Mismatch Negativity in Chronic Schizophrenia and First-Episode Schizophrenia

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Background: Mismatch negativity (MMN) is an event-related brain potential that is sensitive to stimulus deviation from a repetitive pattern. The MMN is thought primarily to reflect the activity of sensory memory, with, at most, moderate influences of higher-level cognitive processes, such as attention. The MMN is reported to be reduced in patients with chronic schizophrenia. However, it is unknown whether MMN is reduced in patients with first-episode schizophrenia (at first hospitalization).

Methods: Subject groups comprised patients with chronic schizophrenia (n=16) and older control subjects (n=13), and patients with first-episode schizophrenia (n=21) and younger control subjects (n=27). The MMN was visualized by subtracting the averaged event-related brain potential to standard tones (1 kHz [95% of all tones]) from the event-related brain potential to pitch-deviant tones (1.2 kHz [5% of all tones]). The MMN voltage was the mean voltage from 100 to 200 milliseconds.

Results: Pitch-deviant MMN was reduced by approximately 47% in patients with chronic illness along the sagittal midline relative to controls. The MMN was not reduced in patients with first-episode schizophrenia. All 4 groups showed approximately 64% larger MMN to pitch-deviant tones over the right hemisphere compared with the left hemisphere.

Conclusions: The pitch-deviant MMN reductions present in patients with chronic schizophrenia are not present at first hospitalization. The sensory, echoic memory functions indexed by MMN seem unaffected early in the schizophrenia disease process. Reductions in MMN amplitude may develop over time and index the progression of the disorder, although that can only be definitively determined by longitudinal assessments.

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Mismatch Negativity (MMN) is a brainwave to stimuli deviating from preceding repetitive stimuli, thought to reflect the operations of echoic memory, generally uninfluenced by cognitive operations.1,2 (However, some studies3,4 report small attention effects.) Mismatch negativity has been elicited by changes in pitch,5 intensity,6 location,7 and tone sequences.8 The MMN is reliable9 across sessions.

Mismatch negativity is generated in the primary auditory cortex,10,11,12 but the secondary auditory cortex may be activated as the stimulus deviance increases.13,14,15 A frontal lobe component may be activated, and is thought to reflect the passive drawing of attention.16,17,18 The MMN likely reflects N-methyl-D-aspartate channel current influx in cortical layers II and III, based on extracellular recordings in the monkey cortex.19 In humans, Oranje et al20 did not detect reduced MMN following ketamine hydrochloride (an N-methyl-D-aspartate antagonist) administration, but Umbricht et al21 did; the latter finding is consistent with N-methyl-D-aspartate/glutamate involvement in MMN generation.

The MMN is intriguing given the interest in gating abnormalities and N-methyl-D-aspartate involvement in patients with schizophrenia. Using pitch deviants, Javitt et al22-27 showed reduced MMN in patients with schizophrenia, a finding replicated by several others28-32 and also observed for MMN measured using magnetoencephalography.33 Several studies27,28 report correlations between negative symptoms and MMN amplitude. The MMN reduction is apparently not ameliorated by either typical (haloperidol [Haldol]) or atypical (clozapine) medication.31

The MMN to duration deviants is consistently reduced in patients with schizophrenia.28,34-37 However, some stud-
PATIENTS AND METHODS

SUBJECTS

Sixteen male inpatients with chronic schizophrenia from McLean Hospital were compared with 13 male control subjects without any history of psychiatric disorder. Chronic illness was defined as 3 or more hospitalizations (mean ± SD duration of illness, 14.3 ± [8.5] years). Also, 21 patients who were first hospitalized for schizophrenia (including 3 women) were compared with 27 control subjects without any history of psychiatric disorder (including 7 women). Controls were recruited from the general population through newspaper advertisement. Patients’ diagnoses were confirmed via the Structured Clinical Interview for DSM-III-R–Patient Edition (SCID-P), 35 and controls were screened using the Structured Clinical Interview for DSM-III-R–Non-Patient Edition (SCID-NP), 36 by trained interviewers (D.F.S. and M.E.S.). Inclusion criteria were age between 18 and 55 years, IQ greater than 85, and normal hearing as assessed by audiometry. Any subject with a documented developmental disorder or a learning disability, a neurological impairment, or a history of electroconvulsive therapy, seizures, head injury, or substance dependence within the past 5 years was excluded. Each patient group did not differ from its respective control group in age or parental socioeconomic status. Subject demographic characteristics and basic cognitive functioning, and clinical scales and medication values for the patients are presented in Table 1. All subjects gave written informed consent and were paid to participate.

