

Aberrant Auditory Processing in Schizophrenia and in Subjects at Ultra-High-Risk for Psychosis

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The N1 and the mismatch negativity (MMN) responses observed in electroencephalographic and magnetoencephalographic (MEG) recordings reflect sensory processing, sensory memory, and adaptation and are usually abnormal in patients with schizophrenia. However, their differential sensitivity to ultra-high-risk (UHR) status is controversial. The current study evaluated the sensitivity of MEG N1m, N1m adaptation, and magnetic counterpart of MMN (MMNm) in 16 UHR subjects, 15 schizophrenia patients, and 18 healthy controls (HCs) during a passive auditory oddball task. N1m adaptation was assessed using the difference in N1m dipole moment between the first and last standard tones in a standard stimulus sequence. N1m adaptation occurred in HCs, whereas neither the UHR nor the schizophrenia groups showed adaptation to the standard tone on repeated presentations. The UHR group had values between those for HCs and schizophrenia patients. Additionally, MMNm dipole moment was reduced in both the UHR and patient groups compared with HCs, whereas the UHR and schizophrenia groups did not differ from each other. These findings indicated that both N1m adaptation and MMNm were altered in UHR subjects and in schizophrenia patients, despite unaffected N1m dipole moment to the first standard tones. Moreover, both UHR and schizophrenia groups failed to show adaptation of the N1m to repeated standard tones. This failure in adaptation was more severe in patients than UHR subjects, suggesting that auditory adaptation may be sensitive to the progression of the illness and be an early biomarker of UHR for psychosis. Deficits in auditory sensory memory, on the other hand, may be similarly impaired in both groups.

Key words: N1m adaptation/MMNm/magnetoencephalography/ultra-high-risk for psychosis/patients with schizophrenia

Introduction

Evidence has accumulated from premorbid, first-episode, and longitudinal studies that schizophrenia is both a neurodevelopmental and a neuroprogressive illness.^{1,2} Electroencephalographic (EEG) and magnetoencephalographic (MEG) studies suggest that abnormal early auditory processing may be a core feature of schizophrenia^{3–5} and may also be evident in individuals at ultra-high-risk (UHR) for schizophrenia.⁶ Although UHR individuals do not satisfy diagnostic criteria for schizophrenia, they are at increased risk for conversion to psychosis and functional decline or attenuated psychotic symptoms are apparent. At 2-year follow-up, the transition rate was 16% according to Yung et al⁷ and Ziermans et al.⁸ Ruhrmann et al,⁹ on the other hand, found that a 36.7% overall rate of transition to psychosis within 1 year calculated. Cognitive deterioration¹⁰ and structural abnormalities¹¹ in UHR individuals have also been reported. Identification of biomarkers that are sensitive to the prodromal phase could assist in the evaluation of interventions that might delay, ameliorate, or prevent the emergence of psychosis.

Auditory event-related potentials are commonly affected in schizophrenia,¹² but the sensitivity of these in measuring prodromal changes is less well established. The N1 component (magnetic counterpart: N1m) can

Table 1. Demographic Characteristics of Study Groups

	HCs (<i>n</i> = 18) Mean ± SD	UHR (<i>n</i> = 16) Mean ± SD	Schizophrenia (<i>n</i> = 15) Mean ± SD	Analysis <i>F</i> or χ^2	df	<i>P</i>
Male/female	12/6	10/6	12/3	1.22	2	.545
Age (y)	22.06 ± 2.04	21.31 ± 3.18	23.80 ± 4.60	2.23	2	.119
Education (y)	14.06 ± 1.16	13.19 ± 1.91	13.27 ± 2.25	1.22	2	.304
Handedness	11.39 ± 1.65	9.63 ± 4.21	10.53 ± 2.59	1.49	2	.235
Parental SES	2.83 ± 0.98	3.13 ± 1.31	2.50 ± 0.78	1.10	2	.341
IQ	107.50 ± 17.13	113.25 ± 14.50	103.33 ± 9.90	1.87	2	.166
GAF	91.06 ± 2.84	54.13 ± 7.36	62.13 ± 12.18	98.34	2	.000
PANSS		55.63 ± 9.35	56.47 ± 13.14	1.715	1	.838
BPRS		43.31 ± 7.55				
CAARMS		37.06 ± 12.27				
Y-BOCS		1.06 ± 4.25				
Duration of illness (y)			6.89 ± 3.14			

Note: SES, socioeconomic status; IQ, Intelligence Quotient; GAF, Global Assessment of Functioning; BPRS, Brief Psychiatric Rating Scale; CAARMS, Comprehensive Assessment of At-Risk Mental States; PANSS, Positive and Negative Symptom Scale; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; UHR, ultra-high-risk; HCs, healthy controls.

be elicited by tones in an auditory oddball paradigm, with a peak latency of approximately 70–130 ms. The N1 and N1m components are likely generated by neurons located within the superior temporal gyrus and possibly in the frontal cortices as well. N1 amplitude is determined by stimulation rate, interstimulus interval, and number of repetitions.¹³ When identical tones are presented sequentially, the amplitude of later tones is reduced compared with that of earlier tones in the sequence,¹⁴ suggesting an adaptation or habituation effect¹⁵ of the N1 component, which may correspond to cortical filtering of incoming event.¹⁶ In the present study, we used this approach to assess N1m adaptation to a series of standard tones obtained from an auditory oddball task in UHR subjects, patients with schizophrenia, and healthy control (HC) subjects.

