RESEARCH PAPERS

The Effect of Laterality of Stimulus Presentation on Auditory P300 Topography in Schizophrenia

Frank Bolsche, MD[1,2], Duncan J MacCrimmon, MD[3], S Kropf[1,4]

[1]Otto-v-Guericke-Universitat, Medizinische Fakultat, Magdeburg, Germany
[2]Abteilung Pathophysiologie, Magdeburg, Germany
[3]Hamilton Psychiatric Hospital, Department of Psychiatry, McMaster University, Hamilton, Ontario, Canada
[4]Institut fur Biometrie und Medizinische Informatik, Magdeburg, Germany

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Reduced P300 amplitude in schizophrenia has been a consistent finding. Recent studies have raised the question of characteristic topographic distribution. This study reports the effects of binaural and unilateral stimuli on the P300 topography in schizophrenia. An auditory "oddball" paradigm was repeated 3 times with left, right and binaural stimulation. Data were recorded using a 19-electrode montage with linked ear reference. Subjects were 18 untreated, hallucinating, paranoid patients with schizophrenia and 24 healthy matched volunteers. For the control subjects, stimulus conditions had no effect on P300 topography. For the sample with schizophrenia, topography under unilateral left stimulation resembled that of control subjects. Binaural and right-sided stimulation shifted peak amplitudes to the right and frontally. In addition to the usually observed parietal peak, a second P300 maximum having a different time course appeared over right frontal areas. The data provide further support for lateralized dysfunction in schizophrenia.

Key Words: stimulus laterality, P300, schizophrenia, drug free, hemispheric dysfunction, evoked potentials

INTRODUCTION

Deficits in attention and short-term information processing, which may represent an enduring trait, have long been recognized in patients with schizophrenia (Asarnow and MacCrimmon 1978). More recently, event-related brain potentials have become a focus of research (Friedman and Squires-Wheeler 1994). Early components, occurring within approximately the first 100 ms, are known as exogenous because they are determined by the physical characteristics of the evoking stimuli; whereas, later or endogenous potentials are determined by the psychological relevance of the eliciting stimuli to the subject. The P300, a large-amplitude positive wave with a peak latency of approximately 300 ms, is thought to be related to information processing (Picton 1988). Reduced P300 amplitude is a consistent finding in studies of schizophrenia (Maurer 1987, 1990), but is not specific to schizophrenia as it has been found in other psychiatric syndromes (Maurer 1988, 1989). With technological advances such as multichannel data acquisition and mapping, the question of characteristic P300 topographic distributions in psychiatric syndromes is raised. Faux and others (1988)

Address reprint requests to: Dr DJ MacCrimmon, Hamilton Psychiatric Hospital, PO Box 585, Hamilton, Ontario, Canada L8L 2B3.

and Strik and others (1994) provide evidence suggesting left temporal deficits in subjects with schizophrenia. However, others failed to find evidence of lateralization (Pfefferbaum and others 1990). Many studies to date have suffered from methodological problems such as small numbers, heterogeneous patient groups, the presence of psychotropic medications, and lack of consideration of handedness. A comprehensive literature search has not found any report of studies using lateralized stimuli in a P300 paradigm.

This study was undertaken to reexplore the P300 topography in drug-free schizophrenia and to include unilateral stimulus presentation in addition to the conventional binaural.

METHODS

The study population included 18 acutely rehospitalized patients with paranoid schizophrenia, 12 females and 6 males, having a mean age of 36.4 years (range 20 years to 45 years). Diagnosis was established by structured clinical interview and took all available clinical information into consideration. All patients met DSM-III-R (295.3.4) criteria for chronic paranoid schizophrenia and were experiencing auditory hallucinations at the time of study. For inclusion in the study, all patients were required to have had 2 prior hospitalizations for which both diagnoses were paranoid schizophrenia. All patients were drug-free for at least 6 months prior to rehospitalization and remained so until testing, which occurred within the first 2 weeks following admission. The patients were compared to 24 healthy volunteers recruited from the community, comprising 16 females and 8 males with a mean age of 33.8 years (range 20 years to 45 years). All subjects gave informed consent, all were free of past or present neurological disorders, hearing loss, drug and alcohol abuse, and met criteria for middle-degree right handedness (Steingrueber Hand Dominance Test: level +33).

