The N2 component of the event-related potential in schizophrenic patients

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Summary Event-related potentials (ERPs) to easy and difficult infrequent visual target stimuli were recorded in unmedicated schizophrenic patients and age-matched controls. N2 difference wave forms were computed by subtracting the ERP to a frequent non-target stimulus from the ERP to each target. The N2 component was identified in these difference wave forms. All subjects showed longer latency N2 and P3 peaks to the difficult target than to the easy target. Schizophrenic patients had longer latency N2 peaks than controls to both targets. Schizophrenic patients also showed reduced P3 amplitudes to both targets compared to controls.

The prolonged N2 latency in schizophrenics accounts for a substantial portion of the delayed reaction time commonly observed in this group. N2 latency prolongation appears to be yet another evoked potential abnormality in schizophrenic patients.

Key words: N2; P3; Amplitude; Latency; Schizophrenia; Event-related potentials

Several features of the event-related potential (ERP) have been linked to stages of information processing in humans, and in the case of the late positive component in primates as well (Arthur and Starr 1984). The N1 (Nd) component has been shown to be responsive to selective attention (Hillyard 1973). The N2 component has been linked with stimulus classification (Ritter et al. 1983) and stimulus deviance (Nääätänen et al. 1980a, 1982). This component also precedes reaction time in target detection tasks (Ritter et al. 1979) and in omitted stimulus paradigms (Renault et al. 1982). The N2 component is modality specific (Simson et al. 1976, 1977) and appears to be attention insensitive in some circumstances (Nääätänen et al. 1980b). The P3 component has been shown to be dependent on subjective probability (Sutton 1965), and task relevance (Squires et al. 1977) and to be sensitive to stimulus incentive value (Begleiter et al. 1983; Homberg et al. 1984). These findings have provided the beginnings of an electrophysiological framework for current concepts of information processing.

Much has been written about the plethora of cognitive deficits observed in schizophrenia (see Neale and Oltmanns 1980 for review). These patients also have abnormal ERPs in a wide variety of experimental paradigms including those used to study information processing in normal subjects. Schizophrenics show a diminished N1 amplitude in tasks which require selective attention (Barbeau-Braun et al. 1980). Several reports have described a reduced P3 amplitude in schizophrenic patients to auditory and visual stimuli in a variety of paradigms including oddball (Roth and Cannon 1972), expectancy (Levit et al. 1973; Verleger and Cohen 1978), continuous performance task (Pass et al. 1980), and incentive level (Brecher and Begleiter 1983). A reduced P3 amplitude has also been observed in schizophrenia in the somatosensory modality (Josiasson et al. 1981). Schizo-
phrenic patients have also manifested slower reaction times (RT) than controls in such a wide variety of tasks (Neuechterlein 1977), that this finding is considered a behavioral hallmark of schizophrenia.

The N2 component in schizophrenic patients has received very little attention in the literature. We report here the results of an investigation of the N2 component in a drug-free sample of schizophrenic patients and relate our results to other ERP abnormalities in schizophrenia and to the well established slower reaction times in patients with this illness.

Methods

Subjects

Fourteen schizophrenic patients were tested. Twelve were patients admitted to an open-door unit of a university teaching hospital, two were referred outpatients. All patients were seen by at least two psychiatrists who concurred on a DSM-III diagnosis of schizophrenia. For inclusion into the study, patients had to be 18–55 years of age, free of acute illness, neurological disease, drug abuse, alcohol abuse and any other current axis 1 diagnosis. The patients were drug free for at least 2 weeks prior to testing. A history of treatment with Prolixin decanoate required a 6 week washout period. The protocol allowed 30 mg of flurazepam or 65 mg of sodium amytal to be given for insomnia at bedtime up to 3 days prior to testing.

Informed consent was obtained from all subjects. Controls were solicited by advertisement and screened for medical illness, alcohol abuse and drug use. A subgroup was selected from a pool of controls to age-match the patients after 4 patients were eliminated from the study because of excessive eye movement artifact. The patient group consisted of 6 males and 4 females with a mean age of 28.9 ± 8.7 years. The controls were 8 males and 2 females whose mean age was 27.5 ± 4.7 years. The sex distribution was not significantly different in the two groups.