In contrast to N1m, which is produced by repetitive stimuli, the mismatch negativity (MMN) component (magnetic counterpart: MMNm) is a neurophysiological index of the automatic detection of deviant auditory stimuli among frequent standard stimuli. MMN typically exhibits a peak latency of 150–250 ms. The MMN/MMNm is thought to be generated in the posterior superior temporal gyrus and to index sensory memory. The amplitude of the MMN is usually reduced in schizophrenia,^{5,17} and MMN abnormalities have been correlated with severity of illness,¹⁸ global functioning, and social cognition.¹⁹ Some studies have indicated that MMN to frequency deviant tones are unaffected in first-episode schizophrenia.^{20,21} Subsequently, Umbricht et al²² demonstrated a relatively smaller attenuation of the frequency deviant MMN in first-episode patients compared with chronic schizophrenia patients, whereas the tone duration MMN was equally attenuated in both patient groups. However, Salisbury et al²³ failed to demonstrate abnormal MMN to frequency deviance in first-episode

schizophrenia patients but reported that MMN was reduced approximately 1.5 years later from the first hospitalization for psychosis, suggesting that this abnormality emerges later in the course of the illness. In contrast, other studies have demonstrated abnormal duration MMN/MMNm responses in first-episode schizophrenia²⁴ and UHR subjects⁶ compared with HCs. In the present study, we examined MMNm, N1m, and N1m adaptation both in UHR subjects and in patients with schizophrenia.

The present study addressed several issues by investigating the early auditory processing both in subjects at UHR for schizophrenia and in patients with schizophrenia using MEG measures of early stage auditory processing. These measures included N1m responses to auditory stimulation, N1m adaptation to repeated stimuli, and MMNm measure of sensory memory. Although we have previously reported reduced MMNm dipole moment in a UHR group,⁶ it remains inconclusive whether impaired MMNm differentiates UHR subjects from patients with schizophrenia who share a similar level of functional impairment and symptom severity. Further, we sought to investigate whether measures of the early auditory response (N1m) or auditory adaptation to repetitive tones were affected in these 2 groups.

Materials and Methods

Subjects and Clinical Assessment

Subjects at UHR for psychosis, patients with schizophrenia, and HC subjects were recruited for this study. Table 1 provides demographic and clinical data for each group. UHR subjects (*n* = 16) were recruited from the Seoul Youth Clinic and fulfilled the Comprehensive Assessment of At-Risk Mental States (CAARMS)²⁵ and Structural Interview of Prodromal Symptoms (SIPS)²⁶ criteria for UHR status. Eleven of the UHR subjects met

criteria for attenuated psychosis; 3 subjects met vulnerability group criteria, and the remaining 2 subjects met criteria for both attenuated psychosis and vulnerability. According to the Family Interview for Genetic Studies,²⁷ 2 of the UHR subjects had a family history of psychotic disorders. Only 3 individuals in the UHR group had received low-dose treatments of atypical antipsychotics at the MEG assessment. At the study intake, a modified version of the Brief Psychiatric Rating Scale (BPRS)²⁸ and the Positive and Negative Syndrome Scale (PANSS)²⁹ were also employed to measure psychotic features. Participants were assessed with the Global Assessment of Functioning (GAF) to rate overall social, occupational, and psychological functioning. UHR subjects were monitored longitudinally by 2 experienced psychiatrists to detect the conversion to psychosis on at least a monthly basis. UHR subjects had followed up 6 months/1 year/2 years/3 years after the enrollment, and at each follow-up, they were reevaluated with structural instrument with the CAARMS and SIPS. In the cases where the psychosis threshold was passed at their follow up evaluation sessions, ie, diagnosed as schizophrenia, the subjects were excluded from the UHR cohort.

The schizophrenia subjects ($n = 15$) were diagnosed with the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* Axis I Disorders (SCID-IV) and were assessed with PANSS and GAF on admission into the study. Of the 15 patients, 11 were receiving antipsychotic medications, 3 were receiving both antipsychotics and antidepressants, no 1 was taking only antidepressants, and the remaining 1 was not receiving any medication at the MEG recordings. All patients were receiving maintenance therapy and had stable clinical status over the previous year. Age-, sex-, and Intelligence Quotient (IQ)-matched HCs ($n = 18$) were recruited. HC subjects were screened using the SCID-IV—Nonpatient Edition (SCID-NP). Exclusion criteria included past or current Axis I diagnoses or any first- to third-degree biological relatives with a psychiatric disorder. Exclusion criteria for all participants included a lifetime diagnosis of substance abuse or dependence, neurological disease or head injury, evidence of medical illness with documented cognitive sequelae, sensory impairments, intellectual disability ($IQ < 70$), or musical training within the previous 5 years. The Institutional Review Board of the Seoul National University Hospital approved the study, and written informed consent was obtained from all subjects and from parents of subjects under 18 years of age. Analysis of MMN for the 18 HC subjects and 16 UHR individuals has been reported in a previous study.⁶