P300 acquisition

AEPs were recorded and analyzed using a Bio-Logic system (Brain Atlas 3.88) and a 19-scalp-electrode montage (International 10/20 System) with linked ear reference. The following paradigm was used: frequent stimulus 1000 Hz; infrequent stimulus 2000 Hz; tone duration 50 ms; fall and rise time 10 ms; fixed interstimulus-interval 1000 ms; ratio 4:1. Stimuli were delivered at 80 dBSL via stereo earphones. Subjects were requested to keep eyes open and fixated on a designated point. They were instructed to press a button held in the right hand as quickly as possible whenever the target stimulus was heard. Correct responses were tallied. This procedure was repeated 3 times, first with left ear stimulation, second with right ear and finally binaurally. Settings for bandpass filters were 0.5 Hz to 30 Hz. Data sampling was 512 data points for each 1024 ms epoch which included a 100 ms prestimulus interval. Gold-cup electrode resistance was maintained at less than 5 Kohm. Blink artifact elimination was accomplished by an automatic, amplitude-defined rejection algorithm (peak-to-peak limit 150 μV maximum) in combination with simultaneous split-screen video display with manual elimination of epochs when blinking was observed. Finally, muscle and low-amplitude eye movement or any other residual artifacts were removed by off-line visual inspection of the EEG tracing of all data channels. Thirty-two artifact-free samples per subject were averaged for each P300 stimulus presentation. For all P300 data reported in this study, a baseline was established as the mean value of the 100 ms prestimulus interval. The P300 was then defined as the voltage maximum above this baseline lying between 250 ms to 400 ms post-stimulus onset.

Statistical analysis

Statistical analysis using the SPSS package was explored. Validation of results of the numerous tests has essentially been supported by checking consistency among related problems rather than by formal statistical techniques such as Bonferroni adjustment.

Because of the non-Gaussian distribution of our data, nonparametric statistics were used for all comparisons. In particular, the Mann-Whitney U Test was used to compare P300 amplitudes and latencies between subjects with schizophrenia and normal subjects for each electrode position. Friedman Tests were performed to evaluate differences in the ranges of P300 latencies. To compute the topographic maps, the 4 nearest neighbor interpolation was used. The Friedman Test, followed by multiple analysis, was used to estimate the differences between frontal-parietal and right-left hemispheric distribution of the P300 topography for each of the stimulus conditions. The following electrode chains were examined:

left longitudinal:	Fp1, F3, C3, P3, O1
right longitudinal:	Fp2, F4, C4, P4, O2
frontal transverse:	F7, F3, Cz, F4, F8
parietal transverse:	T5, P3, Pz, P4, T6

The latency of the P300 maxima varies at different electrodes so that the statistical statement of the Friedman Test relates to the time segment within which the P300 maximum spreads over the scalp.

RESULTS

Because stimulus laterality has no significant effect on P300 maximum amplitudes, a single overall group mean value was used. The mean maximum amplitude for the control subjects (14.4 μV) was significantly greater (Mann-Whitney U Test, $p < 0.001$) than that of the subjects with schizophrenia (7.2 μV).

For the control group, there is no significant effect of stimulus conditions on either mean latency (Mann-Whitney U Test) or standard deviation (Friedman Test). The mean

