의학박사 학위논문

Predicting Remission in Subjects at Clinical High Risk for Psychosis Using Mismatch Negativity

Mismatch Negativity를 이용한

정신증 임상적 고위험군의 관해 예측 연구

2018년 8월

서울대학교 대학원

의학과 정신과학 전공

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이 논문을 의학박사 학위논문으로 제출함

2018년 4월

서울대학교 대학원

의학과 정신과학 전공

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김민아의 의학박사 학위논문을 인준함

2018년 7월

위 원 장 _____ (인)

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위 원 _____ (인)

위 원 _____ (인)

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Submitting a Ph.D. Dissertation of Public Administration

April 2018

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Abstract

Predicting Remission in Subjects at Clinical High Risk for Psychosis Using Mismatch Negativity

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Introduction: The declining transition rate to psychotic disorder and the increasing rate of non-psychotic poor outcomes among subjects at clinical high risk (CHR) for psychosis have increased the need for biomarkers to predict remission regardless of transition. This study investigated whether mismatch negativity (MMN) predicts the prognosis of CHR individuals during a 6-year follow-up period.

Methods: The clinical statuses of 48 subjects at CHR were examined at baseline and regularly assessed for up to 6 years. The subjects were divided into remitter and non-remitter groups. Baseline MMN amplitudes as well as MMN current source density (CSD) strengths at the superior temporal gyri (STGs) and inferior frontal gyri (IFGs) of both hemispheres were compared across groups. Regression analyses were performed to identify the predictive factors of remission, the improvement of attenuated positive symptoms, and functional recovery.

Results: Compared with remitters, non-remitters showed reduced MMN amplitudes at baseline. A logistic regression analysis revealed that the baseline MMN amplitude at the frontal electrode site was the only significant predictor of remission. In a multiple regression analysis, MMN amplitude, antipsychotic use, and years of education predicted an improvement in attenuated positive symptoms. Functional recovery was predicted by MMN CSD strength at the right STG and IFG, age, and antidepressant use.

Conclusions: These results suggest that MMN is a potent predictor of prognosis regardless of the transition to psychotic disorder in subjects at CHR. Early prognosis prediction and the provision of appropriate interventions from the initial CHR status might be aided using MMN.

Keywords: Clinical high risk for psychosis; Event-related potential; Mismatch negativity; Remission; Prognosis; Schizophrenia

Student Number: 2012-21674

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List of Abbreviations

ANOVA: analysis of variance

CHR: clinical high risk

CI: confidence interval

CHR-NR: non-remitter group

CHR-NRNT: subjects who did not remit nor transition to psychotic disorder

CHR-R: remitter group

CSD: current source density

CHR-T: subjects who transitioned to overt psychotic disorder

DUPP: duration of untreated prodromal psychosis

EEG: electroencephalography

ERP: event-related potential

GAF: Global Assessment of Functioning

IFG: inferior frontal gyrus

IQ: intelligence quotient

MMN: mismatch negativity

MNI: Montreal Neurological Institute

MRI: magnetic resonance image

NMDA: N-methyl-d-aspartate

ROI: regions of interest

SCID-I: Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Axis I Disorders

SIPS: Structured Interview for Prodromal Symptoms

SOPS: Scale of Prodromal Symptoms

SPM: Statistical Parametric Mapping

STG: superior temporal gyrus

I. Introduction

1. Prognosis of subjects at clinical high risk for psychosis

Efforts aimed at early detection and intervention in patients with psychotic disorder have led the establishment of “clinical high risk (CHR)”, “ultra-high risk”, or “basic symptoms” criteria (1). The use of these approaches in identifying markers predictive of the transition to psychotic disorder have been a major focus of researchers, and sociodemographic, clinical, neuropsychological, neuroanatomical, and electrophysiological markers of this transition have been suggested (2-5). However, the transition rate in patients at CHR has been declining, which, in turn, has enlarged the proportion of CHR non-converters who do not transition to psychotic disorder within a limited observational period (6-8). Longitudinal studies have reported that CHR non-converters remained at a poor functional status even when they improved during the follow-up period (9,10). In addition, the high prevalence of non-psychotic psychiatric disorders has been consistently reported, and comorbid mental disorders are associated with poor functional outcomes in CHR non-converters (11-14). These findings suggest that attention should be paid not only to conversion status but also to general psychiatric conditions, including functional outcomes in subjects at CHR for psychosis.

2. Biomarkers of predicting remission in CHR

Given the declining transition rate and increasing rate of non-psychotic poor outcomes, predicting remission from initial CHR status might provide useful information, especially for clinical practice. The early detection of putative remitters might reduce the problems of unnecessary treatment and stigmatization. Furthermore, non-remitters, including converters, can receive more intensive care from the beginning of treatment to improve later outcomes. Although the predictors of or factors associated with remission from CHR status have not yet been sufficiently studied, the extant literature has shown that the factors associated with transition also show potential as markers for remission (i.e., symptomatic, functional, or both types of improvement). Baseline sociodemographic characteristics and clinical symptoms do not differ between remitters and non-remitters (15), whereas remitters show better neurocognitive function

than non-remitters at baseline (16). Egerton et al. found that compared with remitters, the baseline thalamic glutamate level is lower in non-remitters and is associated with a change in attenuated positive symptom severity during the course of disease (17). Kim et al. reported that baseline P300 amplitudes predict later improvement in the negative and general symptoms of subjects at CHR, although no baseline P300 difference was found between remitters and non-remitters (18). In addition, recent neuroimaging studies have attempted to predict functional improvements in individuals at CHR using a support vector regression of subcortical volumes (19). Therefore, other suggested biomarkers for schizophrenia pathophysiology or transition to psychosis might predict remission from CHR status.

3. Mismatch Negativity

Of the potential biomarkers for predicting remission in subjects at CHR, auditory mismatch negativity (MMN) is a promising candidate. MMN is an event-related potential (ERP) component that represents pre-attentive auditory processing and depends on the N-methyl-d-aspartate (NMDA) receptor-mediated glutamate system (20,21). Impaired MMN in patients with schizophrenia (at both the surface and the source level) and its association with impaired functional status have been consistently reported (22-25). In subjects at CHR for psychosis, aberrant MMN activity and its relationship with positive prodromal symptom severity were found (26,27). Moreover, baseline MMN predicts the later transition to psychotic disorder and time to conversion (5,28,29). Because symptomatic and functional improvement should be considered simultaneously to better define remission from CHR status (9,10), MMN shows the additional possibility of being a potential biomarker for remission due to its representativeness of positive prodromal symptoms and general functional status.

4. Objectives

Despite the clinical significance of predicting remission from CHR status and the potential use of MMN as a biomarker for remission, no study has attempted to predict remission in subjects at CHR using MMN. Therefore, we aimed to determine whether baseline MMN responses at the surface, source, or both levels predict later remission and symptomatic or functional improvement

during a maximal 6-year follow-up period. We hypothesized that individuals whose CHR statuses go into remission would show larger baseline MMN amplitudes than those whose statuses do not. We also hypothesized that the baseline MMN amplitude at the surface level would predict later remission as well as symptomatic and functional improvement. In addition, because auditory MMN sources have been primarily reported at the superior temporal gyrus (STG) and inferior frontal gyrus (IFG) via different mechanism of action (30-32), we expected that MMN current source density (CSD) measured at the STG and IFG would predict symptomatic or functional outcomes in different directions.

