Auditory event-related potential indices of fronto-temporal information processing in schizophrenia syndromes: valid outcome prediction of clozapine therapy in a three-year follow-up

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Abstract
Reliability, specificity, and validity of three event-related potential (ERP) indices of non-attended and attended auditory information processing [the mismatch negativity (MMN), the novelty-P3a and the target-P3b] were assessed in 21 healthy subjects and 25 schizophrenic patients while performing a visual discrimination task (Ignore condition) and, subsequently, an auditory discrimination task (Attend condition). Re-test reliability, as measured in a subset of 10 healthy subjects and 9 patients respectively, ranged from $r = 0.4$ to $r = 0.8$. In both groups P3a was found to be smaller in the Ignore than in the Attend condition. Patients had significantly larger P3a amplitudes than healthy subjects while their MMN and P3b amplitudes were smaller. Two ERP factors were extracted in healthy subjects: (1) ‘novelty reaction’ with high loading scores for P3a and (2) ‘deviant detection’ with high loading scores for MMN. P3b was predominantly loading on the first factor thus confirming partly overlapping P3a and P3b generators. However, considerable variance was also shared by the second factor, particularly in patients. External validity of the ERP factors was confirmed post hoc. Particularly ERP indices of deviant detection were found to be associated with negative symptoms. In order to assess further clinical relevance, therapy response to clozapine was followed-up over 3 yr in a sub-sample of 17 patients. Poor treatment response was associated with high Novelty Factor scores and large P3a amplitudes whereas good response was associated with high Deviant Factor scores and relatively intact MMN. It is concluded that ERP abnormalities provide a severity index of brain impairment and a measure of predicting therapeutic outcome.

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Introduction
Auditory event-related potentials (ERPs), such as the mismatch negativity (MMN) and the P3, are widely used to investigate cognitive functions. Both were found to be reduced in schizophrenic patients (e.g. Roth et al., 1980; Shelley et al., 1991). However, it remains unclear whether lower amplitudes across these measures reflect a general rather than a specific impairment of the underlying brain function and its neural substrates. Thus, the present study aims to investigate the construct validity of ERP components as specific indices of impaired brain function related to psychopathology and schizophrenia syndromes. The hypothesis derives from neuroimaging studies indicating that schizophrenic symptoms are the expression of the dysfunction of circumscribed brain areas (Andreasen, 1989). While negative symptoms are associated with ‘hypofrontality’ (Andreasen et al., 1992; Wolkin et al., 1992; Yuasa et al., 1995), positive symptoms, such as hallucinations and delusions are related to temporo-parietal dysfunction (Cleghorn et al., 1992; Suzuki et al., 1993; Yuasa et al., 1995).

ERPs provide a function measure of circumscribed brain areas. MMN, for instance, is a pre-attentive neural response to auditory deviant stimuli (Näätänen, 1992) and mainly generated in the temporal cortex (Kropotov et al., 1995; Tiitinen et al., 1993). On the other hand, MMN is also attenuated in patients with unilateral lesions of the dorso-frontal cortex indicating frontal contribution to
MMN generation (Alho et al., 1994). These findings suggest that MMN is an index of dorso-frontal and temporal information processing.

P3 can be related to corresponding structures: P3a as a response to unexpected events (or ‘novelty reaction’) was found to be reduced in patients with prefrontal lesions involving fronto-limbic pathways (Knight, 1984). Intracranial recordings detected two distinct scalp-related P3 potentials, one in the medial temporal lobe and one in the frontal lobe (Baudena et al., 1995; Halgren et al., 1995; Kiss et al., 1989; McCarthy and Wood, 1987; Smith et al., 1990). Relatively small lesions of the posterior superior temporal plane diminish P3a and P3b (Knight et al., 1989; Verleger et al., 1994). The latter component is generated in tasks requiring active stimulus processing (i.e. auditory or visual discrimination tasks; Squires et al., 1975a).

Topographic recordings under different experimental conditions suggest that the P3b component, in particular, is generated by multiple sources depending on the type of information being processed (Johnson, 1993; Ruchkin et al., 1990). This interpretation is supported by a study on patients with unilateral prefrontal lesions (Nasman and Dorio, 1993), where P3 was found to be enhanced to deviant non-target stimuli while target-evoked P3b were unaffected. The authors concluded that the prefrontal contribution to P3b is attention related. While MMN and P3a are elicited even when the stimuli are outside the focus of attention (Grillon et al., 1990; Näätänen et al., 1993), larger P3a amplitudes are generated when attention is increased (Ford et al., 1976). It is concluded that P3a is an index of directing attention towards the stimulus or source of stimulation. By contrast, MMN is present in subjects even when they do not notice the deviant stimuli (Näätänen, 1992). Thus MMN is an index of automatic auditory information processing and a measure of auditory sensory memory (Näätänen et al., 1989).