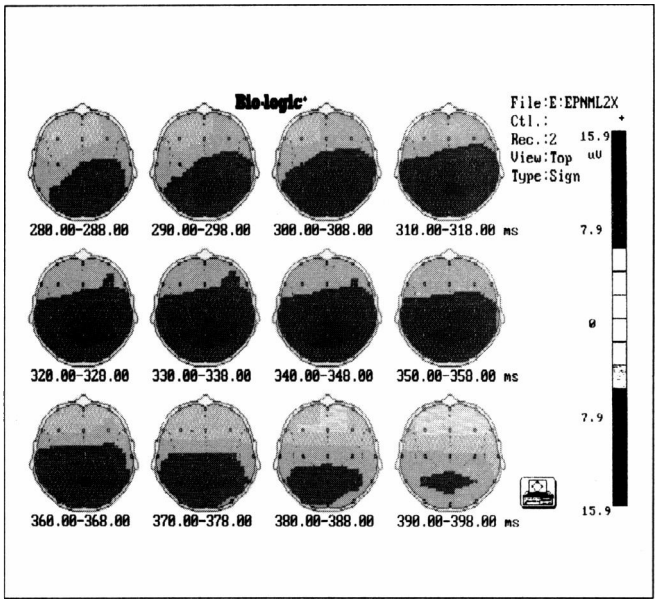

Figure 1a. Normal subjects: left-sided stimulation.

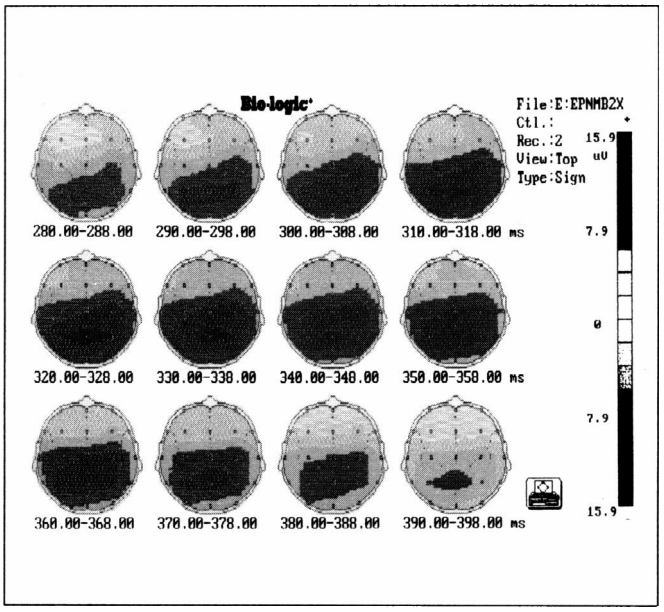

Figure 1b. Normal subjects: binaural stimulation.

latencies for left, binaural and right stimuli were: 328 ± 32 ms, 311 ± 24 ms, 332 ± 41 ms, respectively. For the group with schizophrenia, there is only a trend of latency prolongation going from left stimulation (340 ms), through binaural (342 ms), to right (364 ms) stimulation, but a significant increase in the latency range from left-sided stimulation (range 280 ms to 404 ms) to right-sided stimulation (range 285 ms to 496 ms) (Friedman Test, $p < 0.01$).

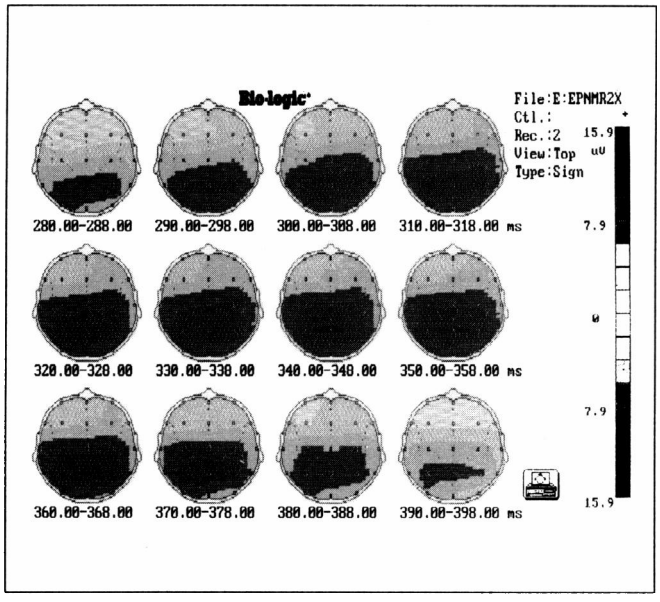

Figure 1c. Normal subjects: right-sided stimulation.