II. Methods

1. Participants

We recruited 140 subjects at CHR between January 2005 and January 2014 via the Seoul Youth Clinic (www.youthclinic.org), a center for the early detection of and intervention for people at high risk for psychosis (33). Among these subjects, 70 individuals at CHR participated in the baseline MMN measurement. CHR status was confirmed using the criteria of the Structured Interview for Prodromal Symptoms (SIPS; (34). The Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Axis I Disorders (SCID-I) was used to determine past and current psychiatric disorders. Prodromal symptoms were assessed using the validated Korean version of the SIPS (35), and the Global Assessment of Functioning (GAF) was used to define general functional status. The duration of untreated prodromal psychosis (DUPP) was obtained from medical records and interviews with the participants and their family members. Medication use was documented, and antipsychotic use was also recorded as mean olanzapine equivalent dose (36). The exclusion criteria included a lifetime diagnosis of psychotic disorder; a history of antipsychotic use; substance abuse or dependence; neurological disease or significant head trauma; medical illness with cognitive sequelae; sensory impairments; and intellectual disability (intelligence quotient [IQ] < 70).

After baseline assessment, the subjects at CHR were followed up and assessed regularly for 1 to 6 years. A total of 48 subjects at CHR who participated in the baseline MMN assessment and were followed up at least once over 6 years were included in this study. Among them, 26 CHR subjects participated in magnetic resonance image (MRI) scan at baseline. Remission from CHR status was defined as an individual at CHR meeting a score of 2 or lower on the Scale of Prodromal Symptoms (SOPS) positive sub-scale and a score of 60 or more on the GAF at the last follow-up point (10,18). The remitter group (CHR-R) included 17 participants at CHR, and the non-remitter group (CHR-NR) included 31 subjects at CHR. Among the non-remitters, 7 CHR subjects made the transition to overt psychotic disorder and finished the last follow-up assessment as CHR at the time of transition.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Seoul National University Hospital. Written informed consent was obtained from all of the participants after a full explanation of the study procedure was provided.

2. EEG recording and MRI acquisition

The electroencephalographic (EEG) recordings and MRI acquisition protocol used in this study were identical to those of a prior study conducted in our lab (27). Participants were assigned to a passive auditory oddball task while their EEGs were recorded. While subjects concentrated on a "Where's Waldo?" picture book, a pseudorandom series of 1,000-Hz (80-dB, 10-ms rise/fall) auditory stimuli were binaurally presented using a STIM2 sound generator (Compumedics, Charlotte, NC, USA). The duration of the frequent standard stimuli (81.8%, 982/1200) was 50 ms, and the duration of the infrequent deviant stimuli (18.2%, 218/1200) was 100 ms. The inter-trial interval was 600 ms.

Before EEG recording, the anatomical landmarks of each subject and the scalp locations of each electrode were obtained using an Isotrak 3D digitizer (Polhemus, Colchester, VT, USA). Continuous EEG recordings were acquired using a Neuroscan 128 Channel SynAmps system equipped with a 128-channel Quick-Cap based on the modified 10-20 international system (Compumedics, Charlotte, NC, USA). The electrodes at the mastoid sites served as the reference electrodes. The EEG data were digitized at a 1,000-Hz sampling rate with an online filter of 0.05-100 Hz. Eye movement artifacts were monitored by recording the vertical and horizontal electrooculogram using electrodes below and on the outer canthus of the left eye. The resistance at all electrode sites was below 5 kΩ.

MRI scans were obtained using a 3-T scanner (Siemens Magnetom Trio, Erlangen, Germany) equipped with a 12-channel head coil. The T1-weighted (T1) images were acquired using a magnetization-prepared rapid gradient echo sequence (TR 1670 ms, RE 1.89 ms, voxel size 1 × 1 × 1 mm3, FOV 250 mm, flip angle 9°, and 208 slices).

3. ERP analysis and source reconstruction

The pre-processing of ERP data and source reconstruction were performed using Curry version 7 software (Compumedics, Charlotte, NC, USA). Bad channels were replaced via the linear interpolation of the adjacent channels (up to 7% per participant). Eye movement artifacts were reduced using the artifact reduction algorithm implemented in Curry 7 software (37). EEG recordings were re-referenced to the common average reference data, band-pass filtered between 0.1 and 30 Hz, epoched to a 100-ms pre-stimulus and a 300-ms post-stimulus, and baseline-

corrected using the averaged pre-stimulus interval voltage. Epochs containing EEG amplitudes that exceeded ±75 μV were rejected automatically, and the number of remaining epochs exceeded 100 in all participants. MMN response activity was obtained by subtracting the ERPs elicited by the standard stimuli from those elicited by the deviant stimuli. A peak detection method was used to determine the peak MMN amplitude and latency, which was defined as the most negative deflection between 130 and 250 ms post-stimulus onset at the F3, Fz, F4, FC3, FCz, and FC4 electrode sites.

For the source-level analysis of MMN, the data of 26 individuals at CHR who had both digitized channel locations and 3T MRI data were used. For each subject, the EEG channel locations were co-registered to the structural MRI map using three anatomical landmarks (nasion and left and right preauricular points) and overlaid with Talairach coordinates (38). Individual realistic head models were constructed using the boundary element method (39), and minimum-norm least-squares (MNLS) estimation was performed to obtain the cortical MMN CSD distribution (40). The peak MMN CSD strengths were between 130 and 250 ms post-stimulus onset and were found within the STG and IFG of both hemispheres. Because functional MRI studies have shown that MMN sources are consistently located in the STG and IFG (31,41,42), these regions of interest (ROIs) were selected to detect the peak MMN CSD strengths. The cortical regions within each subject were differentiated from one another based on the anatomical labeling of the Talairach Atlas (43).

4. Statistical analysis

The demographic and clinical characteristics of the subjects were compared across groups using independent samples t-tests, or Welch's t-test when the variances were unequal. A $\chi 2$ test or Fisher's exact test was used to analyze the categorical data. Group comparisons of MMN amplitudes and latency were performed using a repeated measures analysis of variance (ANOVA) with 6 fronto-central electrode sites (F3, Fz, F4, FC3, FCz, and FC4) as the within-subject factor and group (CHR-R vs. CHR-NR) as the between-subjects factor. In addition, the MMN peak amplitude and latency at each electrode site was individually compared using independent samples t-tests. In addition, an exploratory group comparison of characteristics of subjects at CHR for psychosis who participated follow-up assessment and did not was performed. A comparison of the peak MMN CSD strength at each ROI was performed using the Kruskal-Wallis test because only 8 CHR-R subjects existed among 26 individuals at CHR from whom channel location

information and 3T MRI data were obtained. To identify the factors that predicted remission, a binary logistic regression with the backward selection method was used. A multiple regression analysis with the backward selection method was used to identify the factors that significantly predicted improvement in positive prodromal symptoms or general functional states during the follow-up period. The anticipated predictive factors included MMN peak amplitude at Fz or peak MMN CSD strengths at the STG and IFG of both hemispheres assessed at baseline; demographic characteristics (i.e., sex, handedness, age, IQ, and years of education); SOPS positive sub-scale score or GAF score measured at baseline; follow-up duration; medication use (i.e., mean olanzapine equivalent dose, antidepressant use, mood stabilizer use, and anxiolytic use); and DUPP.