PROCEDURES

Subjects were presented with 1600 binaural tone pips (3 per second). Standard tones were 1 kHz, 75 dB, 100 milliseconds in duration, with 10-millisecond rise/fall times (1520 trials). Deviant tones were 1.2 kHz, 75 dB, 100 milliseconds in duration, with 10-millisecond rise/fall times (80 trials). During tone presentation, subjects sat 1 m from a cathode-ray tube on which was displayed a checkerboard with green and red squares. Subjects were instructed to ignore the tones and to make a right thumb response on a keypad each time the checkerboard squares reversed colors asynchronously, with a range of 430 to 1500 milliseconds. Tracking performance was monitored, and subjects were admonished to maintain the task.

Electroencephalographic activity was recorded from the scalp through 28 tin electrodes in preconfigured caps (ElectroCap International, Eaton, Ohio). Electrode sites included all International 10-20 System sites, excluding T1 and T2 and including Oz, FT1C, FT2C, TCP1, TCP2, P01, P02, CP1, and CP2. Linked earlobes were used as the reference, and the forehead was used as ground. Electrodes were placed at the outer canthi of the eyes were used to monitor horizontal eye movements. Electrode impedances were below 3 kΩ, and the ears were matched within 1 kΩ. The electroencephalograph amplifier bandpass was 0.15 Hz (6 dB per octave roll-off) to 40 Hz (36 dB per octave roll-off). Electroencephalographic activity and stimulus markers were recorded continuously, digitized at 1.96 milliseconds per sample. Averaging and artifact rejection were performed off-line. Continuous data were epoched about the stimulus onset. Each epoch was 350-millisecond duration, including a 50-millisecond prestimulus baseline. Within each 1600-trial block, epochs from each electrode site were baseline corrected by subtraction of the average prestimulus voltage, and mathematically corrected for eye movement artifact. 37 Subsequently, epochs exceeding ±50 μV at F7, F8, Fp1, or Fp2 were rejected. Averages were computed for the brain responses to standard and deviant tones. Event-related brain potentials to standard tones were subtracted from event-related brain potentials to deviant tones. The resulting MMN subtraction waveform was digitally low-pass filtered at 20 Hz to remove any high-frequency artifact. The MMN amplitude was measured as the mean voltage from 100 to 200 milliseconds. 30

DATA ANALYSIS

Analyses used mixed-model repeated-measures analysis of variance. Two main analyses of MMN amplitude were performed. Midline analyses had one within-subjects factor of electrode site (Fz, Cz, and Pz). Group was the between-subjects factor. Regional analyses had 2 within-subjects factors, region (frontal: F1, F2, F3, and F4; central: T3, T4, T5, T6, and CP1, and CP2; and parieto-occipital: P3, P4, P01, P02, O1, and O2) and hemisphere (left and right). Group was the only between-subjects factor. Degrees of freedom were adjusted with the Huynh-Feldt ε for factors with more than 2 levels. For correlations with clinical variables, the Pearson product moment correlation was used. All tests used 2-tailed probabilities. Results were considered significant at P<.05. 41

ies 37-40 of pitch deviants failed to detect reductions. Several possibilities exist for these failures, including different interstimulus intervals and deviant probabilities, and peak vs interval amplitude measurement. 35-38 Another confound is the control of attention. Attention-related potentials (eg, N1 and N2b) might overlap MMN if tones are attended. 41

Two studies 30,33 reported that MMN was more reduced over the left hemisphere in patients with schizophrenia, and Javitt et al 26 reported a trend-level reduction on the left side. One abstract 24 reported that MMN amplitude in patients with schizophrenia correlated with the volume of primary auditory cortex (Heschl gyrus), but not with the remainder of the posterior superior temporal gyrus. Using functional magnetic resonance imaging, Wible et al 43 showed bilateral reduction of Heschl gyrus MMN activation in patients with schizophrenia.