Inspection of Figures 1a, 1b, 1c shows that, for the control subjects, there is virtually no effect of stimulus conditions on P300 topography. For the sample with schizophrenia, P300 topography under unilateral left-sided stimulation (see Figure 2a) resembles that of control subjects. As can be seen in Figures 2b and 2c, binaural and right-sided stimulation had a substantial effect on P300 topography, shifting peak amplitudes to the right and frontally. In addition to the usually observed parietal peak, a second P300 maximum having a different time course appears over right frontal areas. Amplitudes for all maps can be read from the associated side bar. Examination of individual patients' and control subjects' topographic data for these stimulus conditions reveals that none of the controls, but all of the subjects with schizophrenia showed a shift of P300 maxima to the right hemisphere.

Results of the frontoparietal and left-right P300 topographic distribution using the Freedman Test are given in Figure 3. For left-sided stimulation, there is no difference between right and left hemispheres, and the typical frontoparietal gradient is seen in both groups (see Figure 3, top row). Binaural stimulation produced no topographic change in the control group. The group with schizophrenia shows greater right-sided amplitudes frontally and, as a consequence, absent frontoparietal gradient over the right hemisphere (see Figure 3, middle row).

Right-sided stimulation, having no effect on the normal control P300 topography, produces more extensive changes in the subjects with schizophrenia. Greater right-sided amplitudes are seen both frontally and parietally. In addition, the frontoparietal gradient was eliminated for both hemispheres (see Figure 3, bottom row). Error rates for the normal subjects were 3.4% for left, 3.1% for right, and 3.6% for binaural

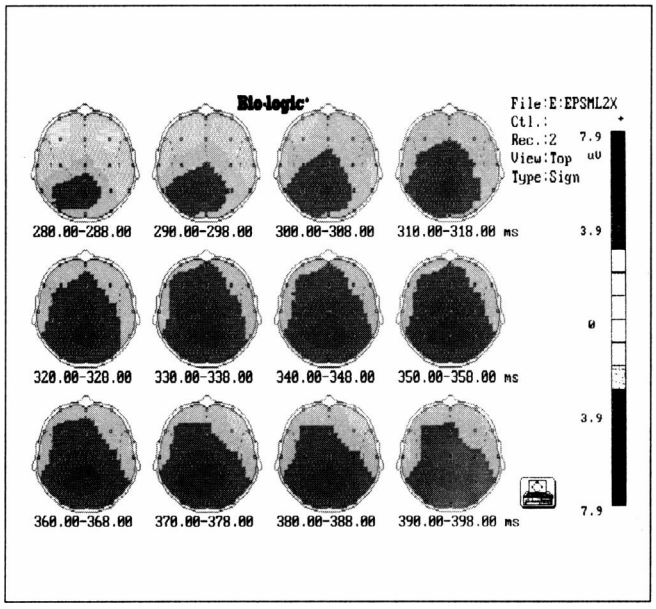

Figure 2a. Subjects with schizophrenia: left-sided stimulation.

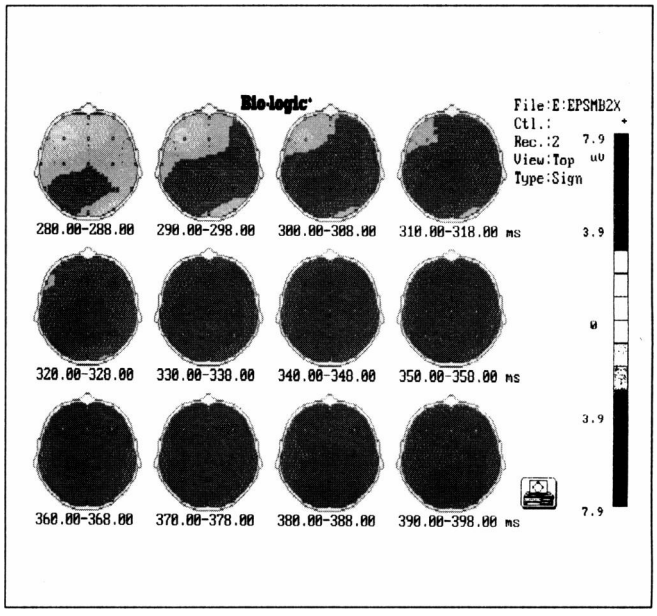

Figure 2b. Subjects with schizophrenia: binaural stimulation.

stimulation; the corresponding values for the group with schizophrenia were 4.2%, 4.4%, and 5%, respectively.