P3b amplitude measures had been shown to be positively correlated with increasing attention (Hink et al., 1978). It is also related to decision confidence and expectancy in an auditory discrimination task thus reflecting the two major factors of the signal detection paradigm (Campbell et al., 1979; Squires et al., 1975b). These findings are providing evidence that P3b is an index of active auditory information processing. However, Javitt et al. (1995) found a low but significant correlation of MMN and P3b amplitude measures across a sample of healthy subjects and both medicated and non-medicated schizophrenic patients, suggesting overlapping neural networks underlying both ERP indices (see also Molnar et al., 1995). Their attenuation may be associated with fronto-temporal brain impairment in schizophrenia and deficient ‘deviant detection’.

In the present study, a different statistical method will be applied to MMN, P3a and P3b data recorded from healthy subjects and schizophrenic patients under non-attend and attend conditions, respectively. As a first step, reliability and dimensional structure of the ERP indices will be assessed in healthy subjects. Secondly, this structure will be externally validated in a sample of schizophrenic patients. Internal validation will be assessed within schizophrenic patients by comparing subjects with (1) high vs. low expression of positive and negative symptoms, (2) high vs. low expression of schizophrenic syndromes (Liddle, 1987) and (3) good vs. poor response to clozapine treatment. The rationale for the latter comparison derived from findings that P3b is sensitive to clozapine treatment response (Schall et al., 1995, Umbricht et al., 1998). By contrast, MMN and P3a remained unchanged (Schall et al., 1998).

Methods

Subjects

The study protocol was approved by the Research Ethics Committee of the South Eastern Sydney Area Health Service. Twenty-one healthy subjects (13 women and 8 men) participated in this study. They were students and staff of the University of New South Wales and selected on the bases of screening criteria (no personal or family history of psychiatric illness, drug dependence, current medication or head injury) through an advertisement on the campus. The mean age of the female subjects (25.5 ± 7.2 yr) did not differ significantly from the mean age of the male subjects (23.1 ± 3.5 yr). Ten subjects were re-tested after 2–6 months (7 women and 3 men) in order to assess the re-test reliability of the recordings.

Twenty-five patients meeting DSM-III-R criteria for schizophrenia constituted the sample for construct validation if they also met the following selection criteria for inclusion: age 18–45 yr, no head injury, or recent history of alcohol and substance abuse (according to DSM-III-R criteria). They were interviewed according to the Structured Clinical Interview for DSM-III-R (SCID; Spitzer et al., 1990) and were rated on the Schedules for Positive and Negative Symptoms (SANS and SAPS; Andreasen, 1982, 1984).

All patients received neuroleptic treatment. Twenty-one patients were on typical neuroleptics (mean dosage: 560 ± 380 mg/d chlorpromazine equivalents) and four were on clozapine (150–400 mg/d). Six patients also received benztpine. Seven subjects were in-patients of the Psychiatric Unit of the Prince of Wales Hospital, while 18 subjects were outpatients cared for by the South Eastern Sydney Health Service. Nine patients were female (36.7 ± 9.2 yr), 15 were male (35.3 ± 10.5 yr). Patients
were significantly older than the healthy subjects (Mann–Whitney U test, \( p < 0.0001 \)). Nine out-patients (6 men and 3 women) with stable symptoms and unchanged medication (all treated with typical neuroleptics) were recorded a second time after 2 months to assess re-test reliability.

The response of a sub-sample of 17 treatment-resistant patients to clozapine was followed-up over 3 yr with the Brief Psychiatric Rating Scale (BPRS; Lukoff et al., 1986). These patients also participated in a parallel study investigating clozapine’s effects on frontal lobe function (Schall et al., 1998). The response criteria in the present study was an improvement of more than 1 s.d. on the BPRS following a treatment period of 2 months.