To our knowledge, MMN has never been reported in patients with first-episode schizophrenia. Javitt et al 26 reported marginal (P=.06) reductions in outpatients within 3 years of their first episode. Salisbury et al 44 and Umbricht et al 45 published abstracts suggesting that MMN is not reduced at the first episode. Measurement in patients with first-episode schizophrenia of variables that are pathological in those with chronic schizophrenia avoids confounds related to chronicity. For example, subjects with first-episode schizophrenia show the same left hemisphere deficit in P30 as patients with chronic schizo-
The patients with chronic schizophrenia showed a reduced MMN relative to their controls over the entire surface of the scalp, yet both groups showed larger MMN to tone-deviants over the right compared with the left temporal sites (Figure 1). Analysis along the sagittal midline (Fz, Cz, and Pz) revealed that the MMN was smaller more negative MMN frontally (F
2,
54
= 21.88, P < .001) and parietal (Pz) (F
2,
54
= 1.0). An analysis of hemisphere effects in each region revealed that MMN amplitude was larger over the right hemisphere for the temporal sites (F
1,
27
= 4.30, P = .048), but not for the parieto-occipital (P = .09) or the frontal (P > .48) sites.

In light of previous reports of left-greater-than-right reductions of MMN in patients with schizophrenia, each lateral site over temporal and parietal lobes was compared between the patients with chronic schizophrenia and their controls. There was no support for a differential hemispheric reduction; the MMN seemed to be equally reduced in patients for each hemisphere. There were no significant associations in the patients with chronic schizophrenia between MMN amplitude at Fz and total BPRS scores or any factor of the BPRS (thinking disturbance, hostile-suspiciousness, withdrawal-retardation, and anxious depression).

Exploratory analyses between clinical measures and MMN across the scalp revealed several significant associations. The MMN at the right frontal site (F4) was associated with the withdrawal-retardation factor (r = 0.49, P = .03); the greater the negative symptoms, the smaller the MMN. The MMN amplitude at the left midtemporal site (T3) was associated with the total BPRS score and the thinking disturbance factor. The greater the total BPRS score, the smaller the MMN at T3 (r = 0.52, P = .04), and the greater the thinking disturbance factor, the smaller the MMN at T3 (r = 0.55, P = .03). The MMN