MEG Recordings and MRI Acquisition

Participants were instructed to look at a picture book and to ignore the acoustic stimuli which were presented using

tubular insert earphones with the STIM2 system (Neuroscan, El Paso, TX). The acoustic stimuli consisted of a pseudorandom series of 1000 Hz (80 dB, 10 ms rise/fall) tones, which could be differentiated by duration. The block was presented in a fixed order for all subjects. Frequent standard tones (81.8%) were 50 ms in duration, and infrequent deviant (18.2%) tones were 100 ms. Subject sat in an electromagnetically shielded room in the MEG Center of Seoul National University Hospital during the measurements. MEG signals were recorded using a 0.1- to 200-Hz band-pass filter at a sampling rate of 1000 Hz using a 306-channel whole-head MEG system (Elekta Neuromag Oy, Helsinki, Finland). A bipolar electrooculogram was simultaneously recorded to monitor eye-blinking and eye-movement artifacts.

All structural magnetic resonance image (MRI) scans were acquired in the axial plane using a 1.5-T scanner (Avento, Siemens, Erlangen, Germany). Parameters were as follows: epoch time/repetition time = 4.76/1160 ms, flip angle = 15°, field of view = 230 mm, voxel size = 0.45 × 0.45 × 0.9 mm³.

Data Analysis

A Maxwell filter, which separates brain-related signals and external interference, was applied to reduce environmental and biological artifacts. Visual inspection was used to identify trials with excessive noise, muscle artifact, and eye blinks.

MEG epochs for each trial extended from 100 ms before stimulus onset to 300 ms after stimulus onset. At least 110 artifact-free epochs from 204 gradiometer sensors were averaged and filtered with a low pass of 40 Hz for standard and deviant epochs, respectively. The N1m component was obtained from the responses to the frequently repeated standard stimuli. Two types of standard tone shared physically identical characteristics; the first standard tone, which immediately followed each deviant tone, and the last standard tone, which immediately preceded each deviant tone (figure 1). These standard tones were separately averaged. The N1m response to the first and last standard tones were compared between groups, and the last standard N1m was subtracted from the first standard N1m to assess N1m adaptation. The MMNm component was obtained by subtracting the averaged response to the last standard stimulus from the averaged response to the deviant tones in each subject.

Equivalent current dipoles (ECDs) were calculated by the least-squares method using Neuromag software (Neuromag Ltd., Helsinki, Finland) to estimate the locations and activation strength of the neural generator of the signals. Only ECDs with goodness of fit values over 80% and confidence volumes below 2000 mm at selected periods of time in the subset of 20–30 channels of planar gradiometers in the vicinity of the left and right temporal regions were analyzed. The individual T1-weighted images were normalized to Talairach space.

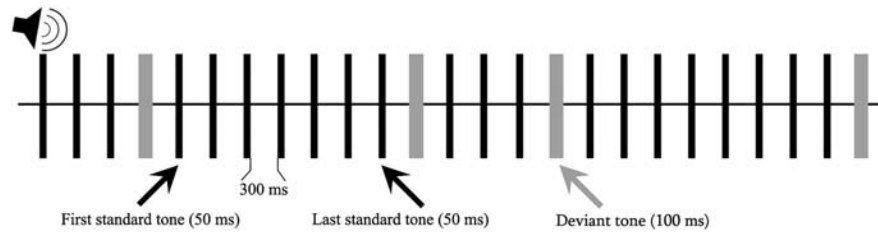


Fig. 1. Schematic diagrams of auditory oddball stimulus presentation paradigm for the magnetic counterpart of N100 and the magnetic counterpart of mismatch negativity.

Statistical Analysis

To test group differences in demographic and clinical data, one-way ANOVA was used. An independent *t* test was used to test for differences between UHR subjects and schizophrenia patients on clinical variables. For MEG measures, statistical analyses were performed on dipole moment and latency within the interval of 70–130 ms for N1m and 130–240 ms for MMNm. A 3 (group: HC, UHR, and SZ) \times 2 (hemisphere: left and right) repeated measures factorial ANOVA was used to evaluate N1m and MMNm dipole moment and dipole latency. To examine the difference between the first and last standard dipole moment, the last standard N1m was subtracted from the first standard N1m dipole moment and then a 3 (group: HC, UHR, and SZ) \times 2 (hemisphere: left and right) repeated measures factorial ANOVA was applied to the difference measure. A repeated measure ANCOVA was performed on dipole moment in each hemisphere with chlorpromazine equivalent dose as a covariate with all subjects. Significant interactions were evaluated with simple effects tests ($P < .05$) of each group using ANOVA; effect sizes are expressed as Cohen's *d*.