DISCUSSION

Our results, consistent with the literature, demonstrate an overall reduced P300 amplitude in our group with schizophrenia. It should be noted that, in most of these studies, only midline electrodes and binaural stimuli were used. In contrast, however, our patients with schizophrenia, under binaural or right-stimulus conditions, showed right anterior quadrant P300 values that were not distinctly lower than those of normal subjects (compare Figures 1b and 2b, 1c and 2c). This observation suggests that findings of hyper or hypo frontality in schizophrenia may be influenced by factors such as asymmetry of hemispheric function in relation to laterality of stimulus input and handedness (Holinger and others 1992).

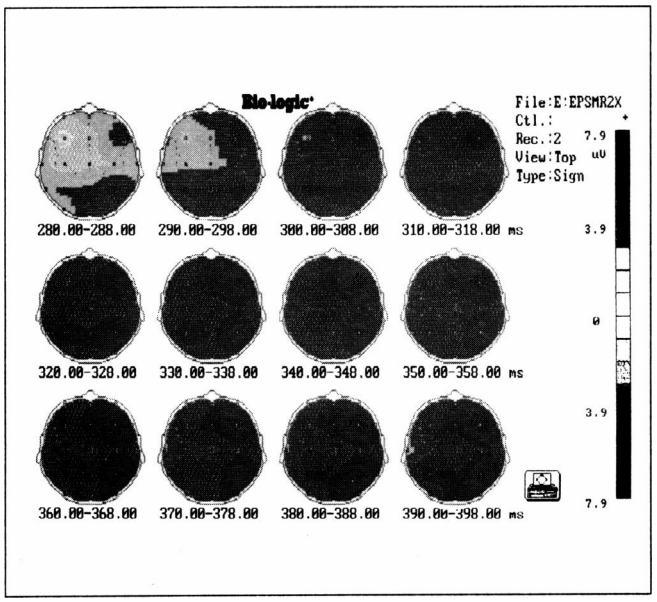

Figure 2c. Subjects with schizophrenia: right-sided stimulation.

While the mean latency values for subjects with schizophrenia did not differ compared to control subjects, the significantly greater range of latency values under all stimulus conditions is consistent with the often postulated disturbed information processing in schizophrenia. Moreover, the significant increase in latency ranges from left- to right-sided stimulation, found only in our patients with schizophrenia, indicates an influence of laterality of input on information processing.

Although auditory pathways are characterized by bilateral representation, most input from unilateral stimulus is directed to the contralateral hemisphere (Kolb and Wishaw 1990). Thus, our latency range data suggest that left hemisphere function is more disturbed in subjects with schizophrenia.

Our topographic data provide further support for lateralized dysfunction in schizophrenia. Thus, left-sided stimulation, which would be expected to activate right hemisphere structures initially, shows a normal topographic distribution, presumably because left hemispheric structures are more morphologically disturbed in persons with schizophrenia (Bogerts 1993; Crow 1990). This may account for the statistical results shown in Figure 3 for left-sided presentation (top row) where there were no differences between subjects

