Impaired Temporal Lobe Processing of Preattentive Auditory Discrimination in Schizophrenia

by Eero Pekkonen, Heikki Katila, Jyrki Ahveninen, Jari Karhu, Minna Huotilainen, and Jari Tiihonen

Abstract

Feature-specific stimulus discrimination related to short-term auditory sensory memory can be studied electrophysiologically using a specific event-related potential (ERP) component termed mismatch negativity (MMN), which is generated in the auditory cortex, indexing automatic comparison of the existing memory trace to incoming novel stimuli. Previous results with electroencephalography (EEG) and magnetoencephalography (MEG) suggest that schizophrenia patients have attenuated MMN response and that preattentive auditory processing preceding MMN appears to be functionally asymmetric in schizophrenia. Here we studied parallel MMN activity of the hemispheres using a whole-head MEG by presenting stimulus blocks consisting of frequent standard and infrequent deviant tones to 15 schizophrenia patients and 19 healthy control subjects. Auditory evoked fields (AEFs) were recorded simultaneously over both auditory cortices. The equivalent current dipole (ECD) modeling revealed that patients had significant MMNm reduction (magnetic counterpart of MMN) in both temporal lobes. In addition, patients had significantly delayed MMNm in the left but not in the right hemisphere to ipsilateral auditory stimuli. These results suggest that patients with schizophrenia have impaired auditory processing in the temporal lobes underlying preattentive stimulus discrimination that is also selectively delayed in the left hemisphere.

Keywords: Schizophrenia, magnetoencephalography (MEG), electroencephalography (EEG), mismatch negativity (MMN), auditory sensory memory.


Abnormalities in early auditory processing have been well documented in schizophrenia using ERPs, which are minute changes to the sensory stimuli observed in EEG (e.g., Pfefferbaum et al. 1980). ERP studies focusing on P3 response, which is an electrical response to the detected task-relevant stimulus with a latency around 300 ms after stimulus onset, suggest that early attentive auditory processing is impaired in schizophrenia (Roth et al. 1980). P3 measures conscious auditory processing, whereas preceding preconscious processing can be investigated with a negative ERP component known as MMN, which indexes automatic comparison of an existing memory trace to incoming novel stimuli ( Näätänen 1992). MMN is generated in the auditory cortex, and it is typically elicited by infrequent deviant sounds embedded in a sequence of frequent standards while the subject’s attention is directed elsewhere. MMN can be elicited not only by simple tones, such as frequency or duration change, but also by more complex sounds, such as phonemes ( Näätänen 1992). Hence MMN provides an objective measure of the preattentive feature-specific comparison process in the auditory system. Several EEG studies have found attenuated MMN to duration and frequency changes in patients with schizophrenia (Shelley et al. 1991; Javitt et al. 1993; Lembreghts and Timsit-Berthier 1993; Catts et al. 1995; Javitt et al. 1995; Hirayasu et al. 1998; Umbricht et al. 1998; Kasai et al. 1999; Shelley et al. 1999), although contradictory results also exist (O’Donnell et al. 1994; Kathmann et al. 1995).

MMN derived from the auditory cortices reflects the automatic feature-specific comparison process. An additional MMN generator involving mainly the right frontal lobe has been proposed based on scalp current density analysis (Giard et al. 1990; Deouell et al. 1998). It has been suggested that the feature-specific comparison process in the temporal lobe evokes MMN activity in the frontal lobe, which in turn initiates attention switching as shown by evoked P3a response (Picton et al. 2000). Both the temporal and frontal MMN components appear around 100–250 ms after stimulus onset, overlapping each other
Material and Methods

