The N2 event-related potential reflects attention deficit in schizophrenia

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Abstract

Schizophrenia involves deficits in detection and filtering of irrelevant stimuli. The N2 event-related potential (ERP), most likely reflecting classification of deviant stimuli, remains largely unstudied in this group. Recently, we reported that N2 amplitude correlated highly with reduced neocortical and medial temporal lobe volumes in schizophrenics. However, little is known about the functional properties of N2 in schizophrenics. To that end, the latency and amplitude of N2 were assessed in schizophrenic and control subjects to differently pitched tones. Subjects pressed a button in response to low probability (p = .15) target tones interspersed among high probability standard tones. Tones were either NEAR (1.4 kHz standard, 1.5 kHz target) or FAR (1 kHz standard, 1.5 kHz target) in pitch. N2 was measured from difference waveforms, subtracting ERPs on a simple reaction time task (target p = 1.0) from those of the detection task. Schizophrenics performed the detection task nearly as well as controls in the FAR condition, and more poorly in the NEAR condition. Schizophrenics displayed virtually no N2 amplitudes in either condition. The results are interpreted as electrophysiological signs of disturbance in stimulus classification and attention processes in schizophrenia directly related to pathology of N2 neural generators, independent of sensory or detectability problems.

Keywords: Attention; Event-related potentials; N2; Schizophrenia

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1. Introduction

1.1. Early attentional deficit

Schizophrenia involves deficits in processing information in a focused manner. Early attentional deficit models propose the problems in attention and thought processes in schizophrenia are due to the inability to filter irrelevant sensations in a hierarchical information-processing system from access to a limited capacity central processor. Subsequent higher-order analyses are performed inadequately under load pressure; too many stimuli need to be analyzed and information is only partially processed before new information arrives (Frith, 1981; Johnson, 1985; McGhie & Chapman, 1961; Miller, Sacuzzo & Braff, 1979; Sacuzzo & Braff, 1981; Venables, 1964). Abnormalities in various short-latency electrophysiological measures in schizophrenia have been proposed to reflect deficits in the automatic detection and filtering of deviant stimuli including the startle/eyeblink response (Graham, 1975; Braff & Geyer, 1978; Braff, Stone, Callaway, Geyer, Glick & Bali, 1978); P50, a positive event-related potential (ERP) generated in the brain approximately 50 ms post-stimulus which is reduced in amplitude to the second of two identical clicks in controls but not schizophrenics (e.g., Adler, Pachtman, Franks, Pecevich, Waldo & Freedman, 1982; Freedman, Adler, Waldo, Patchman & Franks, 1983); MMN, a negative ERP at approximately 150 ms related to stimulus deviance (Näätänen, Gaillard & Mäntysalo, 1978; Ward et al., 1993); and P3a, a positive ERP at approximately 250 ms possibly related to orienting behavior (Grillon, Courchesne, Rezvan, Geyer & Braff, 1990; Paavilainen, Karlsson, Reinikainen & Näätänen, 1989; Squires, Squires & Hillyard, 1975).

1.2. Late attentional deficit

Schizophrenia also involves deficits in the ability to classify and analyze information at the higher-order cognitive level (Callaway & Naghdi, 1982; Gjerde, 1983; Oltmanns, 1978; Yates, 1966). Analysis is compromised primarily by time pressure; due to misallocation of attentional resources, faulty cognitive processing and/or slowed processing, information is not properly assessed before new information arrives (see Schwartz (1982) as applied to language and thought disorder).

