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Auditory Selective Attention and Event-Related Potentials in Schizophrenia

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Brain ERPs were recorded in ten unmedicated schizophrenic patients and age- and sex-matched healthy controls during a multidimensional listening task. Patients showed a marked reduction in a long-duration attention-related negative ERP component, termed 'processing negativity' (PN), which was elicited by attended stimuli. The amplitude of PN was significantly correlated with SANS and SAPS scores of schizophrenic symptoms. The P300 component was also reduced in amplitude in patients, and was significantly correlated with SANS ratings of negative thought disorder. These findings provide neurophysiological evidence of impairment in the maintenance of selective attention and the cognitive processes associated with target detection among schizophrenic patients. The reduced PN in schizophrenics implicates frontostriatal pathways in the aetiology of attentional deficits in schizophrenia.

Attentional deficits have been seen as a fundamental feature of schizophrenic psychopathology since Bleuler first described the 'group of schizophrenias' 80 years ago (Bleuler, 1911). However, the impaired performance frequently observed when schizophrenics perform attentional tasks could also reflect deficits in motivation or organisation of motor activity (Nuechterlein & Dawson, 1984). Neurophysiological indices of attention can be derived from scalp recordings of event-related potentials (ERPs), using paradigms which allow the effects of selectively attending to relevant stimuli to be distinguished from concurrent changes in general alertness or the effects of making an overt response (Hillyard *et al*, 1973). Further studies in healthy subjects have identified an early-onset negative component, termed processing negativity (PN), which is elicited by auditory stimuli to which attention is directed (Naatanen & Michie, 1979; Hansen & Hillyard, 1980). A later, parietal-maximal positive component, termed P300, is elicited by infrequent, task-relevant stimuli, which require a cognitive and/or motor response (Pritchard, 1981).

Hansen & Hillyard (1983) demonstrated that the PN component is extremely sensitive to the ease with which normal subjects discriminate auditory stimuli that differ on simple physical cues. Subjects listened to tone pips presented through earphones to either ear. Half the tones in each ear were of low pitch, the other half of higher pitch. Subjects were required to attend to a particular pitch/ear combination and press a button whenever they detected an occasional longer-duration (100 ms) 'target' tone among more frequently occurring 'standard' (50 ms) tones. By analysing ERPS elicited by standards, which never required an overt behavioural response, electrophysiological measures were derived which were uncontaminated by neural processes underlying response preparation. Standards which matched the target on an easily discriminated cue (e.g. tones delivered to same ear as the target) elicited an early-onset PN compared with tones delivered to the unattended ear. Standards which also matched the target on the more difficult to distinguish cue (e.g. tones of the same pitch and delivered to the same ear as the target) elicited an additional later-onset, long-duration PN. Standards delivered to the unattended ear elicited similar ERPs, regardless of pitch. Results obtained using this task are consistent with the operation of rapid, early selection, based on easily discriminated stimulus characteristics (Hillyard & Hansen, 1986).

Few studies have utilised selective attention paradigms in investigations of schizophrenia, and none have evaluated the late PN component. Previous studies have reported that significant early PN, around 100–200 ms after the stimulus, is elicited by attended stimuli in medicated (Baribeau-Braun *et al*, 1983; Hiramatsu *et al*, 1983), but not unmedicated (Kameyama *et al*, 1987) schizophrenics.

There is an extensive literature attesting to reduced P300 amplitudes in schizophrenics, obtained in a variety of experimental paradigms using auditory, visual and somatosensory stimuli (Pritchard, 1986). Some investigators have reported associations between P300 amplitude and clinical improvement following neuroleptic medication (e.g. Duncan *et al*, 1987), while P300 amplitude reduction has also been associated with other psychiatric diagnoses, such as depression and dementia. Further studies in unmedicated patients are required to establish whether reduced P300 amplitude reflects a generalised cognitive deficit or specific schizophrenic symptoms.