**Stimuli and task**

The task was identical to that described by Schall et al. (1998). ERPs were recorded to deviant and novel auditory stimuli in two conditions: (1) subjects had to ignore the auditory stimuli (Ignore Auditory Condition) and (2) they had to perform an auditory discrimination task (Attend Auditory Condition). Visual stimuli were presented simultaneously with the auditory stimuli in both conditions. They consisted of a fixation cross exposed throughout the run, a red circle (3 cm diameter) presented for 1 s, and a green circle presented either for 2 s or until the subject made a response (only in the Auditory Ignore Condition). Twenty-five pairs of red–green circles (randomly every 3–6 s) were presented in each run.

Three types of auditory stimuli (tones presented with 700 ms ISI) were presented: binaural tone pips (85 dB) of either 1000 or 1064 Hz (200 ms duration, 10% rise/fall time) and novel environmental sounds (160 ms duration). Each run (3.5 min) included 300 auditory stimuli of which 85% were standard (1000 Hz), 10% were deviant (1064 Hz), and 5% were novel (different environmental sounds). Four 3.5-min runs per task were performed. Task 1 (Ignore Auditory Condition): ‘Press button to green circle in order to remove the circle from the screen’ and task 2 (Attend Auditory Condition): ‘Press button to every deviant tone’.

**ERP recording technique**

Fifteen channels of EEG were recorded from midline (Fpz, Fz, Cz and Pz) and lateral (F7–F8, T3–T4, T5–T6; international 10–20 system; Electrocap International) scalp electrodes and from the left and right mastoid with a nose reference (all impedances < 5 k\( \Omega \)). The signal was amplified (Grass Model 12 Neurodata) \( \times \) 20000 and bandpass filtered between 0.01 and 30 Hz. ERPs were averaged (Neuroscan Software) over epochs of 900 ms including a baseline 200 ms prior to the onset of the stimulus. Trials in which the vertical or the horizontal EOG exceeded 50 \( \mu \)V as well as epochs associated with incorrect responses (in the Attend Auditory Condition) were excluded from averaging. Peak amplitudes within a post-stimulus window of 250–600 ms served as the P3a/P3b peak amplitude measures. MMN was calculated as the mean amplitude 150–250 ms post-stimulus estimated in the difference wave of the ERPs evoked by the standard minus the deviant stimuli in the Ignore Auditory Condition. MMN and P3a were measured at the Fz, and P3b at the Pz midline electrode.

**Statistical analysis**

Statistical within-group comparisons were performed on the Wilcoxon Matched-Pairs Signed-Ranks test. Between-group differences were tested with the Mann–Whitney U test. Re-test reliability and associations between measures were calculated with Spearman correlation coefficients. The \( p \) values were Bonferroni-corrected where appropriate. A principal-component factor analysis (varimax rotation) was performed on the four ERP components (MMN, P3a\(_{\text{ignore}}\), P3a\(_{\text{attend}}\), and P3b) separately for healthy subjects and patients.

Factor composite scores of the ERP data were calculated on the bases of the results of the principal-component analysis of healthy subjects by summing the \( z \)-scores from those amplitude measures with high loading on the factor. The \( z \)-scores were standardized against the mean and the standard deviation for the combined group and weighted by the factor loading score. Each score contributed to one factor only. These factor composites were entered into canonical discriminant analyses for evaluation of the factor structure obtained in healthy subjects by group classification (external validation).

Similar \( z \)-standardized composite scores were calculated on the basis of the principal-component factor analysis (varimax rotation) of SAPS and SANS global rating scores of the patients. The resulting syndrome scores and, respectively, the total SAPS/SANS rating scores served as the criterion for median-split group comparisons of patients with high vs. low scores on these measures (internal validation) by multivariate analysis of variance (MANOVA), with age as covariate. Associations of global symptom rating scores were calculated on \( z \)-standardized measures in a linear stepwise multiple regression analysis (PIN = 0.05) with ERPs as the dependent, respectively. Assuming a medium effect size, a sample size of 46 will detect a mean difference between two subgroups equivalent to 1 s.d. for \( \alpha = 0.05 \) (two-tailed probability) with \( \geq 90\% \) probability and between three subgroups with \( \geq 84\% \) probability.
Results

Performance

ERPs recorded from healthy subjects included a minimum of $85.6 \pm 7.2\%$ artifact-free recordings in each condition. Adequate MMN and P3a data ($\leq 18$ sweeps per average) were available from all subjects and P3b from 20 subjects. Patients’ rejection rate was significantly higher ($p < 0.002$) and included a minimum of $63.2 \pm 16.7\%$ artifact-free recordings in each condition. MMN was available from 23 patients, P3a (both conditions) from 21 patients and P3b from 18 patients. Group means were calculated for missing ERP data.