Data collection

Gold cup electrodes were placed at midline frontal (Fz), central (Cz), parietal (Pz), occipital (Oz), left parietal (P3) and right parietal (P4) locations according to the 10-20 system (Jasper 1958). Electrode resistance was less than 5 kΩ. The recordings were monopolar with the linked ears serving as reference and the nasion as ground. Vertical eye leads recorded the electro-oculogram (EOG).

Subjects were seated in a sound attenuated chamber in front of a computer controlled cathode ray screen. Their chins rested on a chin rest and they were instructed to fix their gaze on a green dot in the center of the screen.

A computer generated 3 visual stimuli: a vertical line, a horizontal line (easy target) and a line which deviated by 3° from vertical (difficult target). The stimuli were presented at the center of the screen, were equal in size and intensity, subtended 2.7° of arc, were of 5 msec duration and were presented at randomly varying interstimulus intervals of 2–5 sec. 240 stimuli were presented in random sequence with the vertical line comprising 75% of the stimuli (non-target) and the 3° line and the horizontal line each comprising 12.5% of the stimuli (target). The stimuli were presented in random sequence except that two targets were not presented in succession. Subjects were instructed to press a button as quickly as possible as soon as they detected a non-vertical stimulus. Practice trials were presented before data collection began.

Subjects’ ERPs and RTs were recorded and displayed on-line on another cathode ray screen. The recording epoch for RT was 2500 msec. ERPs were recorded at each of the 6 electrodes and the EOG were amplified 50,000 times. Bandwidth was 0.1–60 Hz. Analog signals were sampled every 7 msec for 700 msec and converted to digital format. The EEG recorded during the 49 msec epoch preceding stimulus presentation was averaged and used as a baseline.

The ERPs were sorted by a computer (PDP 11/40) into 5 categories: one for each of two targets, one for the non-target which preceded the 3° target, one for the non-target which preceded the 90° target, and one for all the non-targets. A computer program checked the single trial ERPs for eye movement artifact, missed hits and false alarms. Trials with Fz lead voltages in excess of 20
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pV or incorrect behavioral responses were excluded. Subjects who did not have at least 50% artifact-free correct trials were not included in the data analysis. This criterion led to the exclusion of 4 patients. The edited trials were then averaged producing 5 averaged ERPs at each electrode.

The averaged ERP recorded to all the vertical non-targets was subtracted from the averaged ERP to the horizontal stimulus and the 3° stimulus respectively, following the method of Simson et al. (1976, 1977). N2 amplitude and latency were determined from the resulting difference wave forms. P3 amplitude and latency were determined from the averaged ERPs to the horizontal and 3° stimuli. The N2 and P3 peaks were identified independently by two of the authors. When they were not in agreement (<10% of peaks), the third author was asked to select the peak. The amplitudes and latencies of the N2 and P3 peaks were subjected to a 3-way analysis of variance (BMDP2V) with 1 between-group factor (diagnosis) and 2 within-subject repeated measures (angle, electrode). Statistical significance for results on repeated measures was based on probabilities using the Greenhouse-Geisser correction for the degrees of freedom (Geisser and Greenhouse 1959).

Results

Grand means of the averaged ERPs at Fz, Cz, Pz and Oz are shown in Fig. 1. Grand means of the subtraction wave forms at Oz are shown in Fig. 2. For both targets, N2 latency occurred significantly later in the schizophrenic patients than in the controls (P < 0.01; Fig. 3). For the