Results

Demographic Data

No significant group differences in gender, age, handedness, IQ, years of education, or parental socioeconomic status were found among groups. However, GAF scores ($F_{2,46} = 98.337$, $P < .001$) differ among the 3 groups (table 1). The post hoc tests revealed that the UHR subjects had significantly lower GAF scores than did the HCs ($P < .001$), whereas scores for patients with schizophrenia fell between those for HCs ($P < .001$) and for UHR subjects ($P = .009$). The PANSS total score did not differ between the UHR and schizophrenia groups.

Neuromagnetic Responses

In figure 2, the spatial distributions of the MMN, the first and the last standard tones of grand averaged data in control, UHR, and SZ groups depict the overall event-related field waveforms in the relevant time windows.

N1m. Prominent responses were seen in both temporal regions across all groups. Responses were localized on individual MRIs. The grand averaged N1m dipole sources were localized on normalized MRI anatomic space, and

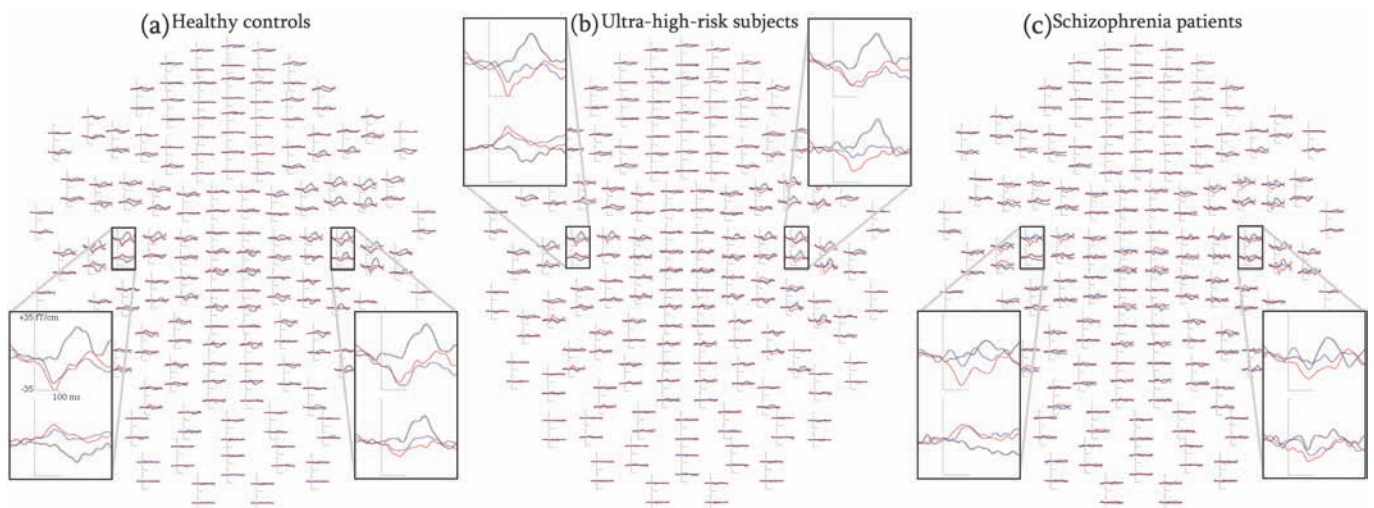


Fig. 2. Grand averaged spatial distribution of the magnetoencephalographic responses to the mismatch negativity (black), first (blue), and last (red) standard auditory tones across 3 groups.