Patients’ performance rate (auditory discrimination task in the attend condition) was significantly lower than those of healthy subjects (response to target stimuli: $68.3 \pm 21.3\%$ vs. $97.8 \pm 3.9\%, p < 0.0001$; response to standard stimuli: $2.1 \pm 2.9\%$ vs. $0.6 \pm 0.7\%, p < 0.01$; response to novel stimuli: $14.6 \pm 11.1\%$ vs. $4.8 \pm 2.9\%, p < 0.01$).

Reliability

In healthy subjects, amplitude and latency measures in the re-test session did not differ significantly from the first recording (Table 1). Re-test latency correlation coefficients were significant for all components in both conditions ($r_s = 0.81, p < 0.01$). However, only the P3a amplitude measure in the Attend Auditory Condition was significantly stable [test/re-test correlation: $r_s = 0.79 (p < 0.01)$ vs. $r_s = 0.54 (p = 0.11)$ in the Ignore Auditory Condition]. The MMN and P3b test/re-test correlations were not significant ($r_s = 0.52$ and $r_s = 0.41$, respectively).

The test/re-test correlations were similar for schizophrenic patients. Amplitude and latency measures in the re-test session did not differ significantly from the first

Table 1. Peak P3a/P3b and mean MMN amplitude and peak latency measures (means ± s.d.) of healthy subjects (H, $n = 21$) and schizophrenic patients (S, $n = 25$)

<table>
<thead>
<tr>
<th></th>
<th>MMN</th>
<th>P3a Ignore</th>
<th>P3a Attend</th>
<th>P3b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amp (µV) Lat (ms)</td>
<td>Amp (µV) Lat (ms)</td>
<td>Amp (µV) Lat (ms)</td>
<td>Amp (µV) Lat (ms)</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>1.4 ± 1.2 185 ± 47</td>
<td>10.3 ± 5.0 327 ± 33</td>
<td>14.1 ± 8.0* 321 ± 33</td>
<td>13.0 ± 7.0 459 ± 53</td>
</tr>
<tr>
<td>S</td>
<td>0.0 ± 2.6† 198 ± 41</td>
<td>12.2 ± 6.0 337 ± 51</td>
<td>19.4 ± 9.1† 327 ± 44</td>
<td>11.9 ± 8.1 478 ± 76</td>
</tr>
</tbody>
</table>

*P3a amplitudes Attend vs. Ignore Auditory Condition, $p < 0.01$. Group comparisons: †$p = 0.01$, ‡$p < 0.04$.

Amp, amplitude; Lat, latency.

Figure 1. Grand means (negative up) of ERP recordings under Ignore (A, B) and Attend Auditory Conditions (C, D) of 21 healthy subjects and 25 schizophrenic patients. A. Mismatch negativity at Fz. B, C. Grand means showing P3a at Fz in both conditions (note the larger P3a amplitudes in schizophrenic patients). D. Grand means showing P3b at Pz.
Factors and positive symptoms [SAPS: avolition, alogia, anhedonia, and affective flattening: \(F(1,24) = 3.5, p = 0.07\), Table 4]. Univariate comparisons of Deviant Detection Factor scores was found to be significant for negative symptoms [SANS: \(F(2,43) = 3.5, p < 0.05\)] and the first syndrome factor [thought disorder, bizarre behaviour, and delusion: \(F(2,43) = 2.1, p = 0.17\)].

In patients, the avolition rating scores predicted significantly Deviant Detection Factor scores [stepwise multiple regression: \(F(1,24) = 5.0, p < 0.04, R^2 = 0.42\)].

**Construct validity**

Multivariate ANOVA group comparison on the basis of the two ERP factors was significant \([F(2,43) = 5.0, p < 0.02]\) while univariate group comparisons of factor composite scores were significant for the Deviant Detection Factor \([F(1,44) = 4.6, p < 0.04]\) but not for the Novelty Reaction Factor \([F(1,44) = 3.5, p = 0.07; \text{Figure} 2]\). The discriminant analysis provided evidence for a significant group separation on the bases of both factors \(\chi^2 = 9.0, \text{d.f.} = 2, p = 0.01; \text{Table} 4\).

