Altered Parallel Auditory Processing in Schizophrenia Patients

by Eero Pekkonen, Minna Huotilainen, Heikki Katila, Jari Karhu, Risto Nääätän, and Jari Tiihonen

Abstract

Patients with schizophrenia have impaired auditory processing that has been demonstrated by diminished P50 response to paired auditory stimuli in event-related potential (ERP) studies. Cerebral processing can also be studied with magnetoencephalography (MEG). With a whole-head MEG, which enables one to simultaneously measure brain activity in both hemispheres, we investigated whether early parallel auditory processing is impaired in schizophrenia. Sequences of tones were monaurally presented to schizophrenia patients and healthy controls in a passive condition, and the event-related magnetic fields were recorded simultaneously over both auditory cortices. The interhemispheric latency difference of the P50m, but not that of the N100m, was significantly shorter in the patient group in the right-ear but not in the left-ear stimulus condition. Further, the ipsilateral P50m was significantly earlier in schizophrenia patients in the right-ear condition. This result suggests that schizophrenia affects the consecutive preconscious auditory processing in a different manner.

Key words: Magnetoencephalography, event-related potentials, P50, N100, schizophrenia.


Event-related potentials (ERPs) are minute electroencephalographic changes time-locked to the sensory stimuli and noninvasively provide neurophysiological data on brain activity with a time resolution of milliseconds. Thus ERPs are an objective tool for studying brain function in psychiatric disorders such as schizophrenia (Pfefferbaum et al. 1995). N200 and P300 waves, which are elicited by the actively detected deviant tones in a sequence of standard tones (Sutton et al. 1965), give an objective estimate of the time required to evaluate deviant stimuli (Pfefferbaum et al. 1995). Several studies have demonstrated attenuated amplitudes of N200 and P300 and, further, a delayed latency of P300 in patients with schizophrenia, suggesting impaired conscious stimulus detection (Roth et al. 1980; Pritchard 1986; Kessler and Steinberg 1989; O’Donnell et al. 1993).

With earlier ERP components it is also possible to study preattentive auditory processing preceding conscious stimulus detection. Two prominent preattentive ERP components are P50 and N100, of which P50 is a positive wave and N100 a negative wave with latencies of about 50 ms and 100 ms after stimulus onset, respectively (Nääätän 1992). ERP studies have demonstrated decreased N100 (Kessler and Steinberg 1989) and diminished inhibition to the second P50 response in a two-stimulus paradigm in patients with schizophrenia (Adler et al. 1982; Boutros et al. 1991; Erwin et al. 1991; Judd et al. 1992; Freedman et al. 1996). The latter finding is assumed to reflect altered inhibitory filtering in the brain (Adler et al. 1982; Erwin et al. 1991; Judd et al. 1992; Freedman et al. 1996).

Cerebral activity can also be studied noninvasively with high temporal and spatial resolution by magnetoencephalography, or MEG (Hari and Lounasmaa 1989). In addition, sophisticated whole-head magnetometers enable the simultaneous measurement of cerebral activity over each hemisphere. MEG studies have demonstrated that the auditory evoked magnetic field responses (AEFs) called P50m and N100m, which are magnetic counterparts of the corresponding electric responses, are generated mainly in or near the primary auditory cortex at the temporal lobe (Hari et al. 1980; Mäkelä et al. 1994). MEG measurements have also shown that the N100m sources are asymmetrical in healthy subjects, the right N100m source being anterior to the left N100m, whereas patients with schizophrenia lacked the same N100m source asymmetry (Reite et al. 1981, 1989; Mäkelä et al. 1994). P50m and especially N100m appear somewhat earlier over the
contralateral than over the ipsilateral auditory cortex to the ear stimulated in young healthy subjects (Mäkelä et al. 1994). Furthermore, a recent MEG study has shown that parallel auditory processing between the hemispheres is impaired in patients with Alzheimer’s disease (Pekkonen et al. 1996).