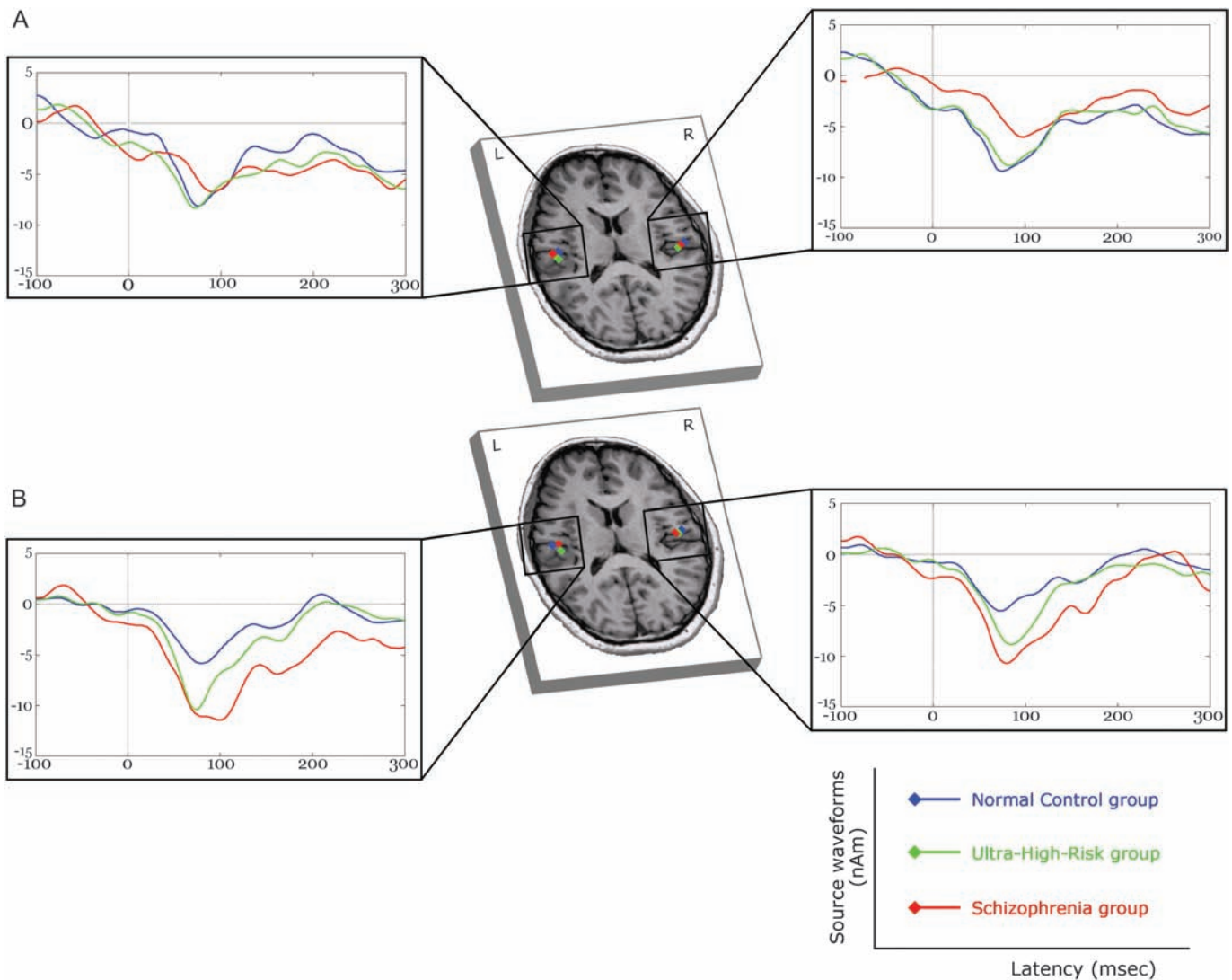


Fig. 3. Magnetoencephalography superimposed on structural magnetic resonance image of each group. Source locations for temporal dipoles in the first (A) and the last (B) magnetic counterpart of N100 for healthy control (blue), ultra-high-risk (green), and schizophrenia (red) individuals mapped onto a representative normalized brain.

grand averaged dipole moments are displayed for all groups in figure 3 and table 2.

N1m Response to the First Standard Tone With regard to the N1m dipole moment for the first standard tone following a deviant tone, no main effects of group ($F_{2,46} = 0.468$, $P = .629$) or hemisphere ($F_{1,46} = 0.046$, $P = .832$), or any group \times hemisphere interaction effects ($F_{2,46} = 0.490$, $P = .616$) were found. Results showed a main effect of group on N1m peak latency to the first standard tone ($F_{2,46} = 4.986$, $P = .011$), but a main effect of hemisphere ($F_{1,46} = 2.914$, $P = .095$) and a group \times hemisphere interaction ($F_{2,46} = 1.130$, $P = .332$) were not observed. Post hoc analyses detected that N1m to the first standard tones were smaller in the schizophrenia group ($P = .003$) and no difference between UHR subjects ($P = .244$) compared with the control group. A marginal difference was observed between UHR

subjects and patients with schizophrenia ($P = .060$) for N1m latency.

N1m Response to the Last Standard Tone ANOVA revealed a significant main effect of group ($F_{2,46} = 11.003$, $P < .001$) on the N1m dipole moment to the last standard stimulus. Post hoc analysis revealed that the HC group had a smaller N1m dipole moment than did UHR subjects ($P = .008$) and patients with schizophrenia ($P < .001$). However, post hoc tests revealed trend level differences between UHR subjects and schizophrenia patients ($P = .067$). For the N1m peak latency to the last standard tone, the main effect of hemisphere was marginally significant ($F_{1,46} = 3.680$, $P = .061$). However, there were no interaction ($F_{2,46} = 71.663$, $P = .513$) or main effect of group ($F_{2,46} = 2.252$, $P = .117$).