Sixteen patients (seven females; mean age 30 years, range 19–39 years) and 19 healthy control subjects (seven females; mean age 32 years, range 22–50 years) participated in the MEG study. The study was accepted by the Ethics Committee of the Department of Psychiatry of Helsinki University Central Hospital, and before the measurements were taken, written informed consent was obtained from all subjects. One patient’s data were eliminated from the analysis because head magnetic resonance imaging (MRI) scan revealed an intracranial cyst. Handedness was determined by using Questionnaire 1 by Annett (Annett 1967). One patient and two controls were left-handed. Patients admitted to the hospital in an acute psychotic state were recruited from the Department of Psychiatry of the Helsinki University Central Hospital. All patients were reentry patients with established schizophrenia diagnoses; duration of the illness ranged from 1 to 15 years. The diagnoses were verified according to DSM–III–R (American Psychiatric Association 1987) criteria in a clinical interview by an experienced senior psychiatrist (H.K.). Eight patients were medicated with typical neuroleptics; mean dose was 443 mg (range 100–1,000 mg per day) of chlorpromazine equivalents (Baldessarini 1985), and four patients had 6 mg risperidone per day. In addition, one patient received olanzapine 5 mg per day, and six patients were taking benzodiazepines (four patients had 10 mg diazepam per day; and two patients, 3 mg lorazepam per day). During the month prior to the admission, all patients had been inadequately medicated, which led to the hospitalization. Of these patients, two subjects had 9 and 12 days’ duration of withdrawal from the drug therapy prior to the MEG recording, respectively. Nine patients had had auditory hallucinations during the present episode of illness. The mean total score on the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) was 88.3. The scores for positive and negative symptoms were 20.3 and 26.8, respectively, whereas the mean Global Assessment of Functioning scale (GAF; American Psychiatric Association 1987) was 37.7. A head MRI was performed on all subjects to exclude focal abnormalities.

For the patients, the MEG recordings were made within 3 weeks of the admission to the hospital. Recordings were performed in a magnetically shielded room (Euroshield Ltd.), where each subject sat under the helmet-shaped dewar with his or her head against the bottom of the instrument. Subjects watched a silent video and were instructed to ignore monaurally presented tones, which were delivered through a plastic tube and an earpiece. Stimulus intensity was adjusted to 60 dB above the measured individual hearing threshold.

Subjects were presented stimulus blocks consisting of frequent standard (80%) and randomly embedded deviant tones (20%) differing in duration. The duration of the standard and deviant tones were 50 and 25 ms, respectively, including 5-ms rise and fall times. The frequency of the standard and deviant tones was 700 Hz, and two stimulus blocks with 0.5-s interstimulus interval (ISI) were separately presented to each ear. AEFs were recorded using a 122-channel
whole-head magnetometer (Neuromag Ltd.) measuring two orthogonal tangential derivatives of the magnetic field component normal to the scalp, at 61 locations over the head (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 150-ms prestimulus period. The recording passband was 0.03–100 Hz, with a 397 Hz sampling rate. 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. Approximately 100 responses for the deviant tone were averaged in each stimulus block. The averaged MMNm responses after subtraction were filtered with a passband of 1–12 Hz for waveforms and 1–20 Hz for the dipole modeling.

Because MMNm is usually larger over the hemisphere contralateral compared with the hemisphere ipsilateral to the ear stimulated (Giard et al. 1990), the AEF sources for the MMNm were modeled as equivalent current dipoles (ECDs) found by a least-squares fit of a subset of 34 channels over the hemisphere contralateral to the ear stimulated. A spherical head model was used for the dipole fitting. The fitting was considered successful if the dipole explained more than 70 percent of the data. Dipole moments were analyzed by a two-way analysis of variance (ANOVA, group × ear), and x-, y-, z- coordinates of the ECD locations were studied by separate unpaired t tests.