III. Results

1. Subject characteristics

All subjects at CHR were antipsychotic-naïve at the time of enrollment; 36 subjects were medication-naïve, 9 subjects were taking antidepressants, and 11 subjects were taking benzodiazepines. Table 1 summarizes the demographic and clinical characteristics at baseline and Table 2 during the follow-up period. No differences were found in the demographic or clinical characteristics between the CHR-R and CHR-NR groups assessed at baseline. The CHR-R and CHR-NR groups did not differ with regard to follow-up duration, change in SOPS positive subscale scores, or use of medication. However, the CHR-NR subjects were prescribed greater olanzapine equivalent doses of antipsychotics ($t = -2.080$, $p = 0.043$) and showed less functional improvement ($t = 4.586$, $p < 0.001$) during the follow-up period than the CHR-R subjects. Explorative group comparison result of subjects at CHR for psychosis who participated follow-up assessment and did not are provided as Table 3.

Table 1. Baseline demographic and clinical characteristics of the subjects at clinical high risk (CHR) for psychosis.

Characteristics	CHR (N=48)		CHR-R[a] (N=17)		CHR-NR[b] (N=31)		Statistical analysis[c]	
	Mean	SD	Mean	SD	Mean	SD	χ^2 or T	P
Sex (Male/Female)	35/13		11/6		24/7		0.899	0.343
Handedness (Right/Left)	45/3		17/0		28/3		-	0.543
Age (years)	19.6	3.4	19.8	3.6	19.5	3.4	0.236	0.814
IQ	107.2	12.2	107.6	12.0	106.9	12.5	0.175	0.862
Education (years)	12.1	1.6	12.1	1.4	12.1	1.7	-0.077	0.939
DUPP (months)	21.5	19.1	22.4	23.0	21.0	17.0	0.237	0.814
SOPS								
Positive symptoms	8.1	4.8	7.8	3.5	8.3	5.5	-0.335	0.739
Negative symptoms	15.1	6.3	15.6	5.9	14.9	6.5	0.376	0.709
Disorganization	4.6	2.5	4.2	1.9	4.7	2.8	-0.665	0.509
General symptoms	7.4	4.2	7.8	3.9	7.3	4.3	0.400	0.691
GAF	44.2	19.4	48.5	8.4	41.9	23.2	1.422	0.163

IQ, Intelligent Quotient; DUPP, Duration of untreated prodromal psychosis; SOPS, Scale of Prodromal Symptoms; GAF, Global Assessment of Functioning.

[a] Remitted at last follow-up point.

[b] Did not remit at last follow-up point.

[c] Independent t test or Welch's t test if the variances were not equal, $\chi 2$ analysis or Fisher's exact test for categorical data.

Table 2. Follow-up duration, medication characteristics and change in attenuated positive symptom severity and functional status of subjects at clinical high risk (CHR) for psychosis during the follow-up period.

Characteristics	CHR (N=48)		CHR-R[a] (N=17)		CHR-NR[b] (N=31)		Statistical analysis[c]	
	Mean	SD	Mean	SD	Mean	SD	T	P
Follow-up duration (days)	1088.8	544.4	1141.7	612.5	1059.8	511.7	0.494	0.624
Antipsychotics dose[d]	3.0	3.1	1.9	2.3	3.6	3.4	-2.080	0.043*
Change in								
SOPS positive symptoms[e]	4.3	6.9	4.7	3.3	4.1	8.3	0.378	0.707
GAF[f]	10.1	13.7	20.4	9.5	4.4	12.4	4.586	<0.001**
	N	%	N	%	N	%	$\chi 2$	P
Use of medication[g]								
Antipsychotics	43	89.6	14	82.4	29	93.5	1.475	0.225
Antidepressants	33	68.8	12	70.5	21	67.7	0.041	0.839
Mood stabilizers	33	68.8	11	64.7	22	71.0	0.200	0.654
Anxiolytics	17	35.4	4	23.5	13	41.9	1.626	0.202

SOPS, Scale of Prodromal Symptoms scores; GAF, Global Assessment of Functioning.

[a] Remitted at last follow-up point.

[b] Did not remit at last follow-up point.

[c] Independent t test or Welch's t test if the variances were not equal, $\chi 2$ analysis or Fisher's exact test for categorical data.

[d] Mean olanzapine equivalent dose.

[e] Which was calculated by subtracting scores at last follow-up point from scores at baseline.

[f] Which was calculated by subtracting scores at baseline from scores at last follow-up point.

[g] Number and percentage of subjects who were prescribed each medication during the follow-up period.

*.The mean difference is significant at the 0.05 level.

**.The mean difference is significant at the 0.005 level.

Table 3. Demographic, clinical, and mismatch negativity (MMN) characteristics at baseline of the subjects at clinical high risk (CHR) for psychosis who participated follow-up assessment and who did not.

	CHR-F[a] (N=48)		CHR-NF[a] (N=22)		Statistical analysis[c]	
	Mean	SD	Mean	SD	χ^2 or T	P
Sex (Male/Female)	35/13		16/6		0.000	0.987
Handedness (Right/Left)	45/3		19/3		1.050	0.305
Age (years)	19.6	3.4	21.6	3.9	-2.022	0.050
IQ	107.2	12.2	110.6	13.5	-1.055	0.295
Education (years)	12.1	1.6	13.1	1.7	-2.395	0.019*
DUPP (months)	21.5	19.1	19.5	17.4	0.429	0.669
SOPS						
Positive symptoms	8.1	4.8	9.5	2.2	-1.266	0.210
Negative symptoms	15.1	6.3	12.6	6.0	1.592	0.116
Disorganization	4.6	2.5	3.5	2.2	1.789	0.078
General symptoms	7.4	4.2	5.9	4.1	1.438	0.155
GAF	44.2	19.4	53.7	6.1	-2.238	0.029*
MMN amplitude (μV)						
F3	-2.1	0.9	-2.3	1.3	0.924	0.359
Fz	-2.5	1.1	-2.7	1.4	0.707	0.482
F4	-2.6	1.0	-2.7	1.1	0.526	0.601
FC3	-1.8	0.7	-2.1	1.1	1.086	0.282
FCz	-2.4	1.0	-2.7	1.1	1.087	0.281
FC4	-2.3	0.9	-2.4	1.0	0.037	0.971
MMN latency (ms)						
F3	171.5	24.3	170.5	23.3	0.149	0.882
Fz	174.5	22.4	173.7	17.0	0.604	0.548
F4	172.3	22.2	166.6	20.0	0.974	0.333
FC3	174.8	26.4	179.0	23.2	-0.602	0.549
FCz	175.9	20.8	167.0	20.0	-0.727	0.470
FC4	167.0	20.0	164.8	16.8	0.407	0.685

Abbreviations: SD, Standard Deviation; IQ, Intelligent Quotient; DUPP, Duration of untreated prodromal psychosis; SOPS, Scale of Prodromal Symptoms; GAF, Global Assessment of Functioning.