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In the present study, a multidimensional listening task was used to examine hypotheses concerning attentional deficits in schizophrenia. For example, Venables (1964) suggested that schizophrenics are unable to ignore irrelevant stimuli. Support for this hypothesis would be provided if schizophrenics' ERPs showed a PN differential on the unattended ear between stimuli which were of the same pitch as the target and those which were not.

To assess the utility of ERP measures in investigating attentional deficits in schizophrenia, we wished to examine the relationship between ERP measures and ratings of psychopathology. Despite the small sample size of the present study, correlations were investigated between measures of PN and P300 amplitude and ratings of thought disorder and total ratings of schizophrenic symptoms.

Method

Three in-patients and seven out-patients who met DSM-III (American Psychiatric Association, 1980) and ICD-9 (World Health Organization, 1978) criteria for chronic schizophrenia were tested (9 men, one woman, mean age 31.0 years, range 22–58). All of the patients had received no antipsychotic medication during the previous six months and three had never received neuroleptics. Previously medicated patients were medication-free because of non-compliance or because their symptoms were not alleviated by neuroleptics. Mean duration of illness was 9.4 years (range 2–20). Eight of the patients were classified as 'chronic residual' under DSM-III, and the two remaining patients were diagnosed as 'chronic paranoid' and 'chronic with acute exacerbation, disorganised type'. At the time of testing, mean total symptom score, assessed using the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962), was 37.8 (range 26–53), reflecting moderate symptoms. A urine drug screen was performed to exclude patients whose symptoms may have been related to acute drug abuse.

Ten age- and sex-matched healthy controls were selected from hospital staff and volunteers who were well known to the research team. None had a history of psychiatric illness or drug abuse. Audiometric screening was carried out in both groups of subjects to exclude those with significant hearing loss.

Patients were interviewed by an experienced research psychiatrist (SVC), who rated patients on the Scales for Assessment of Positive and Negative Symptoms of schizophrenia (SAPS and SANS, respectively; Andreasen, 1982, 1984) based on information obtained during a structured interview and from case notes. These scales include global ratings for positive 'formal' thought disorder and negative thought disorder or alogia, as well as summary scores comprising ratings of hallucinations, delusions, bizarre behaviour and positive formal thought disorder (for the SAPS) and affective flattening, alogia, avolition, anhedonia and attentional impairment (for the SANS). The rater was blind to ERP findings while carrying out the clinical assessment.

The auditory attention task employed in this study was adapted from Hansen & Hillyard (1983). Subjects listened to tone pips (75 dB sound pressure level) presented through earphones to either ear. Half of the tones in each ear were low pitch (1047 Hz) and half were high pitch (1319 Hz). For each pitch/ear combination, 28% of the tones were of longer duration (100 ms) than the remaining 'standard' tones (50 ms). Tones were delivered in random sequences at intervals of 200–500 ms, so that stimuli at each pitch/location combination occurred with equal probability. Subjects were instructed to attend to a particular pitch/location combination (e.g. high pitch/right ear) and press a button whenever they detected an occasional longer-duration 'target' tone among the 'standard' tones. Tones at each of the four pitch/location combinations were attended during different runs. Subjects completed two runs of each attention condition, one responding with the left hand and one responding with the right hand. Each run lasted approximately 1.5 mins and included approximately 30 targets.

An electroencephalogram (EEG) was recorded from electrodes at pre-frontal (Fpz), frontal (Fz), central (Cz) and parietal (Pz) locations along the midline, along with vertical and horizontal eye movements for artefact detection, all referred to a standard potential from linked ears, and amplified using a Grass Model 12 Neurodata system with a bandpass of 0.01–30 Hz (−6dB attenuation points of −6dB/octave passive filters). Overlapping EEG epochs (duration 1280 ms, including a 250 ms pre-stimulus baseline) were averaged after rejecting those contaminated by artefact (vertical or horizontal eye movements exceeding 64 μV) or incorrect behavioural responses, either targets not followed by a button-press response (misses) or button presses following non-target stimuli (false alarms). ERPs were averaged by classifying stimuli according to whether they matched or did not match the nominated target stimulus on a particular run in terms of location (referred to as L+ and L− respectively), pitch (P+, P−) and duration (D+, D−). Thus L+P+D− refers to short-duration stimuli having the same location and pitch attributes as the target (L+P+D+).