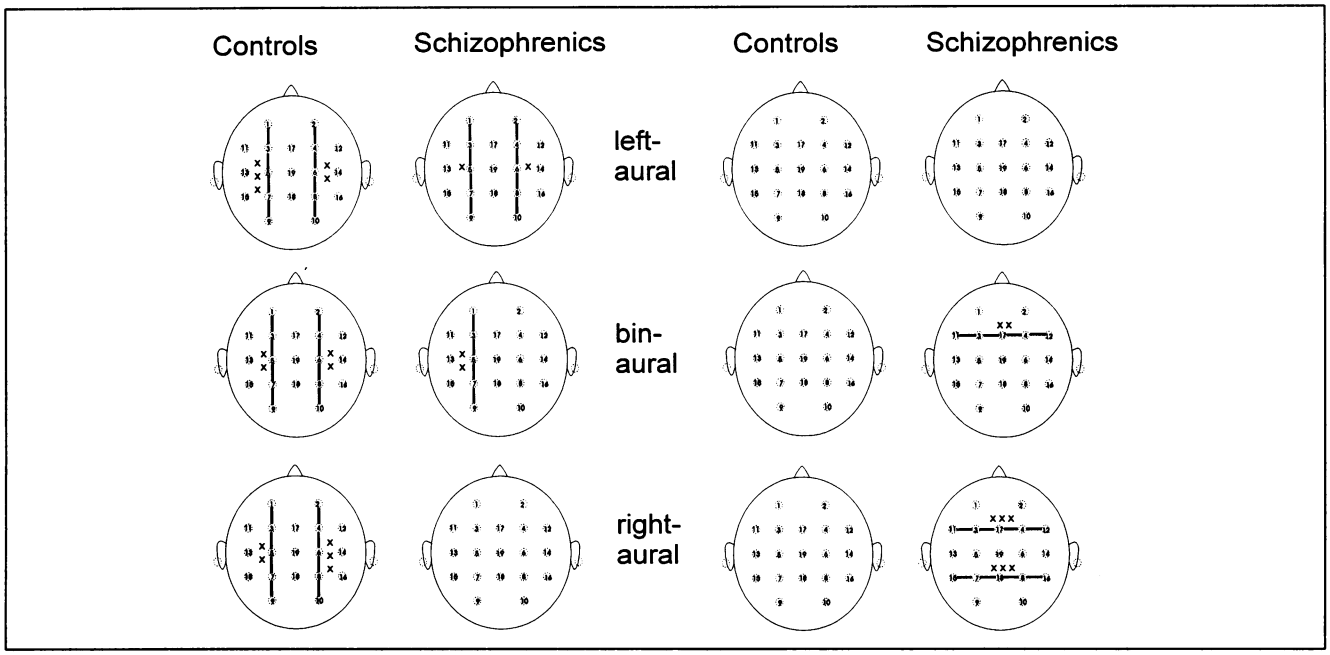

Figure 3. Longitudinal (left 2 columns) and transverse (right 2 columns) Friedman Test results for control subjects and subjects with schizophrenia by stimulus conditions (rows) $x = p < 0.05$, $xx = p < 0.01$, $xxx = p < 0.001$.

with schizophrenia and control subjects in relation to left-right or front-back gradients of P300 activity.

With binaural stimulation, which simultaneously activates both auditory cortices, topographic effects are observed in the group with schizophrenia. These are characterized by the emergence of a right greater than left frontal P300, together with the disappearance of the anterior-posterior gradient in the right hemisphere (see Figure 3, middle row). Why does input to the left hemisphere perturb P300 topography in schizophrenia? The reports of Early and others (1989), Holinger and others (1992) and McCarley and others (1991, 1993) implicate both structural and functional abnormalities involving the left parietal area in schizophrenia. An examination of the time evolution of binaural P300 topography suggests a dynamic model which may account for our findings. Perhaps aberrant information processing of dysfunctional left temporal lobe structures (i.e., Heschel's Gyrus and/or Planum temporale) impedes homologous right-sided temporoparietal functions, prolonging activity there (trend for increased latency range), and also activating ipsilateral frontal structures subserving short-term working memory (Fuster 1991). This impediment would account for the prolonged P300 parietal activity and the emergent right frontal locus of activity. Right-sided stimulation, which is first processed in left hemisphere structures, further accentuates the topographic abnormalities (see Figure 3, bottom row). The left parietal P300 activity is minimized and therefore anterior-posterior gradients disappear bilaterally; right-left asymmetries involve both frontal and parietal areas.

With this model in mind, the obvious progressive abnormality in schizophrenic P300 topography contrasting left-sided stimulation (see Figure 2a), through binaural (see Figure 2b), to right-sided stimulation (see Figure 2c) may be neurophysiologically understandable. Replication of our P300 findings in schizophrenia and extension to other clinical populations is clearly indicated since unilateral evoked P300 has the potential to offer differential diagnostic information in psychiatry.

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