The purpose of our study was to investigate, using the whole-head magnetometer, which detects the strongest signal directly above the cerebral source (Hämäläinen et al. 1993), whether schizophrenia affects parallel auditory processing as reflected by the AEFs.

Material and Methods

Twenty-one healthy controls (8 females and 13 males; mean age 32.5 years, range 22–50 years) and 11 patients (3 females and 8 males; mean age 30.5 years, range 19–49 years) participated in the study. After the study was completely described to the subjects, written informed consent was obtained. The Ethics Committee of the Department of Psychiatry of Helsinki University Central Hospital accepted the study. Data from two control subjects were rejected because of noisy recordings. Handedness was determined by using Questionnaire 1 (Annett 1967); 10 patients and 17 controls were right-handed. Patients were recruited from the Department of Psychiatry of the Helsinki University Central Hospital; all were re-entry patients with an established schizophrenia diagnosis and had been admitted to the hospital in an acute psychotic state. The diagnoses were verified according to the *DSM-III-R* (American Psychiatric Association 1987) criteria in a clinical interview by a senior psychiatrist (H.K.). Six patients met the criteria for paranoid, two for disorganized, and three for undifferentiated form of chronic or subchronic schizophrenia. Seven patients were medicated with a mean dose of 321 mg of chlorpromazine equivalents (Baldessarini 1985), and four patients had 6 mg risperidone per day. Four patients were also taking diazepam and two patients lorazepam in mean daily doses of 10 and 3 mg, respectively. During the month before admission, all patients had had inadequate medication, which consequently led to the hospitalization. Six patients had had auditory hallucinations during the present episode of illness. The mean total score for Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987) was 90.9; positive and negative symptoms scores were 20.7 and 27.6, respectively. Head MRIs were performed on all subjects to exclude focal abnormalities such as ischemic or hemorrhagic changes.

MEG recordings of the patients were made within 21 days of admission. Recordings were performed in a magnetically shielded room where each subject sat under the helmet-shaped dewar with his or her head against the bottom of the instrument. The subject watched a silent video and was instructed not to attend to the tones presented monaurally through a plastic tube and earpiece. The subjective hearing threshold was measured separately for each ear before the recording and the stimulus intensity was adjusted to 60 dB over the threshold.

Each stimulus block consisted of 80 percent standard tones and 20 percent randomly embedded deviant tones, each with a frequency of 700 Hz. The duration of the standard tone was 50 ms and that of the deviant tone 25 ms, with 5 ms rise and fall times in each. Stimulus blocks with 0.5 and 2.5 sec interstimulus intervals (ISIs) were separately presented to each ear. In every block, the first 20 responses were omitted from the analysis. AEFs were recorded using a 122-channel whole-head magnetometer measuring two orthogonal tangential derivatives of the magnetic field component normal to the scalp, at 61 locations over the head (see figure 1). The planar gradiometers of this device detect the strongest signal directly above a cerebral source. The accurate position of the subject’s head relative to the gradiometers was determined by measuring the magnetic field produced by three marker coils attached to the scalp.

The analysis period was 750 ms, including a prestimulus period of 150 ms. The recording bandpass was 0.03–100 Hz and the sampling rate was 397 Hz. The vertical and horizontal electro-oculograms (EOGs) were recorded, and epochs coinciding with EOG or MEG changes exceeding 150 µV or 3000 fT/cm were rejected from averaging. Averaged responses for the standard tone were about 300 in the 0.5 sec condition and about 100 in the 2.5 sec condition. Digital low-pass filtering was performed at 30 Hz and high-pass filtering at 1 Hz.

At first the interhemispheric latency differences of the AEFs were calculated by subtracting the contralateral AEF latency from the ipsilateral AEF latency. The peak amplitudes and latencies of the AEFs were measured from the channel showing the largest response over both hemispheres. The MEG data were analyzed with two- or three-way repeated measures analysis of variance (ANOVA) to assess possible group differences for AEFs. The paired and unpaired two-tailed *t* tests were used when appropriate. Correlations between the AEF latencies and the scores for PANSS were calculated with the Pearson correlation coefficient.