To assess more thoroughly possible hemisphere-related differences based on ECD analysis, a three-way

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**Figure 1. Magnetic field maps of the MMNm over the hemispheres contralateral to the ear stimulated for one patient and one healthy subject when the tones were monaurally presented with the ISI of 0.5 s**

<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>Ear Stimulated</th>
<th>MMNm Field Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td>Contralateral</td>
<td>t = 151 ms, Q = 19.7 nAm</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral</td>
<td>t = 167 ms, Q = 9.8 nAm</td>
</tr>
<tr>
<td><strong>Schizophrenic</strong></td>
<td>Contralateral</td>
<td>t = 156 ms, Q = 11.0 nAm</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral</td>
<td>t = 140 ms, Q = 2.8 nAm</td>
</tr>
</tbody>
</table>

Note.—AEF = auditory evoked potential; ISI = interstimulus interval; MMNm = mismatch negativity, magnetic counterpart. The magnetic field patterns with 5 fT isocontour lines show the maximal activity around 150 ms after stimulus onset in both subjects. The arrows demonstrate the sites and orientation of the equivalent current dipoles of the MMNm. Note that the schizophrenia patient has a weaker MMNm field pattern over both hemispheres compared with the control subject. Additionally, MMNm field patterns of the control subject and patient showed weaker left than right predominance. Enlarged are ipsilateral and contralateral AEFs for the MMNm from the channels where the responses were largest.
Table 1. The mean peak latencies, dipole moments, and goodness-of-fit values of the ECD for MMNm with SD

<table>
<thead>
<tr>
<th>Group/hemisphere</th>
<th>Latency (ms)</th>
<th>Q (nAm)</th>
<th>g (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia/right</td>
<td>164 ± 25</td>
<td>8 ± 5</td>
<td>79 ± 14</td>
</tr>
<tr>
<td>Control/right</td>
<td>174 ± 28</td>
<td>12 ± 7</td>
<td>82 ± 12</td>
</tr>
<tr>
<td>Schizophrenia/left</td>
<td>172 ± 27</td>
<td>5 ± 3*</td>
<td>57 ± 18**</td>
</tr>
<tr>
<td>Control/left</td>
<td>174 ± 27</td>
<td>8 ± 4</td>
<td>76 ± 12</td>
</tr>
</tbody>
</table>

Note.—ECD = equivalent current dipole; g = goodness-of-fit values; MMNm = mismatch negativity, magnetic counterpart; Q = dipole moments; SD = standard deviation. The source modeling was performed to the MMNm data contralaterally to the ear stimulated. When 70 percent g values were applied, only 3/15 patients had satisfactory source modeling for the MMNm compared with 14/19 healthy control subjects in the left hemisphere, and therefore the first data analysis included all ECDs irrespective of g values. Source modeling revealed that schizophrenia patients had significantly reduced dipole moments of the MMNm in the left hemisphere. Note the significantly reduced g value of the left hemisphere in the patient group, indirectly supporting the view of impaired MMNm in the left auditory cortex.

*p < 0.05; ** p < 0.001, unpaired t test

A three-way repeated measures ANOVA (group × ear × hemisphere) for the AEF data showed insignificant group × hemisphere interaction (F[1,32] = 1.75) and a trend for significant group effect (F[1,32] = 2.95) for the MMNm amplitude (table 2), whereas the hemisphere effect was significant (F[1,32] = 27.57, p = 0.000). A priori comparison showed significant left hemisphere MMNm amplitude decrease in the patient group when the tones were delivered to the right ear (p = 0.037, unpaired t test) and a trend for MMNm decrease ipsilaterally in the left ear condition (p = 0.078, unpaired t test). Corresponding analysis revealed insignificant right hemisphere MMNm amplitude differences between the groups. A paired t test showed that schizophrenia patients, unlike control subjects, had significantly decreased MMNm amplitude over the left hemisphere compared with the right hemisphere when the tones were presented to the contralateral ear (p = 0.016, paired t test). There was neither significant main effect for gender, nor gender × hemisphere interaction.

AEF latencies of both hemispheres were subjected to three-way ANOVA (group × ear × hemisphere) to assess possible MMNm latency differences. There was a significant group × hemisphere interaction (F[1,32] = 5.11; p = 0.031) that was caused by significantly delayed MMNm in the left hemisphere when the tones were delivered ipsilaterally (p = 0.007, unpaired t test). The group effect for MMNm latency was insignificant, and in the right hemisphere, the MMNm latencies were quite similar in both groups (table 3). Gender did not affect MMNm latencies across the groups (F[1,32] = 0.012).