Internal validation was obtained on global SAPS and SANS rating scores and on syndrome factor scores based on weighted \(z\)-transformed composites extracted from the principal-component analysis of the clinical ratings (eigenvalue > 1; explaining together 71.2\% of variance; \text{Table} 5). A post hoc MANOVA comparing healthy subjects and patients with low and high expression of positive or negative symptoms or syndrome factor scores (median-split, respectively) was significant (\text{Figure} 2). Univariate comparisons of Deviant Detection Factor scores was found to be significant for negative symptoms [SANS: \(F(2,43) = 3.5, p < 0.05\)] and the first syndrome factor [thought disorder, bizarre behaviour, and delusion: \(F(2,43) = 2.1, p = 0.17\)].

In patients, the avolition rating scores predicted significantly Deviant Detection Factor scores [stepwise multiple regression: \(F(1,24) = 5.0, p < 0.04, R^2 = 0.42\)].

**Specificity**

In order to control for gender bias, ERP measures male vs. females were statistically compared in both groups, respectively, and no significant differences were found \((p > 0.77)\). In healthy subjects, mean peak P3a amplitudes in the Attend Auditory Condition were significantly larger than in the Ignore condition (\text{Table} 1 and \text{Figure} 1). Schizophrenic patients had significantly larger P3a amplitudes in this condition and significantly smaller MMN than healthy subjects. On the other hand, P3b was smaller in schizophrenic patients but group differences were not significant \((p < 0.17)\). The P3a amplitudes in the Ignore and Attend conditions correlated significantly in the control group whereas P3b/P3a\_ignore and P3a\_ignore/P3a\_attend correlation coefficients in patients, respectively, were not significant following Bonferroni \(z\)-correction (\text{Table} 2).

Two factors (eigenvalue > 1) explaining together 79.1\% variance were extracted in a principal-component analysis (varimax rotation) on the basis of the data of the healthy subjects (\text{Table} 3). On the first factor (‘novelty reaction’) the P3a amplitude measures of the Ignore and Attend conditions yielded high factor loading scores. MMN and P3b scored on the second factor (‘deviant detection’). The same analyses performed on data of schizophrenic patients (explaining 73.8\% variance) extracted a different factor structure; P3b scored predominantly here on the first factor while P3a\_attend scored on the second factor.

**Table 2.** Spearman correlation coefficients between amplitude measures (coefficients of schizophrenic patients in parentheses)

<table>
<thead>
<tr>
<th></th>
<th>(P3_a_\text{ignore})</th>
<th>(P3_a_\text{attend})</th>
<th>(P3_b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMN</td>
<td>0.11 (−0.26)</td>
<td>0.23 (0.25)</td>
<td>−0.31 (0.00)</td>
</tr>
<tr>
<td>P3a_ignore</td>
<td></td>
<td>0.64* (0.40)</td>
<td>0.27 (0.42)</td>
</tr>
<tr>
<td>P3a_attend</td>
<td></td>
<td>0.24 (0.16)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(r_{s})</td>
<td></td>
<td>(r_{s})</td>
</tr>
</tbody>
</table>

\(p = 0.002\) (Bonferroni, \(p < 0.008\)).

**Table 3.** Factor loading scores of two principal-component analysis of ERP components (varimax rotation) separately performed on the data of healthy subjects and schizophrenic patients (in parentheses)

<table>
<thead>
<tr>
<th>Factors …</th>
<th>Novelty reaction</th>
<th>Deviant detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variance proportion (%) …</td>
<td>48.6 (43.1)</td>
<td>30.5 (30.7)</td>
</tr>
<tr>
<td>Eigenvalues …</td>
<td>1.9 (1.7)</td>
<td>1.2 (1.2)</td>
</tr>
<tr>
<td>(P3_a_\text{ignore})</td>
<td>0.91 (0.87)</td>
<td>−0.03 (0.26)</td>
</tr>
<tr>
<td>(P3_a_\text{attend})</td>
<td>0.91 (0.26)</td>
<td>−0.01 (0.88)</td>
</tr>
<tr>
<td>MMN</td>
<td>0.20 (−0.55)</td>
<td>0.88 (0.63)</td>
</tr>
<tr>
<td>(P3_b)</td>
<td>0.46 (0.77)</td>
<td>−0.70 (−0.05)</td>
</tr>
</tbody>
</table>

Bold figures indicate factor structure or factor composition.
Figure 2. Comparison of ERP composite scores between healthy subjects and schizophrenic patients (A). Median split comparison of patients with high vs. low SAPS (B) and SANS (C) global scores, respectively, and high vs. low syndrome composite scores (D, E, F). Standard deviation range, 0.8–1.6.