[a] Participated follow-up assessment.

[b] Did not participate follow-up assessment.

[c] Independent t test or Welch's t test if the variances were not equal, $\chi 2$ analysis or Fisher's exact test for categorical data.

*.The mean difference is significant at the 0.05 level.

2. MMN at the surface level predicts remission and symptomatic or functional improvement

Figure 1 displays the grand-average MMN waveforms at F3, Fz, F4, FC3, FCz, and FC4 electrode sites across the CHR-R and CHR-NR groups. Figure 2 (a) shows the MMN peak amplitudes at the F3, Fz, and F4 electrode sites. Figure 2 (b) displays two-dimensional topographic maps of the MMN amplitudes for the CHR-R, CHR-NR, and CHR subjects who transitioned to overt psychotic disorder (CHR-T). Figure 3 (a) shows grand-average MMN waveforms at Fz and FCz electrode sites and Figure 3 (b) shows two-dimentional topographic maps of the MMN amplitudes for the CHR-R, CHR subjects who did not remit nor transition to psychotic disorder (CHR-NRNT), and CHR-T. A repeated measures ANOVA with 6 fronto-central electrode sites as the within-subject factor and group (CHR-R vs. CHR-NR) as the between-subjects factor revealed a significant main effect of group on MMN peak amplitude at baseline ($F_{1,46} = 5.092$, $p = 0.029$). Independent samples t-tests at each electrode site showed that the baseline MMN peak amplitudes at F3, Fz, and F4 were larger in the CHR-R group than in the CHR-NR group. The MMN peak latencies at each electrode site did not differ among the groups (Table 4).

Figure 1. Grand-averaged mismatch negativity (MMN) waveforms across the subjects at clinical high risk (CHR) for psychosis who remitted (CHR-R) or did not remit (CHR-NR) at the F3, Fz, F4, FC3, FCz, FC4 electrode sites.

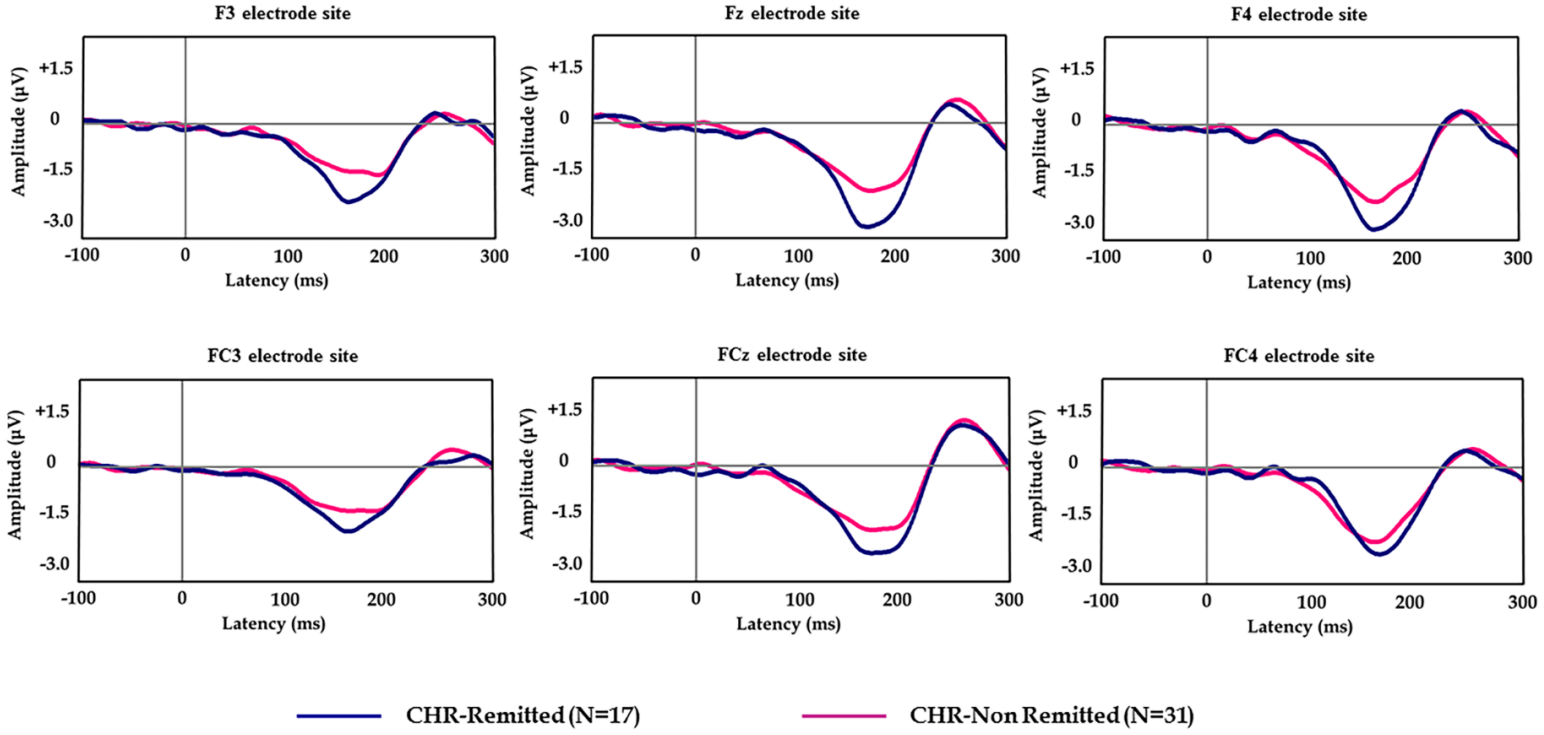


Figure 2. (a) Mismatch Negativity (MMN) peak amplitudes at the F3, Fz, and F4 electrode sites across the subjects at clinical high risk (CHR) for psychosis who remitted (CHR-R), who did not remit (CHR-NR), and who transitioned to overt psychotic disorder (CHR-T; indicated by the open circles). The horizontal lines in the group indicate the means, and the vertical lines in the group indicate 95% confidence interval. (b) two-dimensional topographic maps of the MMN amplitudes for the CHR-R, CHR-NR, and CHR-T groups. The colored bar with numbers indicates the amplitude of MMN (μV).