A reliable source localization analysis could be performed for the data of only 13 patients and 16 control subjects in the right hemisphere using a 70 percent cutoff point for fitting. The MMNm source was more lateral in the patient group (table 4), and there was also a significant MMNm dipole strength decrease in the patient group:

Results

Figure 1 depicts AEFs and field patterns of one representative patient and one healthy control subject to the deviant tones with a 0.5-s ISI. The patient had over both hemispheres MMNm responses that were smaller than those of the control subject.

The source modeling of the MMNm was attempted for all subjects but failed in 12 patients in the left hemisphere, whereas for 13 patients it was successful in the right hemisphere, when the 70 percent cutoff point for fitting was used. The source modeling in the control group failed in 5 cases in the left hemisphere and in 3 cases in the right hemisphere. Therefore, all fitting data underwent a group × hemisphere ANOVA irrespective of g percent (g = goodness of fit). The MMNm dipole strength was significantly decreased in the patient group (F[1,32] = 7.531; p = 0.010), whereas the group × hemisphere interaction was insignificant (F[1,32] = 0.61). An additional analysis revealed that the patients had significantly reduced MMNm in the left hemisphere compared with the control subjects (p = 0.038, unpaired t test), showing a trend of MMNm reduction in the right hemisphere (p = 0.066) (table 1). MMNm dipole was stronger in the right hemisphere across the groups (F[1,32] = 8.750; p = 0.006), whereas there was not a significant gender effect for the MMNm dipole (F[1,32] = 0.037) across the groups.

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Table 2. AEF amplitudes (fT/cm) for the deviant tones (MMNm) in the right and left ear conditions over the right and left hemispheres, mean ± SD

<table>
<thead>
<tr>
<th>Group/ear stimulated</th>
<th>Ipsilateral hemisphere</th>
<th>Contralateral hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia/right</td>
<td>15.6 ± 7.7</td>
<td>14.8 ± 7.7*</td>
</tr>
<tr>
<td>Control/right</td>
<td>14.7 ± 4.9</td>
<td>21.6 ± 10.0</td>
</tr>
<tr>
<td>Schizophrenia/left</td>
<td>13.9 ± 6.9</td>
<td>23.0 ± 11.5</td>
</tr>
<tr>
<td>Control/left</td>
<td>19.0 ± 9.0</td>
<td>26.0 ± 8.6</td>
</tr>
</tbody>
</table>

Note.—AEF = auditory evoked potential; ISI = interstimulus interval; MMNm = mismatch negativity, magnetic counterpart; SD = standard deviation. Tones were presented separately to the left and right ear in all patients and controls with an ISI of 0.5 s. Schizophrenia patients had significantly smaller MMNm amplitude in the right ear condition in the hemisphere contralateral to the ear stimulated. MMNm was obtained by subtracting the standard AEF from the deviant AEF. *p < 0.05, unpaired t test

Table 3. AEF latencies (ms) for the deviant tones (MMNm) in the right and left ear conditions over each hemisphere, mean ± SD

<table>
<thead>
<tr>
<th>Group/ear stimulated</th>
<th>Ipsilateral hemisphere</th>
<th>Contralateral hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia/right</td>
<td>171 ± 31</td>
<td>161 ± 31</td>
</tr>
<tr>
<td>Control/right</td>
<td>174 ± 35</td>
<td>171 ± 36</td>
</tr>
<tr>
<td>Schizophrenia/left</td>
<td>187 ± 29*</td>
<td>168 ± 24</td>
</tr>
<tr>
<td>Control/left</td>
<td>160 ± 25</td>
<td>170 ± 26</td>
</tr>
</tbody>
</table>