### Table 1. Demographic, Neuropsychological, and Clinical Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With Chronic Schizophrenia (n = 16)</th>
<th>Older Control Subjects (n = 13)</th>
<th>t</th>
<th>P Value</th>
<th>Patients With First-Episode Schizophrenia (n = 21)</th>
<th>Younger Control Subjects (n = 27)</th>
<th>t</th>
<th>P Value</th>
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<tr>
<td>Age, y</td>
<td>38.7 (6.9)</td>
<td>33.2 (10.7)</td>
<td>1.67</td>
<td>.11</td>
<td>24.9 (6.2)</td>
<td>24.2 (4.3)</td>
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<td></td>
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</tr>
<tr>
<td>Patient</td>
<td>4.4 (0.9)</td>
<td>2.4 (1.3)</td>
<td>4.99</td>
<td>&lt;.001</td>
<td>3.6 (1.2)</td>
<td>2.2 (0.9)</td>
<td>4.37</td>
<td>&lt;.001</td>
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<td>Parent</td>
<td>2.4 (1.3)</td>
<td>2.0 (1.0)</td>
<td>0.85</td>
<td>.40</td>
<td>2.0 (1.0)</td>
<td>1.6 (0.8)</td>
<td>1.53</td>
<td>.13</td>
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<td>WAIS-R Info</td>
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<td>12.7 (1.8)</td>
<td>2.32</td>
<td>.03</td>
<td>12.1 (3.7)</td>
<td>12.8 (2.6)</td>
<td>0.67</td>
<td>.51</td>
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<td>WAIS-R T</td>
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<td>12.7 (2.8)</td>
<td>4.10</td>
<td>&lt;.001</td>
<td>9.9 (2.6)</td>
<td>11.0 (2.6)</td>
<td>1.48</td>
<td>.14</td>
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<td>2.48</td>
<td>.02</td>
<td>28.2 (1.5)</td>
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<td>GAS score</td>
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<td>BPRS score</td>
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<td>36.1 (14.4)</td>
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<td></td>
<td>219.6 (222.6)</td>
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*Data are given as mean (SD). Two younger control subjects were missing data from neuropsychological testing; hence, df = 44 for those tests. Patients received the following medications during their hospitalization: haloperidol (Haldol) (n = 3); haloperidol and olanzapine (n = 1); haloperidol, divalproex sodium (Depakote), and risperidone (n = 1); haloperidol, divalproex sodium, and clozapine (n = 1); perphenazine (Trilafon) (n = 2); perphenazine and olanzapine (n = 1); perphenazine, divalproex sodium, and clozapine (n = 1); perphenazine, clozapine, and paroxetine (Paxil) (n = 1); risperidone (n = 4); olanzapine (n = 5); olanzapine and divalproex sodium (n = 1); olanzapine and fluoxetine hydrochloride (Prozac) (n = 1); olanzapine, divalproex sodium, and paroxetine (n = 1); olanzapine, citalopram hydrobromide (Celexa), gabapentin (Neurontin), and lithium carbonate (n = 1); fluphenazine hydrochloride (Prolixin) and divalproex sodium (n = 1); clozapine (n = 1); clozapine and divalproex sodium (n = 1); clozapine, trifluoperazine hydrochloride (Stelazine), and lithium carbonate (n = 1); clozapine, divalproex sodium, fluoxetine hydrochloride, and lithium carbonate (n = 1); trifluoperazine hydrochloride and lithium carbonate (n = 1); thiopental sodium (Mellaril) and sertraline hydrochloride (Zoloft) (n = 1); quetiapine fumarate (Seroquel) and lithium carbonate (Stelazine), and lithium carbonate (n = 1); clozapine, perphenazine, divalproex sodium, and clozapine (n = 1); perphenazine, clozapine, and paroxetine (Paxil) (n = 1); quetiapine fumarate (Seroquel) and lithium carbonate (n = 1); olanzapine and fluoxetine hydrochloride (Prozac), and lamotrigine (Lamictal) (n = 1). Three patients did not receive medications. SES indicates socioeconomic status; WAIS-R, Wechsler Adult Intelligence Scale–Revised; Info, scaled scores of WAIS-R information; Digits F, raw score on WAIS-R Digits Forward; Digits B, raw score on WAIS-R Digits Backward; Digits T, scaled score on WAIS-R Digits Total (Forward and Backward); Mini-Mental, total score on the Mini-Mental State Examination; GAS, Global Assessment Scale; BPRS, Brief Psychiatric Rating Scale; Medication, chlorpromazine equivalents at testing; and ellipses, data not applicable.

The patients with chronic schizophrenia showed a reduced MMN relative to their controls over the entire surface of the scalp, yet both groups showed larger MMN to tone-deviants over the right compared with the left temporal sites (Figure 1). Analysis along the sagittal midline (Fz, Cz, and Pz) revealed that the MMN was smaller in the patients with schizophrenia by approximately 43% (F
1,
27
= 7.96, P = .009) (Table 2). Both groups showed more negative MMN frontally (F
1,
27
= 21.88, P < .001, r = 0.69). The MMN amplitudes over each hemisphere from the frontal, temporal, and parieto-occipital regions were compared between groups (Figure 1). Patients with chronic schizophrenia showed smaller lateral MMN amplitudes than their controls (F
1,
27
= 7.61, P = .01). The MMN amplitude was greatest over the frontal sites and reduced more posteriorly (F
1,
27
= 36.85, P < .001, r = 0.73). This topography did not differ between groups (P > .21). The MMN displayed a hemispheric asymmetry that was different for the 3 regions (region \times hemisphere: F
2,
13
= 6.65, P = .003, r = 1.0). An analysis of hemisphere effects in each region revealed that MMN amplitude was larger over the right hemisphere for the temporal sites (F
1,
27
= 4.30, P = .048), but not for the parieto-occipital (P = 0.09) or the frontal (P > .48) sites.
from the site at the junction of the left temporal and parietal lobes (TCP1) was also associated with the thinking disturbance factor. The greater the thinking disturbance, the more abnormal the MMN ($r=0.54$, $P=.03$). By contrast, MMN amplitudes from over the right temporal lobe were associated with the hostile-suspiciousness scale. The greater the hostile-suspiciousness factor of the subject, the larger that subject’s MMN at T4 ($r=-0.49$, $P=.05$), T6 ($r=-0.52$, $P=.04$), and TCP2 ($r=-0.52$, $P=.04$).