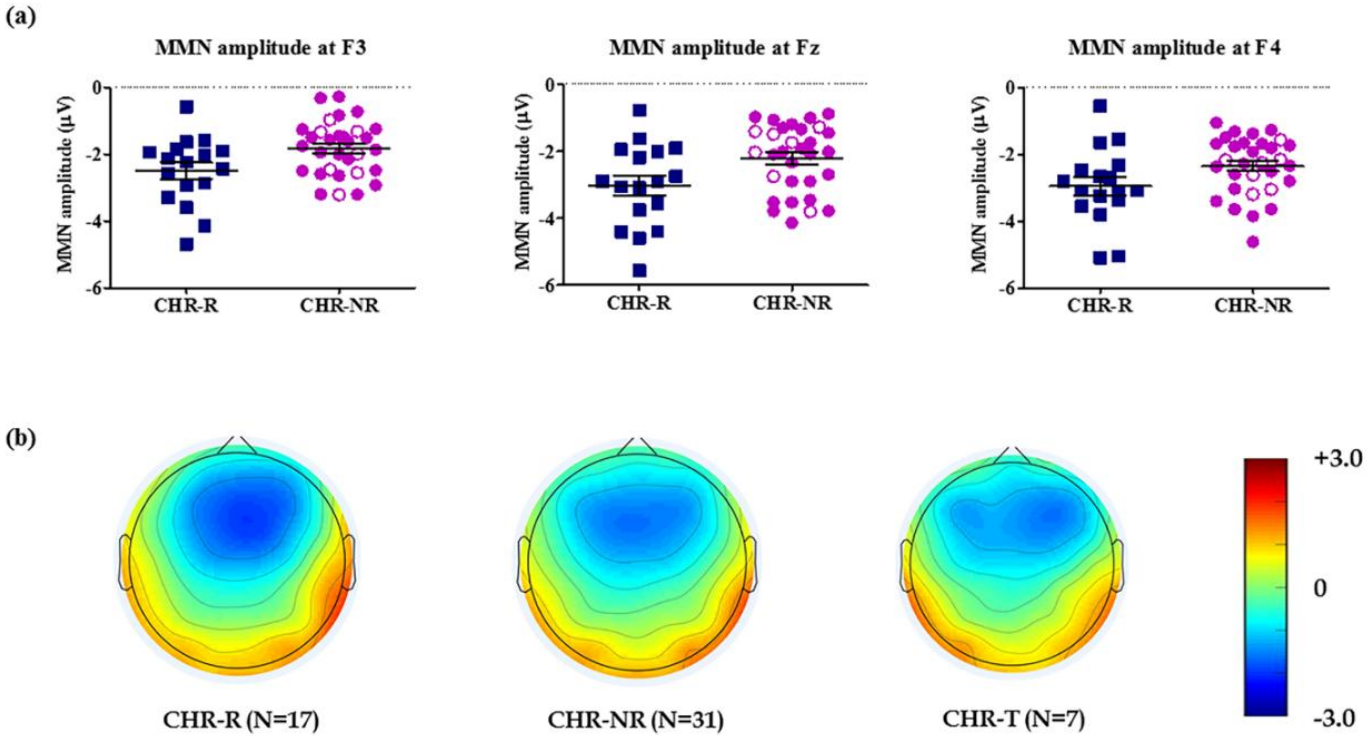


Figure 3. (a) grand-average mismatch negativity (MMN) waveforms at Fz and FCz electrode sites across the subjects at clinical high risk (CHR) for psychosis who remitted (CHR-R), who did not remit nor transition to psychotic disorder (CHR-NRNT), and who transitioned to overt psychotic disorder (CHR-T) (b) two-dimentional topographic maps of the MMN amplitudes for the CHR-R, CHR-NRNT, and CHR-T. The colored bar with numbers indicates the amplitude of MMN (μV).

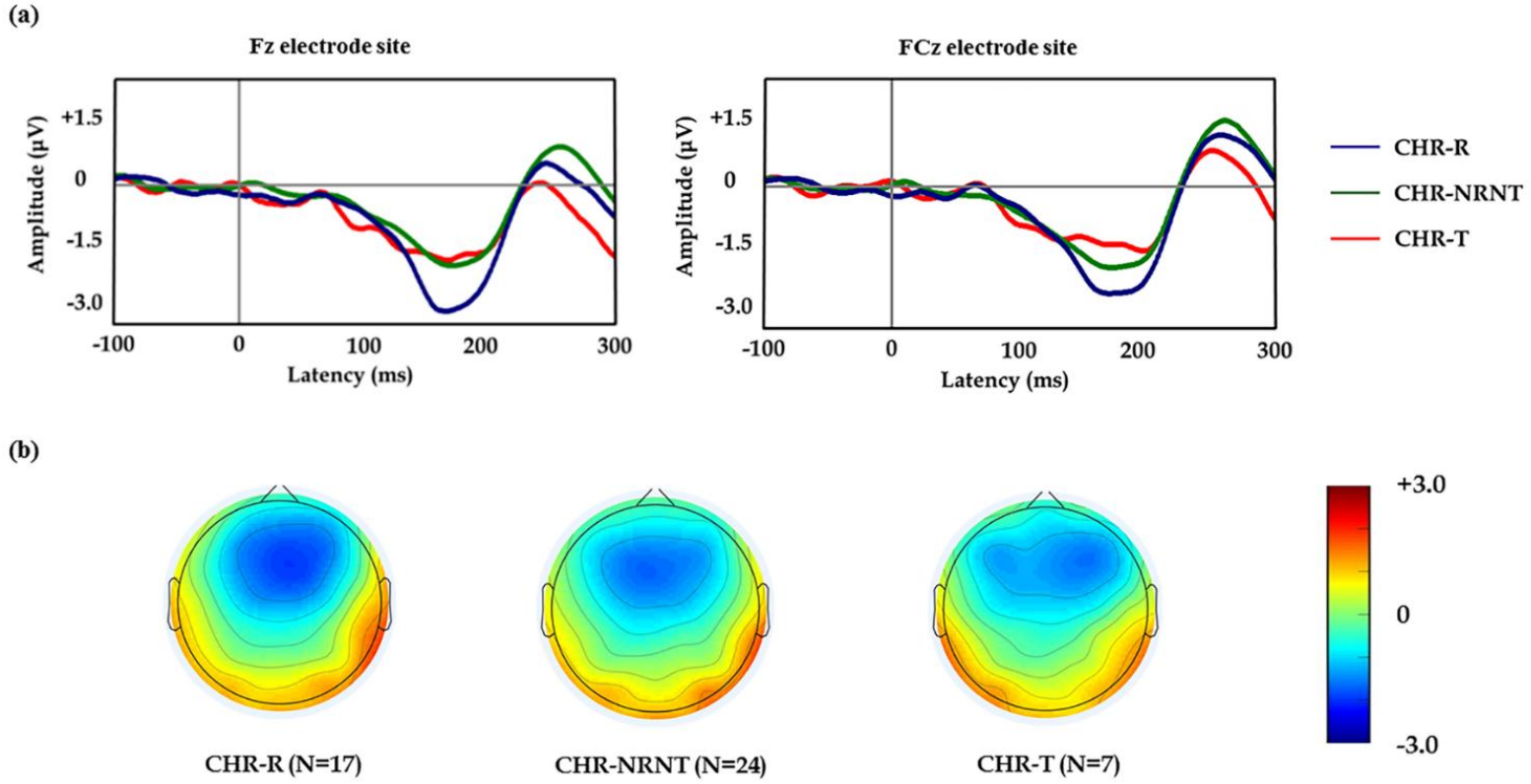


Table 4. Means and standard deviations (SD) of mismatch negativity (MMN) peak amplitudes and latencies.