The long-latency ERPs N2 and P3 reflect processing in the controlled, selective attentional stream (see Triesman, 1969; Shiffrin & Schneider, 1977; Norman, 1984 for discussion of cognitive streams), and are typically evoked by the active discrimination of target stimuli from various other stimuli (Hillyard, Hink, Schwent & Picton, 1973; Picton and Hillyard, 1974). N2 appears to reflect deviance from a centrally maintained standard, and may be the best ERP index of higher-order complex discrimination and stimulus categorization (e.g. Ritter, Simson, Vaughan & Macht, 1982; Ritter, Simson & Vaughan, 1983; Näätänen and Gaillard, 1983; Hoffman, 1990). Although P3 deficits in schizophrenia are robust (Roth, 1977; Begleiter and Porjesz, 1986; McCarley, Faux, Shenton, Nestor & Adams, 1991), P3
likely reflects cognitive activity which occurs after stimulus classification. P3 may reflect some controlled operations related to stimulus analysis, but reaction times may precede P3 if speeded responses are required, suggesting P3 activity does not reflect primary stimulus categorization (Kutas, McCarthy & Donchin, 1977; Ford, Pfefferbaum, Tinklenberg & Kopell, 1982). P3 may primarily reflect the post-perceptual resetting of short-term working memory traces of expected environmental stimuli (Donchin, 1981). Since N2 appears to be more tightly coupled to stimulus categorization, it may reflect controlled operations occurring relatively early in controlled processing, and therefore index faulty processing at an earlier stage than does P3.

The amplitudes of N2 and P3 increase in control subjects as stimuli become progressively greater than threshold and/or more discrepant from one another (Hillyard, Squires, Bauer & Lindsey, 1971; Novak, Ritter, Vaughan & Wiznitzer, 1990; Salisbury, O’Donnell, McCarley, Nestor, Faux & Smith, 1994). Invariance of ERP measures in response to parametric manipulations, despite changes in other functional measures such as reaction time or task performance, imply structural rather than functional deficits. Moreover, this pattern may imply damage to or dysfunction of underlying neural generators.

To date, the N2 component to auditory stimuli remains largely unstudied in schizophrenia. Roth, Horvath, Pfefferbaum, Berger and Kopell (1980) and Barrett, McCallum and Pocock (1986) reported no significant differences in N2 elicited by target stimuli between schizophrenics and controls, but their results may have been confounded by measuring N2 from the raw waveforms, where P2 and N2 overlap, rather than from subtraction waveforms (see Hansen & Hillyard, 1980; Simson, Ritter & Vaughan, 1985 for consideration of this problem). Two definitive papers by Simson, Vaughan and Ritter (1976, 1977) demonstrated that N2 measured from subtraction waveforms was morphologically identical to those measured from omitted stimulus paradigms, i.e. detection of missing stimuli, hence no sensory components. Ogura, Nageishi, Matsubayashi, Omura, Kisimoto and Shimokochi (1991) found that N2 amplitude recorded from mid-line electrodes was indeed reduced in schizophrenics when measured from the subtraction waveform (target ERP-standard ERP). Recently, we (O’Donnell et al., 1993) confirmed this overall N2 amplitude reduction in schizophrenia utilizing a full scalp recording (32 electrodes). Abnormalities in N2 amplitude correlated highly with reduced neocortical and medial temporal lobe volumes in schizophrenics. Whereas that structural study demonstrated links between brain pathology and reduced N2 amplitude, little is known about the functional properties of N2 in schizophrenics. The observed reduction in N2 amplitude might still be more related to performance and motivational factors than to damage to neural generators. Therefore, the latency and amplitude of the N2 component elicited by correctly detected target stimuli, reaction times, and task performance were assessed in schizophrenics (including a subset of our previous schizophrenic sample) while task difficulty was manipulated by changing the pitch disparity of the standard and target tones in an auditory ‘odd-ball’ task.
2. Method

2.1. Subjects

The schizophrenic group consisted of eight right-handed chronic-course male patients (seven from previous study, mean duration of illness: 19 ± 5 years) from the Brockton VAMC. All patients were medicated with a mean daily dose equivalent to 956.9 mg day⁻¹ CPZ, and met DSM-IIIR (American Psychiatric Association, 1987) and RDC (Spitzer, Endicott & Robins, 1978) criteria for schizophrenia. All patients were administered the Schedule for Affective Disorders and Schizophrenia (SADS; Spitzer & Endicott, 1978), the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984), the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1981) and the Thought Disorder Index (TDI; Solovay et al., 1986). This information, in conjunction with chart review and clinical interviews, was used to confirm diagnoses. Subjects showed predominately positive symptoms (mean SAPS 12 (±2), mean SANS 9 (±3)), as well as a high degree of thought disorder (mean TDI 84.12 (± 67.19)).

