentiated patients were unmedicated when tested and are also included when comparing unmedicated patients and healthy adults. Six paranoid patients were taking an atypical and 3 a typical
An analysis was also performed to compare ERPs of 20 patients who had a schizoaffective disorder and 20 schizophrenic patients who were matched in gender, age, education and total BPRS scores. Four schizoaffective patients and 3 schizophrenic patients were unmedicated and the remaining patients in these groups were receiving comparable typical or atypical neuroleptics. ANOVA of the factor scores corresponding to N1, N2, P300 and P420 indicated that there was no significant difference between the schizoaffective and schizophrenic groups in amplitude of these components.

Table 1. Means (and Standard Deviations) for Demographic and Clinical Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Paranoid Patients</th>
<th>Undifferentiated Patients</th>
<th>Unmedicated Patients</th>
<th>Healthy Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 13, 10 male)</td>
<td>(n = 13, 10 male)</td>
<td>(n = 14, 8 male)</td>
<td>(n = 14, 8 male)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>31.0</td>
<td>32.5</td>
<td>32.4</td>
<td>32.9</td>
</tr>
<tr>
<td></td>
<td>8.3</td>
<td>8.4</td>
<td>9.3</td>
<td>9.4</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.5</td>
<td>13.2</td>
<td>13.4</td>
<td>14.6</td>
</tr>
<tr>
<td></td>
<td>4.2</td>
<td>2.6</td>
<td>4.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Onset age (years)</td>
<td>22.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>23.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>23.4</td>
</tr>
<tr>
<td></td>
<td>5.5</td>
<td>5.3</td>
<td>4.0</td>
<td>8.5</td>
</tr>
<tr>
<td>Illness duration (years)</td>
<td>9.8</td>
<td>12.6</td>
<td>11.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.1</td>
</tr>
<tr>
<td></td>
<td>7.2</td>
<td>9.8</td>
<td>7.2</td>
<td>10.1</td>
</tr>
<tr>
<td>Total BPRS</td>
<td>31.8</td>
<td>37.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>29.9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>5.4</td>
<td>10.4</td>
<td>7.2</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> n = 11.
<sup>b</sup> n = 12.
<sup>c</sup> n = 13.

The ERP data for 14 unmedicated patients were compared to those for 14 healthy adults who matched these patients in gender, age, education, and response hand (Table 1). Four of the unmedicated patients had a diagnosis of paranoid schizophrenia, 6 undifferentiated schizophrenia, 2 schizoaffective-depressed and 2 schizoaffective-bipolar. These patients did not receive neuroleptic medication for about 2 weeks prior to testing (M = 15.8 days, SD = 8.7).

Wechsler Memory Scale

The Wechsler Memory Scale–Revised (Wechsler 1987) was administered to 47 of the patients. Three subtests were utilized: (1) logical memory provides a measure of immediate verbal memory; (2) verbal paired associates assesses learning to associate eight word pairs; (3) visual reproduction measures immediate recall of designs.

ERP Recording and Analyses

Details of ERP recording and analyses are given elsewhere (Kayser et al 2001). Briefly, participants listened to a series of tones or syllables in six 50 trial blocks (60 targets, 240 nontargets), in which only two different tones or syllables (infrequent targets and frequent standards) were presented in a block. They were instructed to press a button as quickly as possible after infrequent, target stimuli. Response hand was counterbalanced across participants.

<sup>1</sup> An analysis was also performed to compare ERPs of 20 patients who had a schizoaffective disorder and 20 schizophrenic patients who were matched in gender, age, education and total BPRS scores. Four schizoaffective patients and 3 schizophrenic patients were unmedicated and the remaining patients in these groups were receiving comparable typical or atypical neuroleptics. ANOVA of the factor scores corresponding to N1, N2, P300 and P420 indicated that there was no significant difference between the schizoaffective and schizophrenic groups in amplitude of these components.
Averaged ERP waveforms for the total sample of 98 participants (66 patients and 32 controls) in our study were submitted to a principal components analysis (PCA). The PCA factor loadings for the five components used in this study (N100, N200, P300, P420 and S870) are shown in Figures 1 and 2 for correspondence to the ERP waveforms (see Kayser et al 2001 for additional details).²

Statistical Analyses

PCA factor scores for target stimuli were submitted to repeated measures ANOVA with group (paranoid/undifferentiated or unmedicated patients/controls) and response hand (left/right) as between-subjects factors, and task (phonetic/tonal), electrode site and hemisphere as within-subjects factors. In accordance with Kayser et al (2001), repeated measures ANOVA were conducted for a subset of recording sites at which PCA factor scores were largest and most representative of the associated ERP component (see Table 2). Greenhouse-Geisser epsilon (ε) correction was used to compensate for violations of sphericity when appropriate. The sources of interactions were systematically examined through simple effects (BMDP-4V; Dixon 1992). Significant group differences in topography were confirmed after scaling the amplitudes for each task across hemisphere and site (McCarthy & Wood 1985; Ruchkin et al 1999).