Note.—AEF = auditory evoked potential; MMNm = mismatch negativity, magnetic counterpart; SD = standard deviation. The patients had significantly delayed MMNm in the ipsilateral hemisphere in the left ear condition. *p < 0.01, unpaired t test

Table 4. MMNm source localization in the right hemisphere, mean ± SD

<table>
<thead>
<tr>
<th>Group</th>
<th>x (mm)</th>
<th>y (mm)</th>
<th>z (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>55 ± 8*</td>
<td>4 ± 13</td>
<td>53 ± 10</td>
</tr>
<tr>
<td>Control</td>
<td>47 ± 6</td>
<td>7 ± 14</td>
<td>52 ± 15</td>
</tr>
</tbody>
</table>

Note.—ECD = equivalent current dipole; MMNm = mismatch negativity, magnetic counterpart; SD = standard deviation. MMNm source was more lateral in the patient group. When the 70% cutoff point for MMNm source localization was applied, the data of the right hemisphere from 13 patients and 16 control subjects accomplished the analysis. The statistical analysis could not be performed for the ECD fitting data of the left hemisphere, because fittings of only three patients were reliable (exceeding the 70% limit).

The PANSS scores were compared with the MMNm amplitude and latency over the left hemisphere, where the MMNm was reduced in the patient group. Pearson correlation analysis found no significant correlations between PANSS and GAF scores and MMNm.

Discussion

The major finding was that preattentive auditory discrimination to the duration change was impaired in the patient group, supporting previous EEG findings of reduced duration MMN in schizophrenia (Shelley et al. 1991; Lembrehghts and Timsit-Berthier 1993; Catts et al. 1995; Kasai et al. 1999). Given that the MMN generators in the temporal and frontal lobes are almost simultaneously activated and that MEG is more sensitive to the temporal than to the frontal MMNm, present results indicate that the preattentive memory-based comparison process to duration change is attenuated already at the level of auditory cortices in schizophrenia. Interestingly, Kreitschmann-Andermahr et al. (1999) found in their MEG study a significant MMNm decrease to stimulus omission and to different pitch changes in schizophrenia patients. This finding suggests that the neuropathology underlying schizophrenia affects duration and frequency MMNm generators similarly, although the type of deviant used, deviant probability, and ISI (Javitt 2000) also appear to modulate MMNm amplitudes in schizophrenia patients. Whether the MMN disruption is caused by an impaired preattentive comparison process per se or abnormal memory trace decay in the auditory system remains ambiguous, because only one ISI was employed. Although the present results failed to show significant group X hemisphere interaction, they tentatively suggest more left than right temporal lobe attenuation of auditory discrimination to duration change in schizophrenia patients. This supports previous EEG results, which have found that schizophrenia patients tend to have MMN reduction and that the reduction tends to be greater in the left than the right hemisphere (Javitt et al. 1993).

Our results showed significantly delayed MMNm in patients compared with control subjects in the left but not the right hemisphere, and only when the tones were presented to the ipsilateral ear. In the EEG literature, there are only a few results suggesting delayed MMN in schizophrenia (Kathmann et al. 1995; Shutara et al. 1996),
whereas the only existing MEG study did not find significantly delayed MMNm in schizophrenia patients (Kreitschmann-Andermahr et al. 1999). Activity of the weaker and delayed MMN generator, as shown in this study, may be overlapped by a stronger and earlier MMN generator of the opposite hemisphere, probably blurring the weaker response as measured with conventional EEG. Kreitschmann-Andermahr et al. (1999) did not find significantly delayed MMNm because they measured MMNm activity over only the hemisphere contralateral to the ear stimulated, whereas in this study MMNm activity over both hemispheres was recorded simultaneously.