The control group consisted of eight right-handed males recruited from the local community. Handedness was assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). No subject had a history of neurological involvement, head trauma, drug or alcohol dependence, or Axis II diagnosis. Groups were matched for age (CON 39.8 ± 10.5 years, SZ 39.0 ± 5.4 years, \( t_{14} = 0.18, \ p = .86 \)) as well as handedness and gender. All subjects gave informed consent and received payment.

2.2. Stimuli

Three pure tone binaural stimuli were generated: 1 kHz, 1.4 kHz and 1.5 kHz. Stimuli were delivered over insert earphones at 97 dB nHL against 80 dB white noise. Tones were 50 ms in duration with 20 ms rise–fall times, presented every 1.3 s. For discrimination tasks, two pitch separation combinations were used. NEAR consisted of the 1.4 and 1.5 kHz tones, FAR consisted of the 1 and 1.5 kHz tones. The 1.5 kHz tone was always the target stimulus. The probability of occurrence of the target (1.5 kHz) tone was 0.15, pseudo-randomly distributed among the standard tones. For a simple reaction time (SRT) task, 100 trials of the 1.5 kHz tone (\( p = 1.0 \)) were presented.

2.3. Procedure

Subjects listened to the tones over earphones, and were required to push a mouse button with the right index finger as quickly as possible to the target tone. Task order (NEAR, FAR discriminations, SRT) was counter-balanced. Reaction times were stored as well as response outcomes.
2.4. Recording system

Electroencephalographic (EEG) activity was recorded from 28 electrodes in pre-configured caps, according to the International 10-20 system (Jasper, 1958), excluding T1 and 2. Additional electrodes were placed at Oz, FTC1 and 2 (located in the center of the grid formed by F3/4, F7/8, T3/4 and C3/4), TCP1 and 2 (located in the center of the grid formed by C3/4, T3/4, T5/6 and P3/4), and CP1 and 2 (located between C3/4 and P3/4). Two electrodes placed along the vertical axis of the eye monitored blinks. Similarly, lateral eye movements were monitored with two electrodes placed along the horizontal axis. Linked ears were used as the reference. All electrodes were tin. Impedance was less than 3 KOhms at all sites. Epochs were of 900 ms duration, including a 100 ms pre-stimulus baseline, digitized into 256 points.

All epochs were baseline corrected through subtraction of average pre-stimulus voltage at each lead. Eye movement and blink artifact were mathematically covaried from each epoch according to the procedure of Semlitsch, Anderer, Schuster and Presslich (1986). Any epoch containing ±50 μV was subsequently rejected from averaging. Averages were constructed for correctly detected targets in the discrimination and SRT tasks. Difference waveforms were constructed by subtracting SRT waveforms from discrimination waveforms, according to the procedure of Ritter and colleagues (e.g. Ritter, Simson & Vaughan, 1983; Novak, Ritter, Vaughan & Wiznitzer, 1990). This, in effect, removes major sensory and motor contributions from the discrimination waveform, leaving the endogenous components.

3. Results

3.1. Behavioral measures

Mean behavioral measures are presented in Table 1. The number of correctly detected targets was significantly smaller when stimuli were NEAR in pitch

<table>
<thead>
<tr>
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<th>Near</th>
<th>Far</th>
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<tbody>
<tr>
<td><strong>Hits per 60 targets</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>54.3 (7.7)</td>
<td>59.9 (0.4)</td>
</tr>
<tr>
<td>Schizophrenics</td>
<td>38.6 (20.1)</td>
<td>56.9 (5.4)</td>
</tr>
<tr>
<td><strong>Errors per 400 trials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>8.8 (9.4)</td>
<td>3.4 (4.4)</td>
</tr>
<tr>
<td>Schizophrenics</td>
<td>37.75 (35.8)</td>
<td>5.8 (6.7)</td>
</tr>
<tr>
<td><strong>Reaction time (ms)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>439 (58)</td>
<td>361 (37)</td>
</tr>
<tr>
<td>Schizophrenics</td>
<td>635 (138)</td>
<td>562 (161)</td>
</tr>
</tbody>
</table>
Fig. 1. Individual subject and grand averaged ERP difference waveforms recorded from the vertex (Cz) site (correctly detected target stimuli minus simple reaction time waveform). Note that voltage scales are individually scaled, but that grand averages are at the same scale for comparison purposes. Note fairly well-defined N2 potentials (marked) in controls, but not in schizophrenics.

separation ($F_{1,14} = 11.59, p = 0.004$). Schizophrenic subjects performed worse than control subjects with regard to correctly detected targets ($F_{1,14} = 4.70, p = 0.048$), particularly in the NEAR condition, although the interaction between group and pitch was not significant ($F_{1,14} = 3.24, p = 0.093$).