<table>
<thead>
<tr>
<th>Component</th>
<th>Diagnosis</th>
<th>Angle</th>
<th>Angle × diagnosis</th>
<th>Electrode</th>
<th>Electrode × diagnosis</th>
<th>Angle × electrode</th>
<th>Angle × electrode × diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N2 latency</td>
<td>9.43</td>
<td>4.52</td>
<td>0.19</td>
<td>1.65</td>
<td>0.12</td>
<td>1.03</td>
<td>1.45</td>
</tr>
<tr>
<td></td>
<td>0.007</td>
<td>0.047</td>
<td>0.67</td>
<td>0.15</td>
<td>0.98</td>
<td>0.40</td>
<td>0.213</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.21)</td>
<td>(0.85)</td>
<td>(0.35)</td>
<td>(0.249)</td>
</tr>
<tr>
<td>3 latency</td>
<td>2.17</td>
<td>16.52</td>
<td>1.41</td>
<td>0.53</td>
<td>0.24</td>
<td>2.37</td>
<td>1.56</td>
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<tr>
<td></td>
<td>0.15</td>
<td>0.001</td>
<td>0.24</td>
<td>0.75</td>
<td>0.94</td>
<td>0.045</td>
<td>0.17</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.64)</td>
<td>(0.85)</td>
<td>(0.087)</td>
<td>(0.21)</td>
</tr>
<tr>
<td>N2 amplitude</td>
<td>0.38</td>
<td>0.11</td>
<td>0.83</td>
<td>5.34</td>
<td>0.66</td>
<td>0.84</td>
<td>2.73</td>
</tr>
<tr>
<td></td>
<td>0.54</td>
<td>0.74</td>
<td>0.37</td>
<td>0.001</td>
<td>0.65</td>
<td>0.52</td>
<td>0.024</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.004)</td>
<td>(0.56)</td>
<td>(0.48)</td>
<td>(0.048)</td>
</tr>
<tr>
<td>3 amplitude</td>
<td>7.38</td>
<td>0.01</td>
<td>1.25</td>
<td>9.81</td>
<td>0.16</td>
<td>1.34</td>
<td>0.91</td>
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<tr>
<td></td>
<td>0.014</td>
<td>0.915</td>
<td>0.278</td>
<td>0.000</td>
<td>0.978</td>
<td>0.256</td>
<td>0.479</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.000)</td>
<td>(0.904)</td>
<td>(0.271)</td>
<td>(0.447)</td>
</tr>
</tbody>
</table>

Fig. 1. Grand mean ERPs for controls and schizophrenics. A: 3° target and total non-target. B: 90° target and total non-target.
easy target, N2 measured at Oz occurred at a latency of 244.3 msec ± 32.1 in the controls and at a latency of 296.1 msec ± 59.9 for the schizophrenics. The between-group difference was 51.8 msec \( (P < 0.05) \). For the difficult discrimination, N2 latency at Oz was 270.9 msec ± 26.4 for the controls and 314.3 msec ± 50.4 for the schizophrenics. The difference between groups was 43.4 msec \( (P < 0.05) \). Over all subjects, N2 latency was 22.4 msec longer following the 3° target than following the horizontal target \( (P < 0.05) \). The group × angle interaction was not significant (Table I).

P3 latency at Pz occurred significantly later following the difficult 3° target (389.9 msec) than after the easy horizontal target (365.1 msec; \( P < 0.001 \)). The P3 latencies for the patients at Pz were

**TABLE II**

Behavioral data. Standard deviations in parentheses.

<table>
<thead>
<tr>
<th></th>
<th>3°</th>
<th>Preceding non-target</th>
<th>90°</th>
<th>Preceding non-target</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Correct responses (artifact free)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenics</td>
<td>21.7</td>
<td>23.2</td>
<td>22.4</td>
<td>22.4</td>
</tr>
<tr>
<td></td>
<td>(3.94)</td>
<td>(4.34)</td>
<td>(3.86)</td>
<td>(3.65)</td>
</tr>
<tr>
<td>Controls</td>
<td>26.6</td>
<td>26.7</td>
<td>27.9</td>
<td>26.5</td>
</tr>
<tr>
<td></td>
<td>(4.11)</td>
<td>(2.26)</td>
<td>(2.72)</td>
<td>(3.20)</td>
</tr>
<tr>
<td><strong>Errors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenics</td>
<td>3.8</td>
<td>1.8</td>
<td>2.5</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>(4.10)</td>
<td>(2.29)</td>
<td>(3.06)</td>
<td>(2.52)</td>
</tr>
<tr>
<td>Controls</td>
<td>1.8</td>
<td>(0)</td>
<td>0.5</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>(2.85)</td>
<td>(0)</td>
<td>(0.70)</td>
<td>(1.52)</td>
</tr>
<tr>
<td><strong>Reaction time (msec)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenics</td>
<td>662.34</td>
<td></td>
<td>632.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(200.37)</td>
<td></td>
<td>(200.36)</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>592.02</td>
<td></td>
<td>525.83</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(151.24)</td>
<td></td>
<td>(102.1)</td>
<td></td>
</tr>
</tbody>
</table>