Results

Figure 1 shows the AEFs of one healthy control subject and one patient with schizophrenia to the standard tones with 2.5 sec ISI. In the control subject, the contralateral P50m peaked earlier than the ipsilateral P50m did, whereas the latencies of the ipsi- and contralateral P50m
Figure 1. Gradient field maps of the N100m for one patient and one healthy subject

Note.—Tones were presented to the right ear with an interstimulus interval of 2.5 sec. The helmet-shaped sensor array is viewed from the left and right side. The magnetic gradient field patterns with 10 fT isocontour lines show the maximal activity over the temporal lobes about 100 ms after stimulus onset in both subjects. Arrows indicate the sites and orientation of the equivalent current dipoles of the N100m. Maximum responses from each hemisphere are shown enlarged. Bars demonstrate that the ipsilateral and contralateral P50m peaked nearly simultaneously in the patient with schizophrenia, but the contralateral P50m peaked earlier in the healthy subject; subsequent N100m peaked earlier contralaterally in each subject.

Table 1 shows the interhemispheric latency differences of the AEFs, which were first calculated and then subjected to group by ISI analysis (repeated measures of ANOVA). In the right-ear but not in the left-ear condition, the interhemispheric latency difference of the P50m was significantly shorter in the patient group ($F = 7.30$, df = 1,28, $p < 0.05$, right-ear condition). Additional analysis showed that the difference was significant with the ISI of 2.5 sec, ($p < 0.01$, unpaired $t$ test, two-tailed). The interhemispheric latency differences of the N100m were nonsignificant in the right- and left-ear conditions. An analysis with only right-handed subjects showed that the main effect of the P50m was still significant in the right-ear condition ($F = 11.76$, df = 1,25, $p < 0.01$).

Repeated measures of ANOVA for AEF latencies (group by ISI by hemisphere) were performed to more accurately study what caused the significant interhemispheric latency difference of the P50m in the right-ear condition. Repeated measures of ANOVA showed a significant group by hemi-interaction of the P50m latency ($F = 7.29$, df = 1,28, $p < 0.05$) and significant P50m latency decrease with the longer ISI ($F = 19.15$, df = 1,28, $p < 0.001$), whereas the group and the group by ISI interactions were nonsignificant (table 2). An additional analysis demonstrated that the ipsilateral P50m was significantly earlier in the patient group with the ISI of 2.5 sec ($p < 0.05$, unpaired $t$ test, two-tailed), but not with 0.5 sec ISI. Table 2 also shows that both groups had a considerable interindividual variation of AEF latencies and that the P50m and N100m were significantly earlier contralaterally than ipsilaterally in each group with the ISI of 2.5 sec when the tones were presented to the left ear. In the right-ear condition with 2.5 sec ISI, the responses were significantly earlier contralaterally only in the control group with 2.5 sec ISI. In the right- and left-ear conditions, the collapsed N100m latencies decreased with increasing ISI (right-ear condition: $F = 4.38$, df = 1,28, $p < 0.05$).
Table 2. Contralateral and ipsilateral peak latencies

<table>
<thead>
<tr>
<th>Group/ear/ISI</th>
<th>Contralateral hemisphere</th>
<th>Ipsilateral hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P50m</td>
<td>N100m</td>
</tr>
<tr>
<td>Sch/left/0.5 sec</td>
<td>58.6 ± 16.5</td>
<td>98.4 ± 19.6 (^1)</td>
</tr>
<tr>
<td>Sch/left/2.5 sec</td>
<td>45.3 ± 6.4 (^2)</td>
<td>97.6 ± 10.9 (^1)</td>
</tr>
<tr>
<td>Sch/right/0.5 sec</td>
<td>60.2 ± 10.4</td>
<td>105.3 ± 20.7</td>
</tr>
<tr>
<td>Sch/right/2.5 sec</td>
<td>48.4 ± 7.6</td>
<td>95.9 ± 11.2</td>
</tr>
<tr>
<td>Co/left/0.5 sec</td>
<td>53.0 ± 14.9</td>
<td>100.8 ± 22.5</td>
</tr>
<tr>
<td>Co/left/2.5 sec</td>
<td>43.0 ± 6.0 (^3)</td>
<td>91.4 ± 9.2 (^2)</td>
</tr>
<tr>
<td>Co/right/0.5 sec</td>
<td>55.7 ± 11.9</td>
<td>100.6 ± 16.9</td>
</tr>
<tr>
<td>Co/right/2.5 sec</td>
<td>47.4 ± 7.9 (^2)</td>
<td>94.8 ± 9.4 (^1)</td>
</tr>
</tbody>
</table>