Adaptation of the N1m To measure N1m adaptation to repetitive stimuli, the first dipole moment was subtracted

Table 2. Mean Dipole Location, Moment, and Latency Found in the Superior Temporal Plane

		<i>x</i>	<i>y</i>	<i>z</i>	<i>Q</i> (nAm)	Latency (ms)
First N1m						
Schizophrenia	L	-51 ± 8	-19 ± 6	18 ± 12	-9 ± 6	97 ± 23
	R	52 ± 8	-16 ± 8	16 ± 11	-8 ± 4	105 ± 17
UHR	L	-48 ± 8	-22 ± 12	16 ± 6	-10 ± 6	87 ± 21
	R	50 ± 8	-17 ± 9	18 ± 7	-10 ± 5	94 ± 21
HCs	L	-48 ± 9	-19 ± 7	15 ± 7	-9 ± 5	85 ± 14
	R	53 ± 5	-15 ± 9	13 ± 8	-10 ± 8	84 ± 12
Last N1m						
Schizophrenia	L	-47 ± 8	-17 ± 7	16 ± 9	-14 ± 6	95 ± 18
	R	49 ± 6	-11 ± 7	14 ± 7	-14 ± 6	91 ± 20
UHR	L	-45 ± 7	-23 ± 9	17 ± 6	-12 ± 6	83 ± 12
	R	51 ± 8	-11 ± 6	19 ± 5	-10 ± 7	82 ± 12
HCs	L	-52 ± 7	-17 ± 5	14 ± 5	-7 ± 5	93 ± 19
	R	53 ± 6	-10 ± 6	14 ± 6	-6 ± 5	86 ± 17
MMNm						
Schizophrenia	L	-53 ± 8	-22 ± 6	22 ± 6	-7 ± 3	174 ± 30
	R	51 ± 8	-15 ± 7	9 ± 9	-10 ± 4	174 ± 26
UHR	L	-50 ± 8	-25 ± 13	19 ± 8	-9 ± 5	192 ± 29
	R	54 ± 4	-19 ± 9	16 ± 8	-9 ± 5	184 ± 34
HCs	L	-48 ± 7	-22 ± 10	16 ± 7	-11 ± 6	171 ± 23
	R	51 ± 8	-17 ± 8	12 ± 6	-17 ± 8	169 ± 24

Note: HC, healthy controls; UHR, ultra-high-risk; MMNm, magnetic counterpart of mismatch negativity; N1m, magnetic counterpart of N100.

from the last standard dipole moment, as shown in figure 3. ANOVA revealed a main effect of group ($F_{2,46} = 11.812$, $P < .001$) (figure 3), whereas neither the main effect of hemisphere ($F_{1,46} = 0.669$, $P = .418$) nor the hemisphere \times group interaction ($F_{2,46} = 0.208$, $P = .813$) were significant. Post hoc analysis revealed that adaptation was apparent in HC group, whereas neither the UHR ($P = .027$) nor the schizophrenia group ($P < .001$) showed adaptation to the standard tone on repeated presentations. Values for the UHR group fell between those for the HC ($P = .027$) and the schizophrenia group ($P = .014$).

MMNm. The MMNm source modeling localized dipole sources over the bilateral superior temporal plane for all participants using neuroanatomic reconstructions from individual MRIs. ANOVA revealed main effects of group ($F_{2,46} = 9.677$, $P < .001$), hemisphere ($F_{1,46} = 7.537$, $P = .009$) and a group \times hemisphere interaction ($F_{2,46} = 3.477$, $P = .039$) on MMNm dipole moment. An analysis of simple main effects indicated that there was significant difference in dipole moment between hemispheres in control group, ($F_{1,34} = 7.712$, $P = .011$, Cohens' $d = 0.89$). In addition, there was a trend difference in the dipole moment between hemispheres for the schizophrenia group ($F_{1,28} = 3.358$, $P = .078$, Cohens' $d = 0.67$). However, there was no hemisphere effect in the UHR group ($F_{1,30} = 0.006$, $P = .940$, Cohens' $d = -0.03$).

Post hoc analysis revealed that MMNm was smaller in both the UHR ($P < .001$) and the schizophrenia group ($P < .001$) compared with the HC group. However, the UHR group did not differ significantly from patients

with schizophrenia ($P = .933$). In terms of the MMNm dipole latency, a group effect ($F_{2,46} = 3.495$, $P = .039$) was detected, with no effects of hemisphere ($F_{1,46} = 0.412$, $P = .524$) and no group \times hemisphere interaction ($F_{2,46} = 0.240$, $P = .788$). The post hoc analysis showed a significant difference between HCs and UHR for latency ($P = .014$). The MMNm latency was slower in UHR individuals compared with HCs, whereas the patients with schizophrenia had values intermediate between those of the HCs and the UHR subjects.

Correlations Between Neuromagnetic Responses and Clinical Measures

There were negative correlations between left MMNm dipole moment and CAARMS positive symptom score ($r = -.630$, $P = .009$) and CAARMS total score ($r = -.545$, $P = .029$) and between last N1m dipole moment on left hemisphere and GAF score ($r = -.626$, $P = .009$) in the UHR group. However, no correlations were observed between neuromagnetic responses and clinical measures in patients with schizophrenia.