In contrast to the patients with chronic schizophrenia, the patients with first-episode schizophrenia...
showed an MMN similar in amplitude to their controls (Figure 2). Patients with first-episode schizophrenia and their controls showed larger MMN to tone–deviants over the right hemisphere. The patients with first-episode schizophrenia were not significantly different from their controls along the sagittal midline (P > .44). Both groups showed the largest MMN amplitude frontally, with a decreasing gradient posteriorly (F(2,92) = 40.90, P < .001, η² = 0.46). The midline distribution did not differ between groups (P > .34). To exclude a failure to detect group differences between the controls and the subjects with first-episode schizophrenia because of the larger site factor, each site was separately compared. No midline site was significantly different between subjects with first-episode schizophrenia and controls. The maximum effect size was at T6 (d = 0.4), and would need approximately 99 subjects per group to attain significance, assuming a power of 0.8.

There was no significant association in first-episode schizophrenia between MMN amplitude at Fz and total BPRS scores, the thinking disturbance factor, the hostile-suspiciousness factor, or the withdrawal-retardation factor (r = −0.03, P = .99). However, there were several associations between these clinical scales and MMN amplitude at other sites. All of the significant correlations were negative, which, because MMN is a negative potential, suggest that greater scores on these measures of psychopathological features were related to larger MMN amplitudes. There were widespread associations between the anxious depression factor and MMN amplitude, including Fz (r = −0.51, P = .02). This factor correlated with nearly all sites, except for the inferior temporal sites (r range, −0.44 to −0.68). Greater BPRS total scores were generally associated with larger MMN amplitudes for all but the frontal sites (r range, −0.44 to −0.55). Thinking disturbance and hostile-suspiciousness scores tended to be associated with MMN from parietal and occipital sites (r range, −0.44 to −0.58).

Finally, sex seemed to have no effect. Restricting analyses to men only did not change the significant effects reported.

Patients with chronic schizophrenia showed widespread MMN reductions to pitch deviants with atten-
tion focused on the visual modality. Patients with chronic schizophrenia and their controls showed larger MMN amplitudes over the right hemisphere compared with the left, consistent with the expected lateral distribution of MMN to tone pips.58,59 (The MMN elicited by vowel deviants shows a left-sided augmentation.60,61) The MMN topography did not differ between patients with chronic schizophrenia and their controls, suggesting a similar constellation of active sources.44,62 Left-sided abnormalities of MMN were not observed in the patients with chronic schizophrenia, in contrast to a previous report.30 This difference may reflect the control of attention in this study or that the previous study30 tested patients with negative symptoms who were refractory to treatment in contrast with the current patients with positive symptoms. The correlations with clinical variables were in accord

Figure 2. Mismatch negativity difference waveforms across the surface of the head in patients with first-episode schizophrenia and in a comparison group without any history of psychiatric disorder.
with the literature,27,28 showing smaller frontal MMN with greater negative symptoms. The smaller left temporal MMN associated with greater thinking disturbance was similar to the previous finding of an association between greater hallucinatory behavior and smaller lateral inferior frontal MMN.30

Patients with first-episode schizophrenia did not differ from their controls in MMN amplitude. It remains unclear whether the apparent differences between groups at the posterior sites reflect a spurious signal-to-noise effect or a small but nonsignificant reduction in the patients, perhaps reflecting the beginning of an aberrant reduction. Patients with first-episode schizophrenia and their controls showed larger MMN amplitude over the right hemisphere, consistent with the expected lateral distribution of MMN to tone pips. We saw no evidence for different MMN topographies in the patients vs the controls.