Errors were calculated by summation of missed targets and false alarms. Both groups made more errors in the NEAR condition than in the FAR condition ($F_{1,14} = 9.21, p = 0.009$). Schizophrenic subjects made significantly more errors than controls ($F_{1,14} = 4.77, p = 0.046$), and their performance was affected more by the pitch manipulation ($F_{1,14} = 4.67, p = 0.048$), largely due to an increase in the number of false alarms in that condition.

Reaction times were significantly slower in both groups during the NEAR condition ($F_{1,14} = 8.80, p = 0.010$). Overall reaction times were significantly slower in the schizophrenic group as well ($F_{1,14} = 13.63, p = 0.002$).

3.2. N2 ERP

Subtraction waveforms from each subject and the grand average for each condition are presented in Fig. 1. For analyses, N2 was scored automatically as the most negative point between 100 and 400 ms post-stimulus. In the case of a
Table 2
N2 latencies and amplitudes from difference waveforms at Cz

<table>
<thead>
<tr>
<th></th>
<th>Mean peak latencies (ms)</th>
<th>Mean peak amplitudes (µV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Near</td>
<td>212.1</td>
<td>-10.1</td>
</tr>
<tr>
<td>Far</td>
<td>192.0</td>
<td>-15.9</td>
</tr>
<tr>
<td>Schizophrenics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Near</td>
<td>224.3</td>
<td>-3.8</td>
</tr>
<tr>
<td>Far</td>
<td>197.4</td>
<td>-3.6</td>
</tr>
</tbody>
</table>

biphasic N2 in individual subject averages, the later peak was selected. In the case of multiple negative peaks, the peak immediately preceding P3 was selected. As evident in the individual and grand averages in the schizophrenic group, there was virtually no N2 activity. Owing to the small size of N2 in the schizophrenic group, the potential is poorly distinguishable from background noise. Consequently, N2 amplitude and latency measures were restricted to Cz, and are presented in Table 2. Effects on N2 were analyzed with mixed-model MANOVAs with group as the between subject factor, and pitch the within subject factor. There were no significant effects on N2 latency. Whereas N2s in controls were well defined and modulated by signal detectability, those of schizophrenics were quite small, and about equal in both pitch conditions. Overall, N2 in schizophrenics was significantly smaller than in controls \( (F_{1,14} = 17.33, p = 0.001) \). The effects of the pitch manipulations were significant \( (F_{1,14} = 15.09, p = 0.002) \), but interacted with group \( (F_{1,14} = 16.72, p = 0.001) \). Separate within-groups analyses revealed that N2 amplitudes were smaller with less pitch separation in controls \( (F_{1,2} = 20.85, p = 0.003) \), but not schizophrenics \( (F_{1,2} = 0.04, p = 0.840) \). Voltage from all electrodes were measured at the point in time marked on the grand averages in Fig. 1. The resultant scalp distributions are presented in Fig. 2. Note the parametric effect on N2 amplitude in control subjects, but not schizophrenics, and a more frontal scalp distribution in the schizophrenics, although the reader is again cautioned that the scalp distribution of the schizophrenic group may contain major contributions from activity other than N2.