Note.—Data are peak latencies (± standard deviation) in ms for P50m and N100m with 0.5 and 2.5 sec interstimulus intervals (ISI). Tones were presented separately to the left and right ear in all schizophrenia patients (Sch) and controls (Co). Paired t test (two-tailed) was used to study whether the responses were earlier contralaterally to the ear stimulated inside the groups.

1 \(p < 0.05\).
2 \(p < 0.01\).
3 \(p < 0.001\).

Unpaired t tests were performed inside the groups to study whether gender affects the P50m latency. In both groups, gender did not affect the interpeak latency of the P50m in 2.5 sec condition (controls: \(p = 0.888\); patients: \(p = 0.896\), unpaired t test).

The AEF amplitude differences were also analyzed with the separate repeated measures of ANOVA (group by ISI by hemisphere) for the data of the right- and left-ear conditions. The amplitude differences of the AEFs between the groups were nonsignificant, whereas the N100m became significantly larger with increasing ISI, collapsed N100m amplitude (right-ear condition: \(F = 95.41, df = 128, p < 0.001\); left-ear condition: \(F = 125.89, df = 128, p < 0.001\)). In contrast, the P50m amplitude did not increase significantly with increasing ISI (table 3).

The PANSS scores were compared with the ipsilateral P50m latency in the right-ear condition. A tendency was found toward positive correlation between the ipsilateral P50m latency and the Negative Syndrome Scale score (Pearson correlation, 0.4408, \(p = 0.087\)).

**Discussion**

Our results indicate that early parallel auditory processing, as reflected by P50m, is divergent in schizophrenia and that this divergence is caused by the accelerated signal processing in the right hemisphere when stimuli are delivered to the ipsilateral ear. Specifically, both auditory

Table 3. Contralateral and ipsilateral peak amplitudes

<table>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P50m</td>
<td>N100m</td>
</tr>
<tr>
<td>Sch/left/0.5 sec</td>
<td>14.5 ± 9.8</td>
<td>13.2 ± 8.7 (^2)</td>
</tr>
<tr>
<td>Sch/left/2.5 sec</td>
<td>13.4 ± 7.1</td>
<td>83.4 ± 41.0 (^2)</td>
</tr>
<tr>
<td>Sch/right/0.5 sec</td>
<td>23.4 ± 19.8</td>
<td>16.2 ± 13.8</td>
</tr>
<tr>
<td>Sch/right/2.5 sec</td>
<td>23.5 ± 16.9 (^1)</td>
<td>69.1 ± 43.1</td>
</tr>
<tr>
<td>Co/left/0.5 sec</td>
<td>14.2 ± 8.1</td>
<td>20.1 ± 11.3 (^2)</td>
</tr>
<tr>
<td>Co/left/2.5 sec</td>
<td>16.7 ± 10.2</td>
<td>86.7 ± 30.3 (^3)</td>
</tr>
<tr>
<td>Co/right/0.5 sec</td>
<td>13.8 ± 7.3</td>
<td>14.9 ± 7.0</td>
</tr>
<tr>
<td>Co/right/2.5 sec</td>
<td>19.2 ± 12.4 (^1)</td>
<td>77.0 ± 41.3</td>
</tr>
</tbody>
</table>

Note.—Data are peak amplitudes (± standard deviation) in ms for P50m and N100m with each interstimulus interval (ISI). Sch = schizophrenia patients; Co = controls. Paired t test (two-tailed) was used to study the amplitude differences of the responses inside the groups.

