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Duration and frequency mismatch negativity shows no progressive reduction in early stages of psychosis

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ABSTRACT

The auditory mismatch negativity (MMN) is a component of event-related potentials, which is being increasingly recognized as a candidate biomarker for early stages of psychosis. Although previous cross-sectional studies have demonstrated small MMN amplitude in early stages of psychosis, it remains unknown whether small MMN amplitude is due to progressive reduction during the early course. In this study, we investigated longitudinal changes of MMN in early stages of psychosis. Participant included 14 patients with first-episode psychosis (FEP), 16 individuals with ultra-high risk (UHR), and 16 healthy control subjects (HC). We measured MMN in response to duration deviants (dMMN) and that in response to frequency deviants (fMMN), respectively. The amplitudes of dMMN in FEP and UHR were significantly smaller in comparison to those in HC, which did not show a progressive decrease over time. The amplitude of fMMN did not differ among groups, which again did not show progression. There was no significant correlation between the length of the follow-up period and the longitudinal change of either deviant-type MMN in the FEP or UHR. These results suggest that dMMN is a trait marker in the early stages of psychosis, and that small dMMN amplitude in early stages of psychosis may reflect altered developmental process rather than progressive brain pathology. The amplitude of fMMN may not alter in early stages of psychosis. These findings may contribute to the future establishment of MMN as a biomarker in early stages of psychosis.

1. Introduction

Mismatch negativity (MMN) is a recognized candidate biomarker of psychosis (Light and Naatanen, 2013; Light and Swerdlow, 2015; Naatanen et al., 2015; Naatanen et al., 2016). Many studies have shown that MMN amplitude is reduced in psychotic disorders (Erickson et al., 2016; Umbricht and Krljes, 2005). Reduced MMN amplitude may reflect dysfunction of *N*-methyl-D-aspartate receptor (NMDA-R) in psychotic disorders because NMDA-R antagonists reduce MMN amplitude (Javitt et al., 1996; Umbricht et al., 2000). Because MMN-like responses can be recorded in animals, MMN is a promising candidate of translatable biomarker to develop new treatments for psychosis (Nagai et al., 2013a; Okano et al., 2015; Okano et al., 2016).

Recent studies have focused on the early stages of psychosis because its early detection, and subsequent intervention, may improve the functional outcome of patients (Farooq et al., 2009; Marshall et al., 2005; Perkins et al., 2005). Erickson et al. (2016) performed a meta-analysis of MMN at each clinical stage of psychosis and revealed that patients with chronic schizophrenia showed a large impairment of MMN amplitude compared to healthy controls (HC; effect size = 0.81). Patients with first-episode psychosis (FEP; effect size = 0.42) and individuals with clinical high risk for psychosis (effect size = 0.40) showed a mild impairment of MMN amplitude compared to HC (Erickson et al., 2016). These findings suggest that MMN amplitude may show progressive reduction according to the clinical stage of psychosis. However, the significant effect of deviant type (e.g., duration and frequency) of the auditory stimulus sequence indicates that we should consider the deviant type to discuss MMN impairments in psychosis.

MMN impairments in early stages of psychosis depend on deviant type. In an auditory oddball paradigm, deviant stimuli differ from repetitive standard stimuli in its perceptual characteristics including duration

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and frequency. Our previous study showed that the amplitude of MMN in response to duration deviants (dMMN) was significantly reduced in patients with first-episode schizophrenia and individuals with ultra-high risk (UHR) compared to HC, while the amplitude of MMN in response to frequency deviants (fMMN) showed no significant difference among the three groups (Nagai et al., 2013b). Other studies have also reported similar findings (Atkinson et al., 2012; Jahshan et al., 2012; Nagai et al., 2013a; Todd et al., 2008). Taken together, these findings suggest that dMMN amplitude may be reduced at UHR or earlier stage while fMMN amplitude may be reduced at a stage later than FEP.