Pearson correlations were computed to examine relationships between ERPs, clinical ratings, and Wechsler Memory Scale scores. Significant correlations were validated using nonparametric Spearman rank-order correlations. Correlations were performed separately for each task at the most robust recording sites for each ERP component and task (see Table 3).

Results

Paranoid Versus Undifferentiated Subtypes

There was no difference in performance between paranoid and undifferentiated patients in either task. An ANOVA of the N100 factor scores also showed no difference between groups (Table 2). There was a task-dependent difference in N2 amplitude between groups at the frontocentral sites (Figure 1), which was reflected in a Group × Task × Site interaction. Analyses of simple effects revealed significant Group × Task interactions at sites FC5/6 ($F[1,22] = 5.44, p < .05$) and C3/4 ($F[1,22] = 4.47, p < .05$), but not at other sites. Paranoid patients showed greater N2 when compared to undifferentiated patients at frontocentral sites in the phonetic task (FC5/6; $F[1,22] = 7.59, p = .01$; C3/4; $F[1,22] = 5.46, p < .05$), but not in the tonal task. Moreover, paranoid patients had greater N2 over left than right hemisphere at lateral temporoparietal sites (i.e., at T7/8, CP5/6, P7/8, and P9/10, all $F[1,22] > 4.50, all p < .05$) in the phonetic task, but not in the tonal task. In contrast, undifferentiated patients did not show a significant hemispheric asymmetry of N2 in either task. Although paranoid patients tended to have a larger late positive peak than undifferentiated patients in the tonal task (Figure 1), there was no significant difference between groups in factor scores for P300, P420 or S870.

² Separate PCAs were also calculated for the 26 patients who entered into the paranoid versus undifferentiated comparison and for the 28 participants who entered into the unmedicated patients versus controls comparison. The factors for each PCA closely matched the originally extracted factors for the total sample, which suggests that these factors are stable and reproducible across data sets.
Table 2. Summary of F-Ratios (and ε Corrections) From Repeated Measures ANOVA Performed on PCA Factor Scores for Target Stimuli Comparing Paranoid (n = 13) vs. Undifferentiated (n = 13) and Unmedicated Patients (n = 14) vs. Healthy Adults (n = 14)

<table>
<thead>
<tr>
<th>Variable</th>
<th>df</th>
<th>N100</th>
<th>N200</th>
<th>P300</th>
<th>P420</th>
<th>S870</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paranoid vs. Undifferentiated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group X Site</td>
<td>2, 44</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group X Site X Task</td>
<td>7, 154</td>
<td>4.63 * (0.30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmedicated Patients vs. Healthy Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>1, 24</td>
<td>15.98 ***</td>
<td>5.01 *</td>
<td>6.16 **</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group X Task</td>
<td>1, 24</td>
<td></td>
<td>6.75 *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group X Site</td>
<td>7, 168</td>
<td>6.05 * (0.21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group X Site X Task</td>
<td>7, 168</td>
<td>9.46 *** (0.24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group X Task X Hemisphere</td>
<td>1, 24</td>
<td></td>
<td></td>
<td></td>
<td>9.28 **</td>
<td></td>
</tr>
</tbody>
</table>

Note. Only significant F-ratios with p < .05 involving Group are reported. Task = tonal/phonetic; Hemisphere = left/right; Site = electrode location (representative sites [cf. Kayser et al. 2001] were for N100: F3/4, C3/4; for N200: FT9/10, FC5/6, T7/8, C3/4, TP9/10, CP5/6, P7/8, P9/10; for P300, P420, and S870: P3/4, P7/8, CP5/6).

* p < .05, ** p < .01, *** p < .001.