1 \(p < 0.05\).
2 \(p < 0.01\).
3 \(p < 0.001\).
cortices are excited almost simultaneously by the right-ear stimuli in schizophrenia subjects, whereas healthy subjects seem to process information slightly earlier in the contralateral auditory cortex irrespective of the ear stimulated. Furthermore, the present findings suggest that schizophrenia subjects have similar functional asymmetry for the auditory signal processing after the P50m as reflected by the N100m. In other words, the N100m appears slightly earlier over the contralateral auditory cortex to the ear stimulated in patients with schizophrenia than in healthy subjects. This finding supports previous ERP and MEG findings that have demonstrated no N100 latency difference in schizophrenia subjects (Roth et al. 1980; Pritchard 1986; Kessler and Steinberg 1989; O'Donnell et al. 1993, 1995; Pfefferbaum et al. 1995; Hajek et al. 1997). On the basis of the present P50m and N100m findings, schizophrenia seems to affect in a different manner the consecutive steps in the preconscious auditory processing.

Prior ERP studies have demonstrated reduced N100 amplitude in patients with schizophrenia (Roth et al. 1980; Kessler and Steinberg 1989; O'Donnell et al. 1995) although results showing similar N100 amplitudes have also been reported (Michie and Fox 1990). The present results support previous MEG findings, which have not found significant differences of N100 amplitudes or latencies in schizophrenia subjects (Reite et al. 1988; Hajek et al. 1997). Previous ERP studies have demonstrated diminished P50 in healthy subjects compared with schizophrenia subjects (Adler et al. 1982; Erwin et al. 1991; Judd et al. 1992; Freedman et al. 1996). In contrast, the present results showed nearly similar P50m amplitudes in both groups with each ISI. What is the reason for the differences between the ERP and the present MEG results? In above-mentioned ERP studies, paired clicks were presented, whereas in this study and previous MEG studies, stimuli with longer duration were presented in trains. Thus, different paradigms might to some extent explain the differences. Discrepancies in results may also be caused by the differences in sensitivities of electroencephalography (EEG) and MEG. EEG detects both the tangential and radial current sources, whereas MEG is maximally sensitive to the tangential current sources. In addition, MEG detects mainly cortical activity, whereas EEG picks up activity from both superficial and deep cerebral sources (Hämäläinen et al. 1993). Thus radial or deep source(s) contributing to the P50 and N100 responses might to some extent explain the differences between the ERP and MEG results in schizophrenia subjects.

P50 is usually preceded by the middle-latency component Pa with a latency around 30 ms (Erwin et al. 1991). Therefore it is possible that the magnetic Pa contributed to the activity elicited around 50 ms after stimulus onset. Previous MEG findings suggest that the magnetic Pa usually peaks around 30 to 40 ms after stimulus onset (Mäkelä et al. 1994; McEvoy et al. 1994; Yoshiura et al. 1994). In addition, a recent ERP study demonstrated that using low-frequency tones of 500 Hz with 60 ms duration consistently evoked P50 and that longer ISIs (1.1 sec) more likely elicit the P50 than the Pa. Thus the activity around 50 ms after stimulus onset in this study seems to be mainly P50m in origin. In addition, the present results showed clear P50m with 0.5 sec ISI, supporting previous MEG findings that demonstrated P50m with similar amplitudes using ISIs between 100 and 666 ms (Mäkelä et al. 1994; McEvoy et al. 1994; Yoshiura et al. 1994).

Magnetic resonance imaging studies have found gender differences in the gray matter volume in the superior temporal gyrus (Schlaepfer et al. 1995). Our results, however, did not demonstrate gender-related differences of the auditory responses. Prior MEG findings demonstrated that the parallel auditory processing, as reflected by the N100m, is divergent in Alzheimer's disease (AD) (Pekkonen et al. 1996). The present results demonstrated that interpeak latencies of the N100m were not notably changed in patients with schizophrenia. This suggests that pathophysiology in schizophrenia affects the auditory system in a different manner than it does in AD.