Table 4. Predicted classification (discriminant analysis) on the bases of the ERP composite factor scores (correctly classified: 69.6%; Wilks’ lambda = 0.81)

<table>
<thead>
<tr>
<th>Predicted group membership</th>
<th>‘Healthy’</th>
<th>‘Schizophrenic’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy subjects (n = 21)</td>
<td>15 (71.4%)</td>
<td>6 (28.6%)</td>
</tr>
<tr>
<td>Schizophrenic patients (n = 25)</td>
<td>8 (32.0%)</td>
<td>17 (68.0%)</td>
</tr>
</tbody>
</table>

Table 5. Factor loading scores of a principal component analysis performed on SAPS and SANS item rating scores (varimax rotation; n = 25)

<table>
<thead>
<tr>
<th>Factors …</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variance proportion (%) …</td>
<td>41.2</td>
<td>16.3</td>
<td>13.7</td>
</tr>
<tr>
<td>Eigenvalues …</td>
<td>3.7</td>
<td>1.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Avolition</td>
<td>0.84</td>
<td>0.28</td>
<td>-0.02</td>
</tr>
<tr>
<td>Alogia</td>
<td>0.75</td>
<td>-0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Anhedonia</td>
<td>0.71</td>
<td>0.09</td>
<td>0.32</td>
</tr>
<tr>
<td>Affective flattening</td>
<td>0.68</td>
<td>0.53</td>
<td>0.06</td>
</tr>
<tr>
<td>Inattention</td>
<td>0.20</td>
<td>0.86</td>
<td>-0.02</td>
</tr>
<tr>
<td>Hallucination</td>
<td>0.06</td>
<td>0.84</td>
<td>0.33</td>
</tr>
<tr>
<td>Thought disorder</td>
<td>0.03</td>
<td>0.19</td>
<td>0.82</td>
</tr>
<tr>
<td>Bizarre behaviour</td>
<td>0.51</td>
<td>-0.14</td>
<td>0.69</td>
</tr>
<tr>
<td>Delusion</td>
<td>-0.01</td>
<td>0.58</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Bold figures indicate factor composition.
Event-related potential indices in schizophrenia syndromes

Figure 3. Comparison of (A) symptom composite scores and (B) ERP composite scores between 21 healthy subjects and 17 schizophrenic patients responding good (n = 8) or poor (n = 9) to clozapine therapy within an observation period of 3 yr. (Standard deviation range, 0.9–1.9; statistics, Mann–Whitney U test poor vs. good response; * p < 0.05, ** p < 0.01.)

Figure 4. Baseline recordings (grand means, negative up) of ERPs under Ignore (A, B) and Attend Auditory Conditions (C, D) of schizophrenic patients responding good (n = 8) or poor (n = 9) to clozapine treatment within a follow-up of 3 yr. A. Mismatch negativity at Fz. Responders had a significantly larger MMN amplitude than non-responders. B, C. Grand means showing P3a at Fz in both conditions where poor responders have significantly larger P3a amplitudes in the Ignore condition than good responders. D. Grand means showing P3b at Pz.

A closer examination revealed a significant association with avolition for only MMN ($R^2 = 0.53$) and hallucinations [$R^2 = 0.44$; stepwise multiple regression: $F(2,23) = 8.3, p < 0.002, R^2 = 0.65$]. However, neither median-split comparisons of patients with high and low SAPS/SANS rating scores nor median-split comparisons of patients with high and low syndrome factor scores were significant; also no significant correlation of factor scores with medication was found.