The correlation between MMN amplitudes and clinical scales in the patients with first-episode schizophrenia is paradoxical because more pathological symptoms were associated with larger MMN activity, unlike the inverse association in the patients with chronic schizophrenia. We suggest that the pattern of symptoms at first hospitalization is volatile and statelike rather than stable and traitlike. The difficulty in finding clear-cut understandable correlations between clinical symptoms and structural magnetic resonance imaging findings at the first episode has been noted.31 Longitudinal testing of these patients will help clarify this issue.

The first-episode sample might contain a subset of subjects with reduced MMN who will develop a chronic illness, masked by a larger subset of patients with normal MMN who will not be hospitalized later. An inspection of the distributions revealed no bimodal distribution (Kolmogorov-Smirnov tests failed to detect a nonnormal distribution). It remains a tantalizing possibility that MMN reductions may develop over time from schizophrenia onset and present an objective physiological index of progressive cortical deterioration. Our planned longitudinal testing of these patients with first-episode schizophrenia will help test this hypothesis.

The MMN reduction in the patients with chronic schizophrenia is consistent with decreased preattentive processing in these patients. It remains unclear whether these findings are related to some disease process or to secondary effects, like long-term neuroleptic treatment. Catts et al28 reported that the MMN was reduced in unmedicated patients (including 4 of 11 drug-naive patients), suggesting that medication may not play a role, although a role cannot be excluded because most patients were exposed to neuroleptic agents. The normal pitch-deviant MMN in patients with first-episode schizophrenia suggests little involvement of the MMN cortical generators in pathological processes early in the disease process. Given the robust decrement of MMN in patients with chronic schizophrenia, the normal MMN in patients with first-episode schizophrenia, and the presence of left-localized abnormalities of P300 in patients with first-episode schizophrenia46 that correlate with reduced left posterior superior temporal gyrus gray matter volume,54 we hypothesize that MMN may be an index of progressive neuropathological features in patients with schizophrenia. We speculate that the normal MMN at first hospitalization decreases over time in patients with schizophrenia, reflecting some ongoing neurochemical event such as glutamate-mediated excitotoxic reduction of dendritic fields.63 The abnormal P300 at first episode may reflect more severe pathological features of the tertiary cortex in the posterior superior temporal gyrus gray matter, with the later MMN reduction reflecting the progressive involvement of the primary auditory cortex. The data of Javitt et al29 bear on this possibility: within 3 years of their first episode of schizophrenia, patients showed marginally reduced MMN (P = .06) to pitch deviants, but not as reduced as that of the sample with chronic schizophrenia. (Their duration-deviant MMN was quite reduced, but analysis of tone duration may necessitate more complex processing and likely activates a right posterior MMN generator.69) In a psychophysiological study of auditory just-noticeable differences, Rabinowicz et al53 showed that patients with first-episode schizophrenia did not differ from controls, whereas long-term inpatients did. These data suggest some role of disease duration on simple auditory processing in patients with schizophrenia. Alternatively, the MMN reduction observed in patients with chronic schizophrenia may be secondary to long-term neuroleptic medication effects. A longitudinal examination of this cohort, with subjects taking either typical or atypical neuroleptic agents, will help address this possibility.

Several caveats about the present study should be noted. Because duration deviants were not presented, it remains unknown whether the MMN elicited by this type of deviant would reveal an abnormality in these patients with first-episode schizophrenia. Stimuli with a short interstimulus interval and a low deviant probability were presented; these maximally elicit MMN. It is not known whether MMN abnormalities might be evident with different stimulation parameters. Although removal of the female patients did not alter the effects in the first-episode sample, the relatively smaller sample of women with first-episode schizophrenia and the lack of any women with chronic schizophrenia make any inferences about sex most difficult.

In summary, MMN reduction to pitch deviants is present in patients with chronic schizophrenia but absent in patients with first-episode schizophrenia. Mismatch negativity may reflect an objective psychophysiological index of progressive pathophysiological features during the early course of the disease. It remains to be determined whether MMN amplitude decrements can be ascribed to a primary disease process or to some secondary process, and whether MMN amplitude correlates with the gray matter volume of the Heschl gyrus, the putative source of pitch-deviant MMN.

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