Electrode sites	CHR (N=48)		CHR-R[a] (N=17)		CHR-NR[b] (N=31)		Statistical analysis[c]	
	Mean	SD	Mean	SD	Mean	SD	T	P
Amplitude (μV)								
F3	-2.1	0.9	-2.5	1.0	-1.8	0.8	-2.479	0.017*
Fz	-2.5	1.1	-3.0	1.2	-2.2	1.0	-2.480	0.017*
F4	-2.6	1.0	-3.0	1.1	-2.4	0.9	-2.053	0.046*
FC3	-1.8	0.7	-2.0	0.8	-1.7	0.7	-1.469	0.149
FCz	-2.4	1.0	-2.7	1.2	-2.2	0.8	-1.936	0.059
FC4	-2.3	0.9	-2.5	0.9	-2.3	0.9	-0.781	0.439
Latency (ms)								
F3	171.5	24.3	173.0	25.0	170.7	24.3	0.313	0.756
Fz	174.5	22.4	177.3	23.6	172.9	21.9	0.646	0.521
F4	172.3	22.2	174.8	24.2	170.9	21.3	0.567	0.574
FC3	174.8	26.4	176.8	26.4	173.6	26.8	0.395	0.695
FCz	175.9	20.8	178.2	17.9	174.7	22.4	0.562	0.577
FC4	167.0	20.0	175.4	24.2	162.3	15.8	2.263	0.028*

[a] Remitted at last follow-up point.

[b] Did not remit at last follow-up point.

[c] Independent t test or Welch's t test if the variances were not equal.

*.The mean difference is significant at the 0.05 level.

According to the binary logistic regression analysis, the baseline MMN amplitude at Fz was the only significant predictor of remission (Exp [β] = 0.472, 95% confidence interval [95CI] = 0.254 to 0.877, p = 0.018). According to the multiple regression analysis, improvement in SOPS positive symptoms was significantly predicted by baseline MMN amplitude at Fz (β = -2.028, 95CI = -3.888 to -0.169, p = 0.033), dose of antipsychotics used (β = 1.024, 95CI = 0.326 to 1.721, p = 0.005), and years of education (β = 2.613, 95CI = 0.634 to 4.592, p = 0.011). The only significant predictor of GAF improvement was the baseline MMN amplitude at Fz (β = -3.696, 95CI = -0.692 to -0.410, p = 0.028; Table 5, Figure 4).

Table 5. Significant predictors of remission, improvement of attenuated positive symptoms and general functioning.

Outcome variables	Significant predictors	R^2	Exp (B) or Beta	P	95% CI	
					Lower	Upper
Remission[a]	MMN amplitude at Fz	0.244	0.472	0.018*	0.254	0.877
Improvement of SOPS positive symptoms[b]	MMN amplitude at Fz	0.313	-2.028	0.033*	-3.888	-0.169
	Antipsychotics dose[c]		1.024	0.005*	0.326	1.721
	Education (years)		2.613	0.011*	0.634	4.592
Improvement of GAF[b]	MMN amplitude at Fz	0.168	-3.696	0.028*	-6.982	-0.410

SOPS, Scale of Prodromal Symptoms; GAF, Global Assessment of Functioning; CI, Confidence interval.

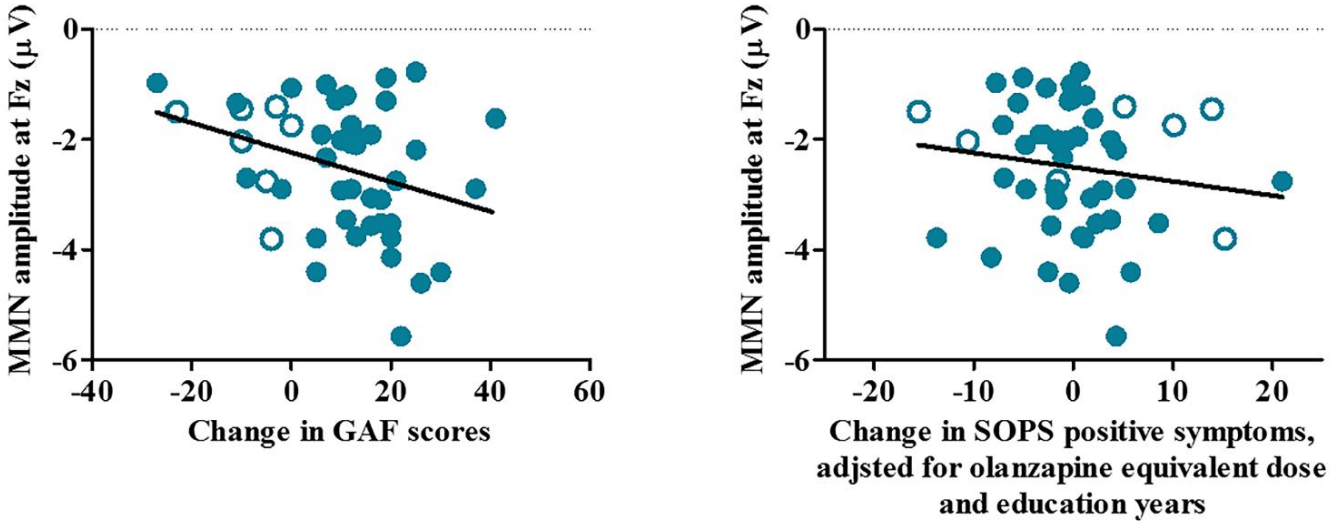
[a] Binary logistic regression with backward method.

[b] Multiple regression with backward method.

[c] Mean Olanzapine equivalent dose.

*.The mean difference is significant at the 0.05 level.

Figure 4. The correlation between the change in the Global Assessment of Functioning (GAF) scores and the mismatch negativity (MMN) amplitude at baseline (left). The partial correlation between the baseline MMN amplitude at Fz and the change in the Scale of Prodromal Symptoms (SOPS) positive symptom scores adjusted for the olanzapine equivalent antipsychotic dose and education years (right). The subjects at CHR who transitioned to psychosis are indicated by the open circle.



3. MMN at the source level predicts symptomatic or functional improvement

Figure 5 (a) presents the MMN CSD distribution of 26 subjects at CHR on each individual's structural MRI map projected onto the standard Montreal Neurological Institute (MNI) space using Statistical Parametric Mapping (SPM) version 8 software (Wellcome Department of Cognitive Neurology, London, UK). No significant difference in peak MMN CSD strength was found at each ROI across groups (Table 6). The multiple regression analysis did not reveal significant predictors of the improvement of the SOPS positive symptoms. However, MMN CSD strength at the right STG (β = 321.185, 95CI = 33.969 to 608.401, p = 0.030) and IFG (β = -355.206, 95CI = -645.387 to -65.024, p = 0.019), age (β = -2.348, 95CI = -4.134 to -0.562, p = 0.012), and the use of antidepressants during the follow-up period (β = 10.870, 95CI = 1.663 to 20.076, p = 0.023) significantly predicted functional improvements, as indexed by the change in GAF scores (Table 7, Figure 5 [b]).