**Prediction of treatment response to clozapine**

After study completion, 17 patients (11 men and 6 women) received clozapine therapy for the first time. Their ERP data recorded whilst on typical neuroleptics were used to predict their treatment response as followed-up for 3 yr. Eight patients (4 men and 4 women) did not respond appropriately to clozapine within a treatment cycle of 2 months (total treatment range: 2–21 months, median 3.4 months) and further treatment reverted to typical neuroleptics. One male patient was treated for 4 wk finally receiving a maximum daily dosage of 150 mg clozapine before the treatment reverted to typical neuroleptics due to non-compliance. The other 8 patients successfully commenced on clozapine as indicated by significantly improved stable clinical rating scores as followed-up over 3 yr (BPRS: $39.5 \pm 5.1$ vs. $29.1 \pm 6.8$; $z = -2.3, p < 0.02$).
Comparing both groups, poor responders had more severe symptoms before introducing clozapine (SAPS, 11.1 ± 3.3 vs. 4.2 ± 2.7; \( z = -2.3, p < 0.02 \); SANS, 14.4 ± 1.3 vs. 9.1 ± 4.5; \( z = -1.9, p = 0.06 \), they were older (38.4 ± 8.1 yr vs. 32.3 ± 5.5 yr; \( z = -2.4, p < 0.02 \)) and had a longer history of illness (75.2 ± 22.8 months vs. 64.0 ± 15.3 months; \( z = -2.0, p < 0.05 \)) than good responders. Significantly high scores were rated on the third syndrome factor (\( z = -2.7, p < 0.01 \); Figure 3A).

P3b recordings were not available from two clozapine responders and two non-responders due to high artifact contamination and poor task performance. The mean P3b amplitude of the remaining 13 patients was used to calculate the deviant ERP factor score in these cases. Calculated on the basis of this data set, poor responders had larger P3 amplitudes (P3a\(_{\text{ignore}}\); \( z = -2.7, p < 0.01 \); P3a\(_{\text{attend}}\); \( z = -1.2, p = 0.22 \); P3b, \( z = -1.5, p = 0.16 \)) and smaller MMN (\( z = -2.2, p < 0.03 \); Figure 4) than clozapine responders. As a result, poor responders were detected by significantly higher Novelty Factor scores (\( z = -2.3, p = 0.02 \)) and, by contrast, good responders by significantly higher Deviant Factor scores (\( z = -2.8, p < 0.01 \); Figure 3B) when recorded before introducing clozapine. Therapy response was predicted correctly on the basis of both ERP composite scores in 94.1% of the cases; there was one patient who was wrongly predicted as a responder (discriminant analyses, \( \chi^2 = 11.8, \text{d.f.} = 2, p < 0.01 \)). In summary, clozapine responders were distinguished by having a relatively intact MMN whereas poor responders had significantly larger P3a amplitudes in the Ignore condition.

### Discussion

The findings suggest that ERP data can provide useful insights into the cognitive processes underlying schizophrenic symptoms. However, the stability of the ERP measurement assessed as re-test reliability in a sub-sample was particularly low for P3b in healthy subjects [see Fabiani et al. (1987) for comparison] and MMN in schizophrenic patients. On the other hand, P3a measures appeared to be more stable in both groups thus providing more statistical power for group differentiation. The relatively small MMN amplitudes in healthy subjects — in comparison to those reported, for instance, by Pekkonen et al. (1995) and our group (Catts et al., 1995; Shelley et al., 1991) — are probably reflecting the use of pitch instead of stimulus duration as mismatch condition. The resulting lower signal-to-noise ratio, particularly in patients, and the fact that all subjects were conditioned to the deviant as target stimulus while performing the subsequent auditory discrimination task, may have contributed to a higher intra-subject variability as indicated by lower re-test correlation coefficients. However, although an unfavourable MMN procedure was used here, a significant smaller mean amplitude of MMN in schizophrenic patients was confirmed (see for comparison Catts et al., 1995; Javitt et al., 1993, 1995; Shelley et al., 1991).

The factor analysis performed on ERP data indicate two separate ERP dimensions in healthy subjects: (1) novelty reaction with high P3a factor loading scores and (2) deviant detection with high MMN factor loading scores and, to a smaller extent, relatively high scores for P3b. This result provides evidence that P3a and MMN, both recorded at the Fz electrode, represent independent dimensions of automatic auditory information processing. It also suggests that P3b and MMN are sharing common neural networks involved in auditory deviant detection (Javitt et al., 1995). Schizophrenic patients had higher composite scores on both ERP factors as a result of smaller MMN and larger P3a amplitudes which indicate frontal ablation (Alho et al., 1994; Nasman and Dorio, 1994).

How is this finding related to schizophrenia syndromes?