375.2 msec ± 46.0 for the easy target and 406.7 msec ± 54.4 for the difficult target \( (P < 0.02) \). For the controls these values were 354.9 msec ± 33.3 for the easy horizontal stimulus and 373.1 msec ± 41.7 for the 3° stimulus \( (P < 0.01) \). The between-group difference showed a trend but was not significant \( (P = 0.15) \).

N2 amplitude varied over the scalp \( (P < 0.005) \). This difference was a consequence of a significantly less negative frontal voltage compared to the other 5 electrodes \( (P < 0.01; \text{Tukey}) \). The mean voltages were: Fz, 0.21 μV; Cz, 0.89 μV; Pz, 0.90 μV; Oz, 1.17 μV; P3, 1.01 μV; P4, 1.18 μV. Voltage differences between the remaining 5 electrodes did not approach significance.

P3 amplitude was significantly reduced in the schizophrenic patients (Fig. 1). For controls, mean P3 voltage at Pz was 6.99 μV for the 3° target and 7.84 μV for the horizontal target. These values for the patients were 5.03 μV for the difficult target and 4.51 μV for the horizontal target. The voltage difference for the controls between easy and hard target was not significant \( (P < 0.05) \). The electrode effect was due to larger voltages at the parieto-central electrodes compared to the frontal and occipital locations.

Table II presents the behavioral data. Schizophrenics made more errors than the controls \( (P <
0.005). The diagnosis by stimulus interaction was not significant. Both groups missed 1.3 more difficult targets than easy targets. The patients also had more eye movement artifact than the controls, resulting in fewer artifact-free correct responses for the patients in each stimulus category \( (P < 0.001) \).

The patients responded more slowly than the controls to both stimuli although the between-group difference was not significant (Table II). Across all subjects RTs were shorter to the 90° target than the 3° target \( (P < 0.005) \). The controls responded significantly more quickly to the horizontal target \( (P < 0.01) \) than to the near vertical target, while the schizophrenics showed a trend in this direction \( (P < 0.2) \).

**Discussion**

The central observation in this study is an N2 component of normal amplitude but prolonged latency in schizophrenic patients. These results differ from those of Pfefferbaum et al. (1984) who reported that schizophrenics had a decreased N2 amplitude at Cz to both deviant targets and deviant non-targets, but that the patients did not differ from controls in N2 latency. This discrepancy is puzzling insofar as both experiments presented deviant visual targets at approximately the same frequency (14% for both target and deviant non-target in their study, 12.5% for each target here). However, in the Pfefferbaum study both target and non-target were easy to distinguish from each other and equally easy to distinguish from the standard. Secondly, half of their patients were taking neuroleptics. Other reasons for the discrepancy may concern the small patient samples in both studies and difficulties in measuring the N2 peak.

The prolonged N2 latency in schizophrenics suggests that the stimulus classification process is slower in these patients. A slower stimulus classification process provides some explanation for the widely observed slower reaction times in schizophrenics, as N2 always precedes RT in target detection tasks (Ritter et al. 1979; Renault et al. 1982). The increased N2 latency in schizophrenics (43.4 msec) accounts for 62% of the between-group RT difference (70.3 msec) to the 3° stimulus and 49% of the RT difference to the horizontal target (51.8/106.2). The slower reaction times in schizophrenics thus result at least in part from a slower stimulus evaluation process that can be detected electrophysiologically. Other factors contributing to the prolonged RTs in schizophrenic patients may include a longer response selection process (McCarthy and Donchin 1981) and a slower motor response.

N2 latency was studied at Oz because previous work by Simson et al. (1976, 1977) had shown that N2 amplitude following visual stimuli was greatest at the occipital electrode. This result, largely confirmed here, facilitated peak selection.