Table 6. Means and standard deviations (SD) of mismatch negativity (MMN) current source density (CSD) peak strengths at each region of interests (ROI).

Region of interests	CHR (N=26)		CHR-R[a] (N=8)		CHR-NR[b] (N=18)		Statistical analysis[d]	
	Mean	SD	Mean	SD	Mean	SD	χ^2	P
CSD (μA/mm2)								
Left STG	0.023	0.033	0.039	0.052	0.014	0.018	0.444	0.505
Left IFG	0.029	0.067	0.057	0.113	0.017	0.029	0.522	0.470
Right STG	0.022	0.026	0.033	0.035	0.018	0.021	1.235	0.267
Right IFG	0.020	0.028	0.024	0.024	0.019	0.030	0.790	0.374

Abbreviations: CHR, clinical high risk; STG, superior temporal gyrus; IFG, inferior frontal gyrus.

[a] Remitted at last follow-up point.

[b] Did not remit at last follow-up point.

[c] Independent t test or Welch's t test if the variances were not equal.

[d] Kruskal-Wallis test.

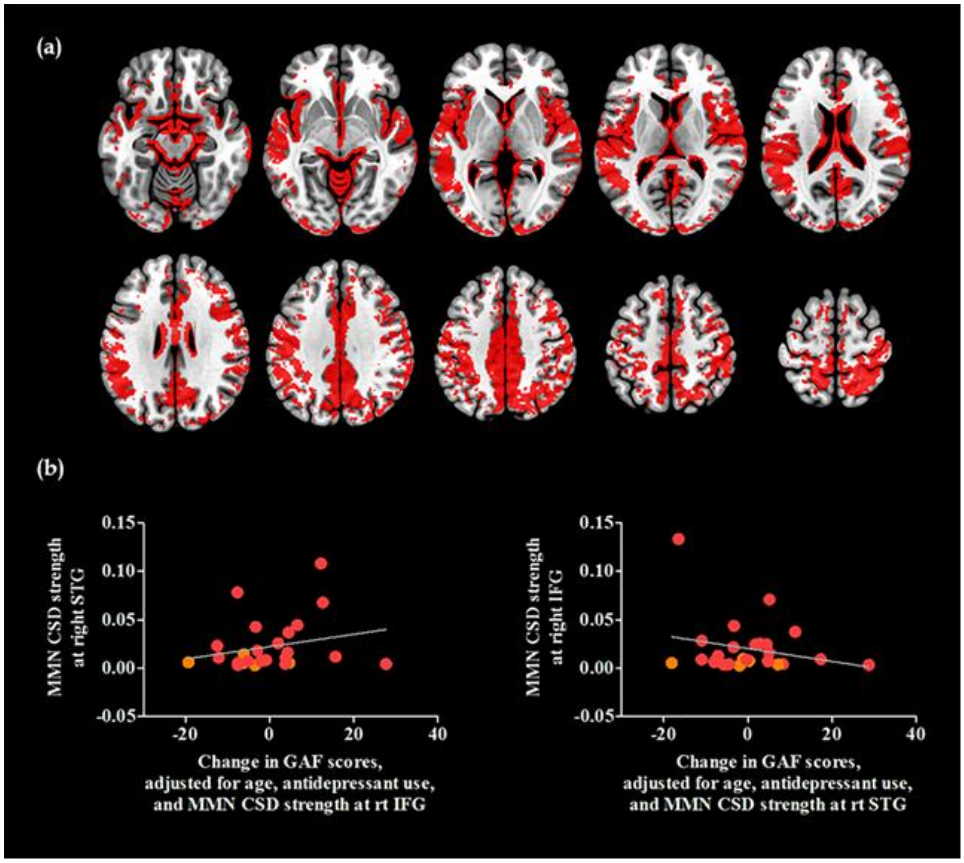
*.The mean difference is significant at the 0.05 level.

Table 7. Backward multiple regressions predicting functional improvement from baseline demographic characteristics, medication use, follow-up duration and mismatch negativity (MMN) current source density (CSD) at each region of interests (ROI).

Outcome variables	Significant predictors	R^2	Beta	P	95% CI	
					Lower	Upper
Improvement of GAF	MMN CSD strength at right STG	0.488	321.185	0.030*	33.969	608.401
	MMN CSD strength at right IFG		-355.206	0.019*	-645.387	-65.024
	Age (years)		-2.348	0.012*	-4.134	-0.562
	Antidepressant use		10.87	0.023*	1.663	20.076

GAF, Global Assessment of Functioning; STG, superior temporal gyrus; IFG, inferior frontal gyrus; CI, Confidence interval.
*.The mean difference is significant at the 0.05 level.

Figure 5. (a) Mismatch negativity (MMN) current source density (CSD) distribution of total clinical high risk (CHR) subjects calculated with statistical parametric mapping (threshold at $p < 0.01$, uncorrected); the left hemisphere is depicted on the left in the axial slices. (b) The partial correlation between the change in the Global Assessment of Functioning (GAF) scores and the baseline MMN CSD at the right STG (left) and IFG (right). Subjects at CHR who transitioned to psychosis are indicated by orange, filled circles.



IV. Discussion

1. Summary

This study investigated MMN as a predictor of prognosis after a 6-year follow-up period among subjects at CHR for psychosis. As expected, the baseline MMN amplitudes at the frontal electrode sites were reduced in non-remitters compared with remitters, and a larger baseline MMN amplitude was the only significant predictor of remission. The MMN amplitude obtained at baseline predicted improvement in general functional status during the follow-up period in the whole CHR group. The significant predictors of reduction in attenuated positive symptoms were baseline MMN amplitude, antipsychotic dosage, and years of education. According to the source-level analysis, though a significant model that predicted a change in attenuated positive symptom severity was not created, MMN CSD strength at the STG and IFG of the right hemisphere, age, and antidepressant use predicted a change in functional status. In other words, greater MMN CSD strength at the right STG, lesser MMN CSD strength at the right IFG, younger age, and antidepressant use significantly predicted a better general functional status measured at the last follow-up point.

2. MMN amplitude at surface electrode and remission from CHR status

Because non-transition or the amelioration of attenuated positive symptoms does not ensure a positive prognosis, especially in terms of functional outcomes (9,10,44), to be clinically relevant, the concept of remission from CHR status should include both symptomatic and functional improvement. The results of the current study show that the baseline MMN amplitude predicts later remission, which was defined using both the SOPS positive sub-scale score and the GAF score; these findings suggested that MMN can be used as a putative biomarker for the early detection of clinically relevant remission in subjects at CHR. Furthermore, we found that the baseline MMN amplitude separately predicted the improvement of attenuated positive symptoms and general functional status in the CHR group as a whole. These results are consistent with the previous literature, which reports a relationship between MMN and positive symptom severity or general functional status in patients with schizophrenia and those at CHR for psychosis (24,26,45-

47). In addition, Thomas et al. showed that early auditory processing significantly predicted functional outcomes in patients with schizophrenia, which further supports the results of the current study (48).