Statistical analyses were carried out using repeated-measures analysis of variance (BMDP2V), and the probabilities reported were obtained following Greenhouse–Geisser adjustment (ϵ) of degrees of freedom to allow for violation of sphericity (Vasey & Thayer, 1987). Significant interactions were examined by calculating multiple comparisons using separate error estimates for each contrast. The Bonferroni argument was used to determine significance, with family-wise α set to 0.05.

Results

Scores for positive and negative symptoms are reported in Table 1.

Schizophrenics performed the task less accurately than controls (64% v. 78% hits; $P<0.05$; 4.9% v. 1.2% false alarms; $P<0.002$) and tended to respond more slowly (means (s.d.): 618 (76) ms v. 558 (82) ms, $P=0.09$). Patterns of false alarms were examined for both groups. In controls, 27.9% of false alarms occurred 200–1500 ms following L+P+D− stimuli, versus an average of 16.3% for the other equiprobable standards. The pattern for schizophrenics was similar: 27.7% following L+P+D−

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Table 1
Global scores and total scores for ratings of positive (SAPS) and negative (SANS) symptoms

	Mean	Range
SAPS		
Hallucinations	1.0	0-3
Delusions	2.3	0-5
Bizarre behaviour	1.1	0-5
Positive 'formal' thought disorder	2.5	1-4
Total	6.9	2-14
SANS		
Affective flattening	2.4	1-3
Alogia	3.2	3-5
Avolition	3.5	3-5
Anhedonia	3.5	2-5
Attentional impairment	2.1	0-5
Total	14.7	8-22

versus an average of 16.2% following the other three classes of standard stimuli. These results suggest both schizophrenics and controls found the duration dimension most difficult to discriminate and indicate that patients were attempting to follow task instructions.

ERPS to standard tones

Group mean ERPs of controls to standard tones (Fig. 1(a)) showed an early PN (onset 60–70 ms after stimulus), elicited by L+P+ and L+P− standard stimuli, which was prominent at Fpz, Fz, and Cz electrodes. Schizophrenics showed a similar, although smaller, early PN. When measured as the mean amplitude over 100–200 ms after the stimulus, early PN was significantly larger for stimuli at the attended location (L+) than stimuli at the unattended location (L−) (stimulus main effect: $F(3,54)=19.01$, $P<0.0001$, $\epsilon=0.73$). The group × stimulus interaction was not significant ($F(3,54)=1.57$, $P=0.21$, $\epsilon=0.73$). However, a significant group × stimulus × electrode interaction was found ($F(6,108)=3.66$, $P<0.02$, $\epsilon=0.51$). Multiple comparisons at each electrode were calculated for L+ ERPs (100–200 ms epoch), and revealed significantly smaller mean (s.d.) early PN in schizophrenics (−0.50(0.69)μV) than controls (−1.37(0.61)μV) at the vertex (Cz) electrode ($P<0.05$ with Bonferroni correction).

The most striking differences between the group mean ERPs was the marked reduction of late PN in schizophrenics. The late PN was elicited by L+P+D− stimuli (i.e. the stimuli which were subjectively the most difficult to discriminate from the attended targets) in controls and was prominent at anterior scalp locations. A preliminary series of repeated-measures ANOVAs was calculated for 100 ms epochs from 200–1000 ms. No significant group main effects or interactions were observed in the 200–300 ms or 300–400 ms epochs. However, group effects were present for each subsequent 100 ms epoch, up to 1000 ms after the stimulus.