It is noteworthy that the P3 amplitudes recorded in our controls in response to non-targets in this paradigm were larger than the P3 amplitudes typically recorded to non-targets in the 'oddball' paradigm. This result is probably a consequence of the similarity between the 3° target and the vertical non-target. The subjects had to attend closely to all stimuli in order to detect the 3° targets. The vertical stimuli thereby became to some extent 'targets' and elicited atypically large P3 peaks.

A clear-cut reduction in P3 amplitude in schizophrenics to rare, task-relevant stimuli has been consistently reported (Pass et al. 1980; Roth et al. 1980). In addition, the controls had a larger (though not significant) P3 amplitude to the easy target compared to the difficult target, whereas the patients' responses to the 90° target were slightly smaller than their responses to the 3° target. A similar finding of increasing P3 amplitudes in controls in response to increasing stimulus incentive value, and no increase in P3 amplitudes in schizophrenics to these incentives, has been reported using a different paradigm with these same patients (Brecher and Begleiter 1983). This type of experiment using a series of graded P3 eliciting stimuli accentuates the P3 amplitude differences between schizophrenics and controls. Strandborg et al. (1984) have similarly reported that schizophrenic children did not respond to increased information processing demands with corresponding changes in associated ERP measures.
Kovelman and Scheibel (1984) and Bogerts et al. (1985) have drawn attention to the hippocampus as an anatomic candidate for a schizophrenic 'lesion.' Their observation is supported by electrophysiological studies which have located a possible generator for P3 in the hippocampus and hippocampal gyrus (Halgren et al. 1980; Okada et al. 1983). The finding of a diminished P3 in schizophrenics in a variety of paradigms in all 3 sensory modalities supports the view that this structure may be abnormal in at least a subset of schizophrenic patients. These structures receive input from multiple 'higher' cortical centers, are an integral part of the limbic system and are critically involved in recent memory and knowledge acquisition. An abnormality in a sub-organ of the brain involved in both affective and cognitive processes as well as learning and memory would account for many of the central symptoms of schizophrenia. To the extent that these structures integrate perceptions of the external world with internal homeostatic systems, they can be viewed as possible loci for the loss of 'reality testing' and the loss of 'ego boundaries' so commonly seen in schizophrenia.

McCarthy (1985) has recently identified a second intracranial generator for P300 in the frontal lobe. The contribution of each source of electrical activity to the P300 measured at Pz is currently unknown. Decreased frontal blood flow has been reported in schizophrenics (Ingvar and Franzen 1974) and decreased frontal glucose uptake has been observed in schizophrenics through the use of positron emission tomography (Buchsbaum et al. 1982). These findings suggest that the P300 deficit in schizophrenia may also reflect frontal pathology.

The findings reported here extend the profile of abnormal evoked potentials in schizophrenic patients to include the N2 component. Further work needs to be conducted to examine N2 in conditions of inattention in schizophrenic patients, and to further explore the relation of the N2 component to the P3 which follows. The import of these components in interpreting schizophrenia awaits further electrophysiological exploration of information processing and a more detailed profile of ERP abnormalities in schizophrenia and other brain diseases.

Résumé

La composante N2 du potentiel lié à l'événement chez des patients schizoides

Les potentiels liés à l’événement (ERP) à des stimulus cibles visuels peu fréquentes et difficiles ont été enregistrés chez des patients schizoides non médicamenteux et chez des témoins d'âge comparable. Des ondes N2 de différence ont été calculées en soustrayant l'ERP à un stimulus non cible à cadence rapide de l'ERP à chacune des cibles. Une composante N2 a pu être identifiée dans les configurations de ces ondes de différence. Tous les sujets ont montré une latence plus grande pour les pics N2 et P3 à la cible difficile que pour la cible facile. Les patients schizoides avaient une latence des pics N2 plus grande que les témoins pour les deux types de cibles. Par rapport aux témoins, les sujets schizoides présentaient également une réduction de l'amplitude des pics P3 avec les deux cibles.

La plus grande latence N2 pour les schizoides rend pour une part importante compte de l'allongement habituellement observé dans ce groupe. L'allongement de la latence de N2 apparaît être une anomalie de plus du potentiel évoqué chez les patients schizoides.

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References