Figure 1. Grand average ERP waveforms at central and parietal recording sites for tonal and phonetic target stimuli, comparing 13 paranoid and 13 matched undifferentiated patients. Distinct ERP components closely corresponded to the extracted PCA factors, as is evident from the time course of the PCA factor loadings (see thin solid lines at sites C3 and P3 for tonal targets, and at sites C3 and P7 for phonetic targets).
**Unmedicated Patients versus Healthy Adults**

There was no difference in performance between unmedicated patients and healthy adults. N1 tended to be smaller in unmedicated patients than in controls (Figure 2), but this difference did not achieve statistical significance ($F[1,24] = 3.58, p = .07$). N2 amplitude was significantly reduced in the unmedicated patients compared to controls. This reduction was larger in the tonal than the phonetic task and was most marked at central sites, which is reflected by interactions involving Group, Task and Site (Table 2). An ANOVA of P420 factor scores revealed a main effect of Group and a Group × Task × Hemisphere interaction. This late P3 subcomponent was more positive in unmedicated patients than in controls, and this difference was greater in the tonal than phonetic task, particularly over left hemisphere sites. In contrast, the late positive slow wave (S870) was significantly smaller in unmedicated patients than in controls.

![Figure 2](image)

**Correlational Analyses**

Greater severity of illness, as indexed by total BPRS scores, was associated with smaller early P3 in the tonal task and late P3 in the phonetic task (Table 3). This inverse relationship was also seen between severity of negative symptoms and early P3 in both tasks. Positive symptoms were not significantly

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3 The ANOVA performed on the vector-scaled ERP amplitudes for each task across all 30 recording sites (McCarthy & Wood 1985; Ruchkin et al 1999) yielded somewhat smaller effects for the N200 interactions of Group × Site ($F[7,168] = 2.81, p = .08, \epsilon = .25$) and Group × Site × Task ($F[7,168] = 3.90, p = .03, \epsilon = .25$), and the Group × Task × Hemisphere interaction for P420 ($F[1,24] = 3.75, p = .06$), indicating that these group differences in ERP topography were partially dependent on the overall group differences of N200 and P420 amplitude.
Table 3. Pearson Correlations of Symptom Severity and Verbal Memory with ERP Components (PCA Factor Scores)

<table>
<thead>
<tr>
<th></th>
<th>Tonal</th>
<th></th>
<th></th>
<th></th>
<th>Phonetic</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N100</td>
<td>N200</td>
<td>P300</td>
<td>P420</td>
<td>N100</td>
<td>N200</td>
<td>P300</td>
<td>P420</td>
</tr>
<tr>
<td>BPRS (^a)</td>
<td>-</td>
<td>-</td>
<td><strong>-0.27</strong></td>
<td>-0.10</td>
<td>-</td>
<td>-0.14</td>
<td>-0.14</td>
<td><strong>-0.28</strong></td>
</tr>
<tr>
<td>PANSS: Negative (^a)</td>
<td>-</td>
<td>-</td>
<td><strong>-0.36</strong></td>
<td>-0.09</td>
<td>-</td>
<td>-0.14</td>
<td>-0.14</td>
<td><strong>-0.28</strong></td>
</tr>
<tr>
<td>PANSS: Positive (^a)</td>
<td>-</td>
<td>-</td>
<td>-0.08</td>
<td>-0.05</td>
<td>-</td>
<td>0.01</td>
<td>0.01</td>
<td>-0.14</td>
</tr>
<tr>
<td>Thinking Disturbance (^a)</td>
<td>0.15</td>
<td>-</td>
<td>-0.18</td>
<td>-0.08</td>
<td>0.17</td>
<td>-0.18</td>
<td>-0.23</td>
<td></td>
</tr>
<tr>
<td>TDI total (^b)</td>
<td>-0.03</td>
<td>-</td>
<td>-0.15</td>
<td>0.03</td>
<td>-0.05</td>
<td>-0.15</td>
<td>-0.17</td>
<td></td>
</tr>
</tbody>
</table>

| Wechsler Memory:      |                 |                 |                 |                 |                 |
|-----------------------|------------------|------------------|------------------|------------------|
| Verbal Associates \(^c\) | -        | 0.06  | 0.24  | **0.30** | -        | -0.20  | 0.25  | 0.17  |
| Logical Memory \(^d\) | -        | 0.01  | 0.27  | 0.14  | -        | **0.30** | 0.15  | 0.07  |
| Visual Memory \(^c\)  | -        | 0.04  | 0.09  | 0.19  | -        | -0.18  | -0.07 | 0.25  |

**Note:** Only predicted correlations are shown. Correlations given in bold face indicate a significance level of \( p < .05 \) (two-tailed). Correlations were computed for mean PCA factor scores at representative recording sites (cf. Kayser et al 2001): for N100, from frontocentral sites (Fz, Cz, F3/4, C3/4); for N200, from lateral sites over the right hemisphere for the tonal task (FT10, FC6, T8, C4, TP10, CP6, P8, P10), over the left hemisphere for the phonetic task (FT9, FC5, T7, C3, TP9, CP5, P7, P9); for P300 and P420, from parietal sites (Pz, P3/4, P7/8, CP5/6).

\(^a\) \( n = 60 \).