As a means of summarising the group differences in this latency range, late PN was defined and measured as the mean amplitude over the 400–1000 ms epoch. Late PN was significantly larger for L+P+D− stimuli than other standard stimuli (stimulus main effect: $F(3,54)=12.25$, $P<0.002$, $\epsilon=0.65$). The group × stimulus interaction was significant ($F(3,54)=3.72$, $P<0.04$, $\epsilon=0.88$), as was the group × electrode × stimulus interaction ($F(6,108)=3.07$, $P<0.03$, $\epsilon=0.63$): multiple comparisons were performed on mean amplitudes for L+P+ ERPs at Fpz, Fz, and Cz electrodes, and significantly reduced mean (s.d.) amplitudes in patients (0.05(0.61) v.−1.09(0.99)μV) were only found at the Fz electrode ($P<0.05$ after Bonferroni correction). There were no significant differences in late PN between L−P+ and L−P− ERPs for either controls or schizophrenics at Fpz, Fz, or Cz electrodes.

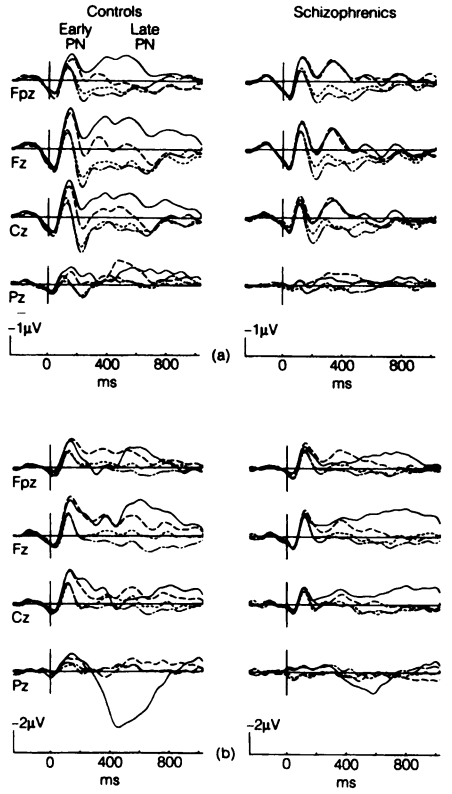


Fig. 1 Group mean ERPs recorded from midline scalp electrodes for ten unmedicated schizophrenic patients and ten healthy controls. ERPs were sorted according to whether or not stimuli matched the target on location (L+, L−) and pitch (P+, P−). (a) ERPs elicited by the short duration (D− or standard) stimuli. (b) ERPs elicited by the long duration (D+ or target) stimuli (L+P+, ——; L+P−, - - -; L−P+, —; L−P−, -·—·—·—) (negative potentials appear above the *x*-axis).

ERPs to targets

The P300 component, which was maximal for attended target (L+P+D+) stimuli at the parietal electrode in controls,

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was substantially smaller in schizophrenics (Fig. 1(b)). Both peak amplitude and mean amplitude at the Pz electrode were calculated within the 300–800 ms interval for ERPs elicited by correctly identified L+P+D+ stimuli. Both P300 amplitude measures were significantly reduced in schizophrenics compared with controls (mean (s.d.) peak amplitude: 2.31 (2.36) v. 5.24 (1.96) μV; $F(1,17)=8.80$, $P<0.01$; mean (s.d.) amplitude: 0.80 (2.27) v. 3.14 (1.52) μV; $F(1,17)=7.10$, $P<0.02$).

A substantial long-duration frontal negativity elicited by correctly detected target stimuli (L+P+D+) was apparent in both group grand means (see Fig. 1(b)). Mean amplitudes for the 400–1000 ms epoch at Fz were measured and did not differ significantly between patients and controls (2.07 (1.77) v. 1.96 (2.60)μV).

ERP measures and clinical ratings

Pearson correlations (one-tailed tests) were calculated between ERP measures and clinical ratings obtained from the SAPS and SANS. The amplitude of P300 at Pz was significantly correlated with negative thought disorder (the alogia score) ($r=-0.61$, $P<0.05$; Fig. 2), and the correlation with positive thought disorder approached significance ($r=-0.50$, $P=0.09$), but the amplitude of P300 was not significantly correlated with SAPS and SANS total scores after partialling out the correlations with ratings of thought disorder ($r=0.03$ for total negative symptoms and $r=0.13$ for positive symptoms).