Discussion

The present study investigated early auditory processing indexed by N1m, N1m adaptation, and MMNm in UHR subjects and patients with schizophrenia compared with HCs. N1m moment to the first standard tones did not differ among groups, but N1m latency was affected in schizophrenia patients. Additionally, comparison of

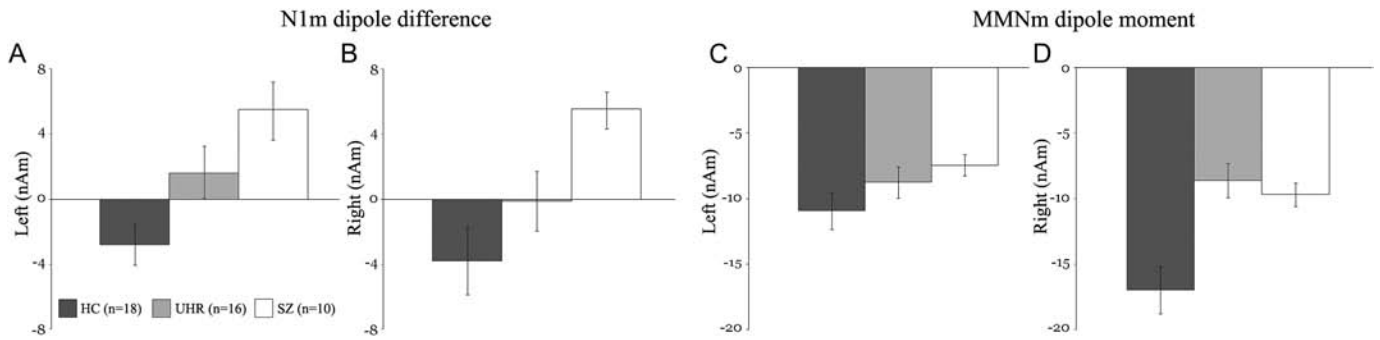


Fig. 4. Dipole difference between the first and last standard tones in the magnetic counterpart of N100 (N1m) (A, B) and the magnetic counterpart of mismatch negativity (MMNm) (C, D) dipole moment for healthy controls, ultra-high-risk, and schizophrenia groups at the time point with maximum peak in each hemisphere. The error bars denote SE of the mean.

N1m dipole moment between the first and last standard tones in a series suggested that both UHR and schizophrenia groups failed to adapt or habituate to standard tones. Moreover, this failure of adaptation was more severe in patients with schizophrenia than in UHR subjects, suggesting that it may be sensitive to the progression of the illness. Finally, the MMNm deficit in dipole moment in the UHR and schizophrenia subjects was consistent with findings in schizophrenia⁵ indicating that this component is sensitive to the pathophysiology of schizophrenia.⁶

The N1/N1m reflects auditory processing and transient encoding of physical stimulus features.³⁰ Auditory N1m shows amplitude reduction during repeated presentations of an identical stimulus. Several lines of evidence suggest that repetitive standard sounds cause refractoriness,³¹ habituation, or attenuation in the generation of brain responses, which are often termed “adaptation”.¹⁵ In accordance with the adaptation model, repetitive auditory stimuli result in adaptation of neurons in the auditory cortex,³² resulting in attenuation of the N1m dipole moment in HC subjects. An auditory-attenuation and short-term habituation paradigm revealed that suppressed responses of N1 occur to repetitively presented stimuli in HCs.³³

Previous studies provide conflicting evidence with respect to whether the auditory N1 amplitude is decreased^{34,35} or intact³⁶ in patients with schizophrenia during a passive oddball paradigm. Some familial studies have identified reduced N1/N1m as a heritable vulnerability factor, with a deficit in N1m reported in discordant twin samples³⁴ and first-degree relatives of schizophrenia probands.³⁷ However, other investigators have reported enhanced³⁸ or intact³⁹ N1 amplitude in genetic high-risk samples. To date, however, no published EEG and MEG studies have examined N1m changes in high-risk populations experiencing prodromal symptoms. In the present study, no statistical differences were found among the groups for the first standard N1m. The N1m to the last standard tone in a series, however, differed among the groups: the N1m to the last standard tone was larger in patients with schizophrenia compared with HCs,

whereas the UHR individuals had values intermediate between those of the HCs and the schizophrenia patients. Consequently, both patients with schizophrenia and UHR individuals showed altered processing of repetitive stimuli.

The present data showed increased or sustained N1m dipole moment for the last standard tone than the first tone in the UHR and schizophrenia groups compared with HC subjects (figures 3A and 3B), which was consistent with evidence from studies demonstrating deficits in N1 filtering, startle habituation, and sensory gating to auditory stimuli in schizophrenia.^{40–42} Our data suggest that adaptation or habituation may impact N1 and N1m findings. This adaptation process is thought to correspond to cortical filtering of irrelevant events.¹⁶ In the UHR group, the repetitive auditory input does not produce habituation comparable to that in the control group, leading to a larger N1m dipole moment and less efficient filtering in the cortex. Kiskey and colleagues⁴³ reported that the N1 suppression was associated with over inclusion of irrelevant stimuli into the focus of attention. To reveal the adaptation effect of repetitive standard tones, we separated the trains of standard tones (figures 4A and 4B) and calculated ECDs on temporal regions rather than analyzing the average for all the standard tones. Thus, the direct comparison with N1/N1m responses from passive oddball paradigm used in previous studies^{34,36,44} is problematic.