The factor analysis performed on SAPS and SANS global rating scores separated three syndrome factors. The first factor predominantly extracts negative symptoms while the third factor represents positive symptoms which can be related to tempo-parietal brain dysfunction (Andreasen, 1989). However, the second factor with relatively high loading scores for inattention and hallucination (partly also affective flattening and delusion) did not follow the positive/negative dichotomy and is probably partly an artifact due to the small sample size. By applying the ERP factor structure, originally extracted in healthy subjects to patients, approx. 70% of all subjects were correctly classified, thus achieving a better classification performance than, for instance, reported by Boutros et al. (1997). In the present study, the best fit was found for the first syndrome factor which is similar to the Psychomotor Poverty Syndrome described by Liddle (1987). Mainly the Deviant Detection ERP factor and, as the major element, MMN was found to be significantly associated with negative symptoms thus confirming former results (Catts et al., 1995). MMN was also found to be correlated with hallucination rating scores. This association pattern confirms the assumption that MMN is an index of frontal and temporal brain dysfunction (Alho et al., 1994; Tiitinen et al., 1993).

Comparing the factor structure of both groups also provides an insight into the cognitive processes impaired in schizophrenia. Smaller P3b amplitudes, for instance, are an index of reduced sustained attention allocated to task-relevant stimuli (Hink et al., 1978). A closer look at the ERP factor structures, which was independently extracted in each group, reveals that P3b in healthy subjects was
predominantly associated with MMN on the Deviant Detection Factor. Patients’ P3b had higher loading scores on the Novelty Reaction Factor together with P3a in the Ignore condition. This shift to a relatively more ‘frontal’ P3b was mainly the result of smaller parietal P3b amplitudes in schizophrenic patients. It suggests that attention-related frontal P3b generators relatively dominate in schizophrenia.

This study also demonstrates that P3a amplitude is not generally reduced in schizophrenia (cf. Roth et al., 1980). By contrast, P3a amplitudes were found to be significantly larger than those of healthy subjects and predicted a poor treatment response. Grillon et al. (1991) also found reduced P3s in schizophrenic patients using a similar procedure. In support of the findings here, P3s recorded as a response to the most salient task-irrelevant stimuli were not significantly reduced in schizophrenic patients in comparison to healthy controls. Similar findings have been reported for patients with unilateral prefrontal lesions (Nasman and Dorio, 1993) where P3a was also measured as the response to non-target deviants using visual stimuli. In this case, P3a was the response to a distracting stimulus. Under this condition, larger P3a indicate more distractibility and reduced capability in suppressing the response to non-target deviant stimuli (Woods and Knight, 1986). Accordingly, schizophrenic patients more often responded to novel stimuli (or the non-target deviants) than healthy subjects in the present study. Correspondingly, their P3a recorded in the Attend condition was predominantly loaded on the Deviant Detection Factor together with MMN. Also the waveform of the patients’ P3a indicate a late positivity similar to the P3b component suggesting more ‘target-like’ stimulus processing of novel stimuli. Since target and non-target P3bs may be functionally distinct entities (Jodo and Inoue, 1990), overlapping frontal P3a/P3b generators associated with the suppression of non-target responses seems to be likely (Schall et al., 1996, 1997; Schall and Ward, 1996).

The present study also provides clinically relevant data. Although regarded as preliminary findings, significant ERP abnormalities as indexed by high scores on the Novelty Factor (due to high P3a amplitudes in the Ignore Auditory Condition) were found to be associated with poor treatment response to clozapine. On the other hand, good responders had relatively high scores on the Deviant Detection Factor and were less symptomatic than poor responders. In this respect, the grade of P3a deviation can be interpreted as severity index of brain impairment determining treatment response. However, a relatively intact MMN was found to be associated with better prognosis. Thus, poor outcome was predicted correctly in 16 of 17 patients on the basis of the recordings obtained prior to clozapine. However, the specificity of this finding remains to be re-investigated in a larger sample combining ERP measures together with neuropsychological assessment. Such a study should also be controlled for gender bias and medication prior to onset of clozapine treatment.

In conclusion, an association of negative symptoms and ERP indices of deviant processing was found, although there was no sufficient empirical bases for further differentiation into schizophrenia syndromes (only a statistical trend towards an association of auditory novelty processing and positive symptoms). These findings suggest that a distributed fronto-temporal neural network is involved in auditory sensory memory processing as indexed by MMN. Impaired information processing in this network may underlie negative symptoms in schizophrenia. Particularly enhanced P3a responses in the context where the eliciting stimulus has to be ignored seem to be associated with the severity of brain impairment and indicate poor therapeutic outcome.

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