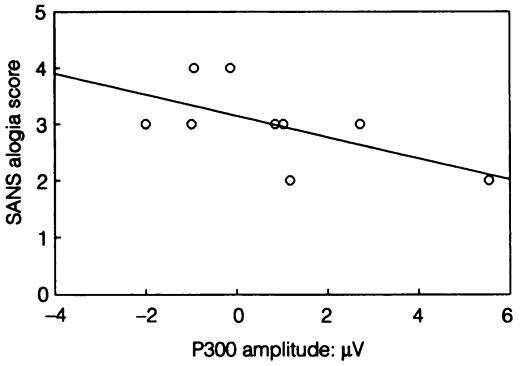


Fig. 2 SANS alogia score plotted against P300 amplitude at Pz ($r=-0.61$, $P<0.05$).

In contrast, early PN, measured at the Fz electrode as the difference between L+P+D− and L−P−D− ERPs, was significantly correlated with ratings of total positive ($r=-0.69$, $P<0.02$; Fig. 3) and negative ($r=-0.66$, $P<0.05$; Fig. 4) symptoms, and remained significant after partialling out correlations with ratings of thought disorder ($r=-0.69$ for total positive symptoms and $r=-0.72$ for total negative symptoms). A similar pattern of correlations was observed with the amplitude of late PN responses ($r=-0.77$, $P<0.005$ for total positive symptoms and $r=-0.81$, $P<0.005$ with total negative symptoms).

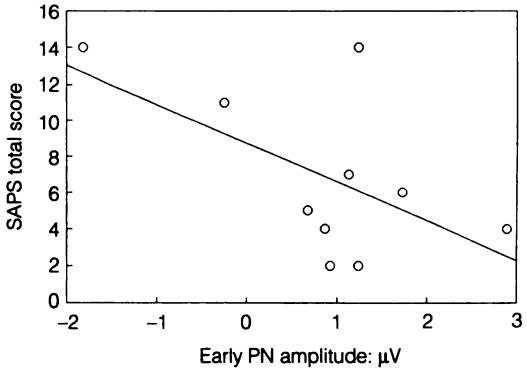


Fig. 3 SAPS total score plotted against early PN amplitude, measured as the difference between L+P+D− and L−P−D− ERPs at Fz ($r=-0.69$, $P<0.02$).

Discussion

The present study compared ERP indices of selective attention in unmedicated schizophrenics and healthy controls. As a psychiatric control group was not included, the group differences obtained in this study cannot be regarded as reflecting attentional deficits specific to schizophrenia. Investigation of patients with other psychiatric diagnoses using this task is currently being carried out in our laboratory.

By utilising a multidimensional selective listening task, we have shown that an early PN was present in both patients and controls, as reflected by significantly larger amplitudes to attended-location (L+) standards. Neither group showed any effect of pitch at the unattended location, suggesting that schizophrenics are capable of making a rapid selection on the basis of an easily discriminated feature (i.e. ear of delivery). This finding does not support the hypothesis that schizophrenics cannot ignore irrelevant stimuli, at

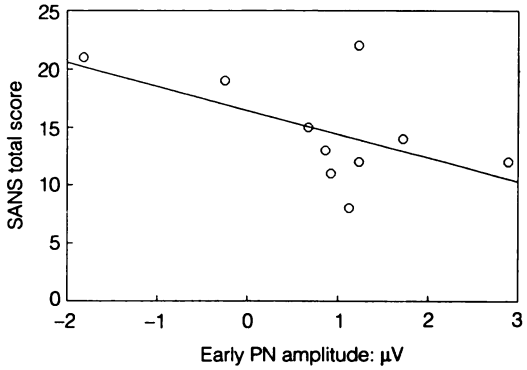


Fig. 4 SANS total score plotted against early PN amplitude, measured as the difference between L+P+D− and L−P−D− ERPs at Fz ($r=-0.66$, $P<0.05$).