3. MMN generator activities and remission form CHR status

In the source-level analysis of the CHR subgroup, we created a model that predicted functional outcomes that included MMN CSD strength at the STG and IFG of the right hemisphere, age, and antidepressant use as significant predictors. Interestingly, the MMN CSD strength at the right STG and IFG predicted a change in functional status in the opposite direction in a single model. Previous fMRI studies have suggested that the IFG contribution to the MMN mechanism is the top-down control of STG function, which might be activated especially when the STG system has difficulty discriminating stimuli (31,41,42). Because the MMN generator at the IFG partially compensates for STG generator functioning, smaller MMN source activity at the IFG might predict greater functional improvement in the case of larger MMN source activity at the STG. On the other hand, the baseline MMN CSD strength did not predict later improvements in attenuated positive symptoms. The reduced activity of the temporal MMN source might be correlated with positive symptoms, whereas dampened frontal MMN source activity might be associated with negative and cognitive symptoms in patients with schizophrenia (49,50). Therefore, unlike the prediction of functional improvement that might have resulted from the composite of favorable change across various symptom dimensions, the simultaneous examination of the STG and IFG sources might not create a model predictive of changes only in positive prodromal symptoms.

4. MMN as a potent biomarker of remission from CHR status

To date, all other CHR studies using MMN as a biomarker have attempted to reveal its potential utility to predict the transition to psychotic disorder (29). In particular, Perez et al. showed that MMN was compromised prior to and a significant predictor of time to psychosis onset among subjects at CHR (5). However, the transition rate has declined from an initial 54% within 1 year to 10-15% within 2-3 years (7,34,51), and a large proportion of subjects at CHR

have shown poor prognoses, although they did not transition to psychotic disorder (11,13). This phenomenon has raised questions about the clinical relevance of predictions limited to transition in CHR prognosis; in turn, the prediction of remission from initial CHR status has gained as much clinical importance as the prediction of transition (17,18,44). The early classification of remitters and non-remitters among individuals with initial CHR statuses would be helpful for earlier clinical decisions regarding intervention factors such as timing and intensity. In line with the trend toward at-risk mental state research, the current study provides the first suggestion that MMN serves as a biomarker in predicting the prognosis of subjects at CHR, regardless of psychotic conversion.

5. Limitations

This study has several limitations. First, the follow-up period varied among subjects at CHR, although the observational period of 1 to 6 years was relatively long. Although the follow-up duration of the CHR-R and CHR-NR groups did not differ and the prognostic changes were not explained by the length of the follow-up period according to the multiple regression analysis, a potential bias caused by the varying lengths of follow-up duration warrants caution when interpreting the results. Second, the cross-sectional design of the MMN assessment in our study prevents us from defining causal relationships among MMN, symptoms, and functional change over time. Third, the range of change in the clinical characteristics examined in the present study is limited to the scores derived from the SOPS positive sub-scale and the GAF scale following the definition of remission. Other important clinical variables, including negative, disorganization, and general symptoms, as well as neurocognition, are beyond the scope of the present study and would further augment the meaning of our findings.

V. Conclusion

The present study is the first to examine the possibility that baseline MMN predicts later functional and symptomatic prognoses in subjects at CHR for psychosis. We observed that the baseline MMN amplitude at the surface level was associated with later remission as well as improvements in attenuated positive symptoms and general functional status. Furthermore, the composite MMN activity of the right STG and IFG predicted change in the general functioning of individuals at CHR. Our results not only suggest that MMN is a potent biomarker of remission in subjects at CHR but also provide biological background for previous studies that argued for the importance of non-psychotic outcomes and clinically relevant remission criteria, including functional improvement (9,10,12,18,52). Although challenges remain in translating electrophysiological findings into clinically feasible prognostic tests, the early prediction of prognosis and the provision of appropriate interventions for individuals at CHR for psychosis might be aided using MMN.

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요약(국문초록)

서론: 조현병을 조기에 발견하고 발병을 예방 및 지연시키기 위하여 조현병 전구기 증상을 보이는 정신증 임상적 고위험군에 대한 연구가 활발히 이루어져 왔다. 그러나 정신증 임상적 고위험군에서 실제로 정신병이 발생하는 사람의 비율이 줄어들고, 정신병이 발생하지 않더라도 나쁜 예후를 보이는 사람이 많음이 알려지면서, 정신병 발생과 상관 없이 정신증 임상적 고위험군 상태에서 관해를 예측하기 위한 생물학적 표지자 발굴의 필요성이 대두되고 있다. 본 연구는 조현병 임상적 고위험군에서 Mismatch Negativity (MMN) 를 이용하여 6년의 추적 관찰 기간 동안의 예후를 예측하고자 하는 목적으로 수행되었다.

방법: 총 48명의 정신증 임상적 고위험군에서 연구 참여 시점에 임상 평가를 시행하였고, 이후 추적 임상 평가를 최대 6년까지 일정한 간격으로 시행하였다. 임상 평가 결과를 바탕으로 정신증 임상적 고위험군을 관해군과 비관해군으로 나누고, 연구 참여 시점에 측정된MMN 진폭과 양 대뇌 반구의 상부측두이랑과 하부전두이랑에 재구성된 MMN 생성 부위 전류 크기를 집단 비교하였다. 정신증 고위험군 상태로부터의 관해, 약화된 양성 증상, 전반적 기능 상태의 회복을 예측하는 인자를 찾아내기 위하여 회귀 분석을 시행하였다.

결과: 정신증 임상적 고위험군에서 관해군과 비교하여 비관해군은 연구 참여 시점에서 더 작은 MMN 진폭을 보였다. 로지스틱 회귀분석에서 전두 부위 전극에서 측정한 MMN 진폭이 관해를 예측할 수 있는 유일한 인자로 도출되었다. 다중 회귀분석에서 MMN 진폭과 항정신병제의 사용, 교육 연 수가 약화된 정신병적 증상의 호전을 예측하였다. 우측 상부측두이랑과 하부전두이랑의 MMN 생성 부위 전류 크기, 나이, 항우울제의 사용이 기능의 회복을 예측하였다.

결론: 본 연구의 결과는 MMN이 정신증 임상적 고위험군에서 정신병 발병과 상관없이 예후 자체를 예측하는데 유망한 예측 인자가 될 수 있음을 시사한다. 정신증 임상적 고위험군 초기 단계에서부터 MMN을 이용하여 조기에 예후를 예측하고 적절한 치료를 제공하는 데 도움을 받을 수 있을 것이다.

주요어: 정신증 임상적 고위험군, 사건 관련 전위, Mismatch negativity, 관해, 예후, 조현병

학번: 2012-21674