\(^b\) \( n = 42 \).

\(^c\) \( n = 46 \).

\(^d\) \( n = 47 \).

Correlated with early or late P3. Nor were N1, early P3 or late P3 related to measures of Thinking Disturbance on the BPRS. There was also no significant correlation between log TDI scores and early or late P3 in either task. Since thought disorder has been hypothesized to be related to reductions of P3 over left temporal cortex (McCarley et al 1993), correlations were also performed focusing on the left temporal site (T7). Again, there was no significant correlation between log TDI and either early or late P3 in either task (\( r = -.06 \) to -.11, \( ns \)).

Verbal memory was associated with P3 amplitude in the tonal task, but not in the phonetic task. Larger late P3 amplitude was associated with better verbal paired-associates performance. A similar trend was also evident for larger early P3 to be associated with better immediate recall on the logical memory subtest (\( p = .07 \)). In the phonetic task, larger N2 from lateral sites over the left hemisphere was associated with better logical memory performance.

**Discussion**

There was no difference in P3 between the paranoid and undifferentiated subtypes of schizophrenia in either tonal or phonetic oddball tasks. This agrees with the findings of prior studies using oddball tasks with tones (Boutros et al 1997; St Clair et al 1989). Although there was also no difference between these subtypes in N1 or N2 during a tonal oddball task, paranoid patients showed greater N2 at
frontocentral sites in a phonetic task. This is of interest given reports of better verbal processing in paranoid than undifferentiated schizophrenia (Seltzer et al 1997). The likelihood that larger N2 to syllables in paranoid patients may indicate more intact left hemispheric language processing is supported by an additional finding. Paranoid patients showed greater N2 over left than right temporoparietal sites in the phonetic task consistent with findings in healthy adults (Kayser et al 1998), whereas undifferentiated patients did not. Dichotic listening studies have similarly found larger left hemisphere advantages in paranoid than nonparanoid schizophrenia (Friedman et al 1999; Gruzelier & Hammond 1980; Nachson 1980).

In accordance with prior findings (Ford et al 1999; Turetsky et al 1998), greater severity of illness was associated with smaller P3 amplitude in schizophrenic patients. The inverse relationship between clinical severity and P3 was evident for negative symptoms, but not positive symptoms. Neither P3 nor N1 amplitude was related to thought disorder, as indexed by TDI scores, or to Thinking Disturbance scores on the BPRS. It is difficult to account for the difference in findings of this study and those finding a relationship between P3 and thought disorder (McCarley et al 1993; Shenton et al 1989). It could stem from a difference in patient characteristics, e.g., in severity of illness or chronicity, or a difference in oddball paradigms. Also, the correlations observed between P3 and total BPRS scores or negative symptoms were relatively weak, which may reflect the marked individual differences in P3 amplitude and the cross-sectional nature of this study (Mathalon et al 2000). We have previously reported stronger correlations between P3 amplitude and behavioral performance, particularly in the phonetic oddball task (Kayser et al 2001). Therefore, individual differences in P3 among patients reflect not only symptom severity but also cognitive disturbances (Pallanti et al 1999).

The association of P3 and cognitive function was also evident in the correlation of greater P3 amplitude in a tonal oddball task and better verbal paired-associates memory, which agrees with prior findings (Nagasawa et al 1999). P3 reduction over the left temporal region and associative memory loss in schizophrenia were associated with reduced volume of the posterior superior temporal gyrus (McCarley et al 1993; Nestor et al 1993). P3 in our phonetic task was not, however, correlated with verbal paired-associates performance, which might be expected given a left-lateralized deficit. Larger N2 over left hemisphere sites in the phonetic task was associated with better verbal memory on the logical memory subtest. This relationship is understandable given the role of the left temporal lobe in recognition memory and N2 for word stimuli (Kayser et al 1999).

Unmedicated schizophrenic patients showed a marked reduction of N2 amplitude, despite the absence of any difference in behavioral performance. This indicates that the N2 reduction in schizophrenia is not a byproduct of medication, lack of attention, or poorer performance in patients. Unlike N2, amplitude of N1, which reflects earlier sensory and attentional processing, was not significantly reduced in unmedicated patients. Pfefferbaum et al (1989) similarly found that schizophrenic patients off medication did not differ from controls in N1. ERPs for the unmedicated patients agreed with the full sample in showing no reduction of the P3 potential (Kayser et al 2001). Although some studies have found an increase in P3 amplitude during neuroleptic treatment (Coburn et al 1998; Umbricht et al 1998), it is unlikely that the medication status alone could account for the absence of a P3 reduction for schizophrenic patients our study.
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