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least those that are easily distinguishable from relevant stimuli. The size of the early PN effect was significantly reduced at the vertex electrode site in schizophrenics as compared with healthy subjects, consistent with previous research using schizophrenics who were receiving antipsychotic medication (Baribeau-Braun *et al*, 1983; Hiramatsu *et al*, 1983). Kameyama *et al* (1987) failed to find a significant early PN effect in unmedicated schizophrenics. The latter finding may be related to the correlations obtained between PN amplitude and total scores for schizophrenic symptoms in the present study, such that patients with more severe symptoms had a smaller early PN amplitude. The schizophrenics in the study by Kameyama *et al* had higher mean total BPRS scores than the patients who participated in the present study (48.5 v. 37.8).

The present study also demonstrated significant reduction of P300 amplitude elicited by correctly detected target stimuli in unmedicated schizophrenic patients, and a significant association between reduced P300 amplitude and increased ratings of negative thought disorder (alogia). This finding is consistent with some previous studies which used other measures of thought disorder (Roth *et al*, 1979, 1980). In addition, we have previously reported a significant association between an object-sorting test of conceptual loosening and reduced P300 amplitude in two groups of psychiatrically healthy university students (Ward *et al*, 1984; 1991).

The present report provides the first evidence of marked attenuation of the late-PN component in schizophrenic patients. The significant early-PN effect and better than chance performance indicates that absence of late PN does not simply reflect schizophrenics' failure to engage in the task, or a general cognitive deficit. The virtual absence of late PN in schizophrenics cannot be attributed to inaccurate perception of stimulus characteristics, as EEG epochs contaminated by incorrect behavioural responses (misses or false alarms) were excluded from averaging.

Late PN in normals persisted well beyond the time at which correct button presses were usually made to the infrequent, long-duration 'targets'. This suggests that late PN reflects the maintenance of selective attention rather than perceptual and/or response-related processes. Naatanen (1982) has suggested that late PN reflects the process of updating or maintaining a sensory representation or 'attentional trace' for attended stimuli. The markedly reduced late-PN amplitude found in schizophrenics indicates that schizophrenic patients fail to maintain and direct the focus of attention, and the strong correlations between this ERP measure and ratings of total positive and negative symptoms, if replicated in future studies, would suggest a strong link between disability in information processing and schizophrenic symptoms.

The functional significance of the prolonged frontal negative potential found in both patients and controls for correctly detected target stimuli is not clear. If it can be regarded as evidence of differential pitch processing on the attended ear for long-duration stimuli, it indicates that schizophrenic patients distinguish these stimuli but, unlike normals, do not similarly process short-duration stimuli in the attended ear. This may indicate that patients utilise different strategies to controls in performing this complex listening task. Alternatively, the frontal negative potential elicited by correctly detected targets may reflect processes associated with response activation and resolution of motor activity, as these stimuli are the only ones that require a motor response.

The frontal-maximal group difference in late PN with the standards is consistent with neuropsychological test results indicating the importance of frontal-lobe structures for the maintenance of selective attention (Fuster, 1980). Although the frontal scalp distribution of late PN suggests the frontal lobe as a source of this activity, a study of patients with focal unilateral frontal lesions found bilateral reduction of PN amplitude (Knight *et al*, 1981). This finding is more consistent with subcortical generators receiving input from ipsilateral pre-frontal areas. The caudate nucleus has been suggested, as it receives projections from the frontal lobes and contains neurones involved in the maintenance of attention (Woods, 1990). The findings of the present study may thus be related to post-mortem (Seeman *et al*, 1984; Hess *et al*, 1987) and *in-vivo* (Crawley *et al*, 1986; Wong *et al*, 1986) evidence of neurochemical abnormalities in caudate and other striatal structures in schizophrenics.

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