ERP responses peaking 200 ms or longer after stimulus onset, which reflect conscious stimulus processing, are usually delayed or attenuated in schizophrenia (Roth et al. 1980; Pritchard 1986; Kessler and Steinberg 1989; O'Donnell et al. 1993, 1995; Javitt et al. 1995; Pfefferbaum et al. 1995). On the basis of the present data, it seems improbable that early accelerated auditory processing in the right hemisphere, as shown by P50m, might significantly contribute to the following conscious signal processing and to the psychotic symptoms in schizophrenia, because the following N100m response had normal functional asymmetry and there was no significant correlation between the P50m latency and the psychotic symptoms as measured by PANSS. On the other hand, the antipsychotic medication may have affected the severity of both the psychotic symptoms originating mainly from the heteromodal association areas (Kandel 1994; Ross and Pearlson 1996) and the event-related magnetic field responses elicited in the primary auditory cortices. However, it is improbable that medication alone can explain selectively accelerated P50m response, because medication would most probably have accelerated P50m and N100m responses in both hemispheres. The present finding shows only functional abnormalities, however, and therefore accelerated ipsilateral P50m cannot be regarded as specific to schizophrenia.

The reason for the selectively accelerated signal processing in schizophrenia subjects is speculative. In
humans, auditory information is transmitted from each ear to both auditory cortices via two ascending neural pathways. The major proportion of fibers crosses the midline in the brainstem and reaches the contralateral auditory cortex, while the smaller proportion of fibers ascends to the ipsilateral auditory cortex (Kelly 1994). The thalamus, which is modulated by the basal ganglia, is the main relay nuclei gating auditory input to the cortex (Carlsson and Carlsson 1990). Basal ganglia are rich in the neurotransmitter dopamine, overactivity of which is regarded as one probable cause of the psychotic symptoms in schizophrenia (Olney and Farber 1995). The increased dopamine activity in the basal ganglia leads to inhibition of the inhibitory GABAergic neurons projecting to the thalamus, facilitating sensory flow in the thalamus (Carlsson and Carlsson 1990). The present findings suggest that in patients with schizophrenia the right thalamus selectively facilitates the small ipsilateral ascending auditory pathway, leaving the larger contralateral crossing auditory pathway relatively unimpaired. Although the present hypothesis is only tentative, a recent nuclear magnetic study has demonstrated regional abnormalities in right thalamus and adjacent white matter in patients with schizophrenia (Andreasen et al. 1994).

In conclusion, schizophrenia seems to affect in a different manner the consecutive parallel auditory processing. The present findings suggest that patients with schizophrenia have accelerated ipsilateral auditory processing in the right hemisphere possibly caused by altered inhibition.

References


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**The Authors**

Ero Pekkonen, M.D., Ph.D., is Researcher, Cognitive Brain Research Unit, Department of Psychology, University of Helsinki; Researcher, BioMag Laboratory, Medical Engineering Centre, Helsinki University Central Hospital; and Senior Physician, Department of Neurology, University of Helsinki, Finland. Minna Huotilainen, Ph.D., is Physicist, Cognitive Brain Research Unit, and Physicist, BioMag Laboratory; Heikki Katila, M.D., Ph.D., is Senior Physician, Department of Psychiatry, University of Helsinki; Jari Karhu, M.D., Ph.D., is Senior Physician, Department of Clinical Neurophysiology, University of Kuopio, Finland; Risto Näätänen, Ph.D., is Professor, Department of Psychology, University of Helsinki; and Jari Tiitinen, M.D., Ph.D., is Professor, Department of Forensic Psychiatry, Niuvanniemi Hospital, University of Kuopio, and Consulting Physician, Department of Clinical Physiology, Kuopio University Hospital, Finland.