Our present findings of bitemporally attenuated MMNm with left hemisphere MMNm delay are probably caused by several factors. Auditory information from one ear ascends to both auditory cortices via the smaller ipsilateral and larger contralateral pathway, although there are several brainstem nuclei where the input from both ears converge (Greenstein and Greenstein 2000). The auditory processing in the left temporal lobe, which appears to be reduced in size in schizophrenia (Petty and Abukmeil 1998), might be functionally more vulnerable than the corresponding processing in the relatively well-preserved right temporal lobe in schizophrenia. For the same reasons, the smaller nerve bundle in the left hemisphere could first show functional impairments as reflected by the delayed MMNm response. Subcortical abnormalities in the region of the thalamus and basal ganglia have also been proposed in schizophrenia (Lawrie and Abukmeil 1998). MEG results, however, suggest that MMNm is mainly generated in or near the auditory cortex (Hari et al. 1984). Hence it is plausible that the decreased MMNm in schizophrenia patients observed here is mainly caused by dysfunction of cortical structures of the temporal lobes.

Auditory processing preceding MMNm, as shown by P50m and N100m responses, and a subsequent P200m response, appears to be selectively impaired in schizophrenia. Accelerated P50m in the right hemisphere with bilaterally unaffected N100m (Pekkonen et al. 1999), reduced N100m, and enlarged P200m (Kreitschmann-Andermahr et al. 1999), as calculated by mean global field power, have been reported in schizophrenia. There is also evidence of impaired left-hemisphere dominance of auditory processing to right-ear stimulation among schizophrenia patients as shown by loss of N100m dipole moment asymmetry (Rockstroh et al. 1998). Although the existing results are somewhat contradictory, present MMNm findings together with previous results suggest that consecutive auditory responses underlying preattentive processing are affected differently in schizophrenia.

Both the standard and deviant tones elicit N100m responses, which may differ in amplitude and latency based on different stimulus duration. N100 response is mainly elicited by the onset of the sustained stimuli (Näätänen 1992), and further, increases in the stimulus rise time are associated with smaller peak amplitude and latency prolongation of the N100 (Kodera et al. 1979). In the present study, however, the rise time for the standard and deviant stimuli were the same, and thus there should not have been a significant N100m effect for the MMNm responses. In addition, MMNm was obtained by subtracting the standard tone response from the deviant tone response, thus eliminating N100m responses from the MMNm response.

Most patients in this study were taking antipsychotic medication that may have affected cortical processing and thus contributed to the observed MMNm decrease. Our recent results indicate that a single dose of haloperidol, a dopamine D2-receptor antagonist, does not attenuate electric and magnetic MMNm (Pekkonen et al. 2002). Therefore, it is unlikely that medication alone contributed to observed MMNm reduction in the schizophrenia patients.

The auditory generator location between the hemispheres preceding MMNm appears to have loss of normal anterior-posterior asymmetry in schizophrenia (Reite et al. 1997; Tiihonen et al. 1998). Our results did not reveal significant changes of the MMNm location in the right hemisphere in the anterior-posterior direction, although the MMNm source was more lateral in the patient group. However, because of strongly attenuated left hemisphere MMNm in the patient group, a possible ECD location difference in the left hemisphere remained elusive.

The present results, together with previous MEG (Kreitschmann-Andermahr et al. 1999) and EEG findings (Javitt 2000), suggest that both the duration and frequency MMN generators are impaired in schizophrenia at the level of the auditory cortex when short ISIs are employed. Interestingly, patients with Alzheimer’s disease (AD) appear to have rather a well-preserved frequency MMN generator at short ISIs, whereas the duration MMNm appears to be more sensitive to age-related changes than the frequency MMN at short ISIs (e.g., Pekkonen 2000) probably because of different sensitivities of the frequency and duration MMN to cholinergic transmitters (Pekkonen et al. 2001). Hence the differences of underlying neuropathology in schizophrenia and in AD may give rise to divergent MMN results in these diseases.

In conclusion, present results showed reduced MMNm activity at the level of the temporal lobes, indicating that auditory processing underlying the preattentive memory-based comparison process is impaired in schizophrenia. In addition, MMNm activity was selectively delayed in the left hemisphere to ipsilaterally delivered stimuli.
References


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