3.3. P3 ERP

For a complete discussion of these and other parametric effects on P3 in schizophrenics and controls, see Salisbury, O'Donnell, McCarley, Nestor, Faux and Smith (1994). P3 latency was measured from Pz at peak. P3 amplitude was measured as the mean voltage from 25 ms before Pz peak latency to 25 ms after from Fz, Cz, and Pz. These measures are presented in Table 3. Effects on P3 were analyzed using mixed model repeated measures MANOVAs with pitch and electrode site as within subject factors, with Huynh–Feldt epsilon used to adjust degrees of freedom for the electrode site factor. P3 latency was not significantly different between groups, and was significantly shorter in both groups with greater
Fig. 2. Topographic maps of N2 amplitude from grand average difference waveforms. Each point on the surface reflects the peak amplitude of N2 at that point on the head. This map reflects N2 distribution at one static time interval, namely time of peak N2 amplitude at Cz from the grand averaged waveform (controls: FAR 192.5 ms, NEAR 192.5 ms; schizophrenics: FAR 192.5 ms, NEAR 203.7 ms).

Pitch separation ($F_{1,14} = 17.90$, $p = 0.001$). P3 amplitude was not significantly different between groups, nor affected by pitch. Of primary importance, however, was an interaction between pitch and group ($F_{1,14} = 4.66$, $p = 0.049$). P3 amplitude in control subjects displayed a strong trend towards larger values with greater pitch separation ($F_{1,7} = 4.45$, $p = 0.073$), whereas P3 amplitude in schizophrenics was unaffected. Scalp distributions were markedly distributed towards Pz in both groups ($F_{2,28} = 18.47$, $p < 0.001$, $e = 0.67$).
4. Discussion

Schizophrenics performed nearly as well as controls on the FAR detection task, with only minor variations in the number of hits and errors, but rather worse on the NEAR task (see Table 1). Despite these parametric effects on task performance in the schizophrenic group, which suggest that their behavior is functionally modulated by task parameters even more so than controls, there were no parametric effects on N2 amplitude in this group. In fact, ERP responses in the schizophrenic group to only correctly detected targets revealed virtually no N2 activity at all. These data are congruent with the hypothesis that N2 reductions in schizophrenics are not due to poorer task performance or lack of attention to task, but to abnormalities of the neural substrates of N2, and is compatible with our previous demonstration of correlations between reduced medial and lateral temporal lobe volume and N2 deficits in schizophrenia.

The performance of the schizophrenic subjects on the task was more affected by the pitch manipulation than that of controls. Schizophrenic subjects made more errors and less correct detections than controls on the NEAR condition, but groups were quite comparable on the FAR condition. This data suggests that schizophrenics show faulty stimulus classification processes in late stages of selection when task demands are high. The N2 reductions observed in schizophrenics in this study are associated with performance problems, particularly in the NEAR condition, which suggests that the cognitive operations presumably compromised by damaged/dysfunctional neural substrate in schizophrenics can be compensated for if the task is relatively easy, but not if the task is difficult. Schizophrenics may need to use intensive attention processes to perform the more difficult classification task, controlled operations being slowed by task difficulty in contrast to automatic operations which presumably use large capacity, parallel processors. Slade (1971) has argued that schizophrenic subjects are disproportionately affected by increases in task complexity, and this may be paralleled by the effects in this study of task difficulty on task performance. These disproportionate effects may be due to damaged neural substrate, with corresponding cognitive operations necessary for difficult tasks compromised.

Although schizophrenics show abnormalities in N2, there appears to be relatively intact information transmission to P3 generators, with comparable latencies
and latency effects in both groups. Both N2 and P3 potentials remain reduced in amplitude in schizophrenic subjects in the FAR condition, despite task performance similar to controls. N2, but not P3, amplitudes differ between groups in the NEAR condition, but the lack of P3 difference is likely due to a reduction of P3 amplitude to near schizophrenic levels in the controls in this condition (cf. Group × pitch interaction). The possibility arises that reductions of P3 amplitude in schizophrenics may be related to reductions in N2, although as mentioned above, there appears to be intact transmission temporally. N2 and P3 show different scalp distributions, indicative of different neural generator configurations, and whereas P3 correlated only with superior temporal gyrus volume in our previous examination (O’Donnell et al., 1993), N2 was also correlated with medial temporal lobe structures including hippocampus and parahippocampal gyrus. The inference from these data is that N2 and P3 have different neural sources, which presumably reflect different cognitive operations, although these operations may be wholly related. The cognitive deficits observed in schizophrenics may be attributable in some part to pathology of cortical areas and, in turn, reflected in abnormalities of N2 and P3, and may be compensated for during task performance if the task demands are relatively light.

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