Supporting the previous observations, MMNm is impaired in patients with schizophrenia^{4,5,17} and in individuals at UHR for schizophrenia⁶ compared with HC group. However, MMN has been reported to be unaffected in patients with first-episode schizophrenia²⁰ and prodromal subjects⁴⁵ in other studies. These findings may be indicative of alterations in auditory function that occur with the transition from the prodromal state to schizophrenia. The UHR is heterogeneous in this respect because only one-fifth of UHR subjects ultimately receive a diagnosis of schizophrenia according to the Seoul Youth Clinic data. In accordance with results from these

studies, we suggest that MMNm dipole reduction reflects a deficit in the preattentive detection of stimulus change that triggers an involuntary attention-shifting process toward novel stimuli.

Significant correlations with clinical measures were found only in the UHR subjects. There were negative correlations between left MMNm dipole moment and CAARMS total and the positive symptom score. These correlations indicating that the greater scores on the measure of psychopathological features were associated with larger left MMNm dipole moment. Moreover, there was a correlation between last N1m dipole moment on left hemisphere and GAF score, showing that the higher scores on general functioning was related to the worse adaptation. Similarly, Salisbury et al.²⁰ reported unexpected and intriguing inverse relationship between MMN amplitude and the BPRS total and sub factors in first-episode schizophrenia, while positive correlations were found in schizophrenia group. Compared with chronic schizophrenia patients, prodromal subjects and first episode for psychosis patients are in rapidly altering state, and these may be related to the pathophysiological basis for the change in direction of correlation. Speculatively, the negative correlations in the prodromal and first-episode phase may reflect hyperactivation of the glutamatergic system possibly secondary to NMDA hypofunction,⁴⁶ and this glutamatergic hyperactivation causes excitotoxic cortical neuronal damage and a subsequent diminution of MMNm amplitude.

There are notable differences in sample characteristics between the present data set and previously studies. The patients with schizophrenia who participated in this study were in maintenance therapy after the recovery from their first-psychotic episodes, and the clinical status of the patients was relatively stable. For the purpose of testing our hypothesis, we recruited only stable outpatients who were receiving maintenance therapy, who exhibiting no increase in symptoms over the past year, and who had similar or better performance on clinical measures relative to UHR individuals according to PANSS and GAF scores. Although both UHR individuals and schizophrenia patients showed similar scores by clinical assessment, the groups were belonged to different psychotic stages of the illness. Interestingly, it is possible to detect the functional role of N1m adaptation as a physiological marker, which grew worse over the progression of psychosis.

Several limitations in the present study should be taken into account. We examined the possible confound of antipsychotic medications and observed nonsignificant covariance with chlorpromazine dosage on first N1m ($F_{1,45} = 1.166$, $P = .286$), last N1m ($F_{1,45} = 0.878$, $P = .354$), N1m adaptation ($F_{1,45} = 0.057$, $P = .812$), and MMNm ($F_{1,45} = 0.021$, $P = .886$) which informs us that results remained the same after controlling medication as covariate. However, we still cannot rule out the possibility of

a medication confound in comparisons between schizophrenia and UHR groups because only 3 UHR subjects were medicated. Studies using experimental manipulation of antipsychotic medication administration, or testing of unmedicated subjects, will be required for definitive resolution of this issue.

As with any cross-sectional design, we cannot ascertain whether the deficit was present before the psychotic factors arose and if so, whether these were specific or non-specific to the development of schizophrenia. To evaluate the characteristics of functional outcomes indexed by N1m and MMNm, a longitudinal follow-up investigation of larger samples of UHR subjects will be needed. Among the 16 UHR participants, 3 developed psychosis, and the transition rate was 18.8% during 26.6 months. This conversion rate is comparable to that in previous prodromal research.⁴⁷ During the follow-up period, 10 subjects received psychotropic medications; 4 received antipsychotics, 2 were taking antidepressants, and 4 took both types of medication. The transition rate might be partly due to the provision of medication and education to the UHR group, which might have reduced transition rates.⁴⁸

In summary, the present findings revealed a deficit in early auditory processing indexed by N1m adaptation in UHR subjects, some of whom were in a prodromal phase of schizophrenia. Further analysis revealed that group difference on the N1m adaptation (first N1m–last N1m) differed between UHR and schizophrenia groups. As reported earlier, MMNm was decreased in UHR group,⁶ and the present data revealed no statistical difference between UHR individuals and schizophrenia patients. Therefore, we can conclude that the early auditory processing indexed by N1m adaptation, and MMNm is impaired in groups of UHR and patients with schizophrenia compared with HCs. Further, aberrant N1m adaptation may be sensitive to the early progression of psychosis and might serve as a biomarker of UHR for psychosis.

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