However, longitudinal studies are needed to clarify the point at which MMN amplitude shows a reduction during the early stages of psychosis. Previous longitudinal studies of dMMN reported progressive reduction in one study (Kaur et al., 2013), but no progressive reduction in another study (Light and Braff, 2005b). However, these studies were limited in that Kaur et al. (2013) included patients without psychosis and Light and Braff (2005b) included patients with chronic schizophrenia. Previous longitudinal studies of fMMN reported progressive reduction in first-episode schizophrenia (Devrim-Ucok et al., 2008; Salisbury et al., 2007), with no progressive reduction in chronic schizophrenia (Shinozaki et al., 2002). These findings indicate progressive reduction of fMMN in first-episode schizophrenia while no previous study investigated the longitudinal change of dMMN in early stages of psychosis or the longitudinal change of fMMN in UHR.

In this study, we investigated the longitudinal change of both dMMN and fMMN in the early stages of psychosis. If MMN showed progressive reduction, the pathological process associated with MMN might occur in early stages of psychosis. If MMN showed no progressive reduction, the pathological process associated with MMN might occur before or after the early stages of psychosis. Therefore, it is important to know whether dMMN and fMMN show progressive reduction in early stages of psychosis, and the aim of this study is to reveal that point.

2. Methods

2.1. Subjects

The current study was conducted as part of a multimodal, neuroimaging, and psychophysiological project focused on the early stages of psychosis (Integrative Neuroimaging Studies for Schizophrenia Targeting Early Intervention and Prevention; IN-STEP; Koike et al., 2013). For the IN-STEP project, we recorded electroencephalography (EEG) of patients with FEP, individuals with UHR, and HC. In the current study, we included 14 patients with FEP, 16 individuals with UHR, and 16 HC who participated in EEG recordings twice (Table 1). Out of these 46 participants in total, 24 had participated in our previous cross-sectional study (Nagai et al., 2013b), and the remaining 22 were newly recruited. Only one EEG measurement was acquired for 17 out of 31 patients with FEP (54.8%), 26 out of 42 individuals with UHR (61.9%), and 30 out of 46 HC (65.2%).

FEP or UHR were recruited from outpatient and inpatient units at the University of Tokyo Hospital, and most participants were registered at outpatient unit specialized for early intervention. HC was recruited through advertisements at several universities in Tokyo. Inclusion criteria of FEP were diagnosis of psychosis using the Structured Interview for Prodromal Symptoms (SIPS) (Kobayashi et al., 2007), age 15–40 years, no history of antipsychotic drug treatment for >16 cumulative weeks, and continuous psychotic symptoms within the past 60 months. Inclusion criteria of UHR were diagnosis of UHR using SIPS, age 15–30 years, and no history of antipsychotic drug treatment for >16 cumulative weeks. Inclusion criteria of HC were age 15–40 years and no personal history of psychiatric disease or a family history of axis I disorders in first-degree relatives. Exclusion criteria for all groups were neurological illness, traumatic brain injury with any known cognitive consequences of loss of consciousness for more than 5 min, history of electroconvulsive therapy, low premorbid intelligence quotient (IQ; below 70), previous alcohol/substance abuse or addiction, and hearing impairment assessed with a hearing test in both ears at 30-dB sound pressure level tone at 1000 Hz and 40-dB at 4000 Hz by audiometer. Written informed consent was obtained from each subject before participation. The Research Ethics Committee of the Faculty of Medicine, The University of Tokyo, approved this study (approval No.629, 2094, & 2226).

Estimated premorbid intelligence quotient (IQ) was assessed using the Japanese version of the National Adult Reading Test in all participants (Matsuoka and Kim, 2006; Matsuoka et al., 2006). The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) and the Global Assessment of Functioning (GAF; American Psychiatric Association, 1994) were used to measure clinical symptoms and global functioning, respectively, of all participants with FEP or UHR. Thirteen patients with FEP and eight individuals with UHR were on antipsychotic medication, which was converted to chlorpromazine equivalent dose (Inada and Inagaki, 2015).

2.2. Stimuli and procedure

A two-tone auditory oddball paradigm with 2000 stimuli was used for duration MMN (dMMN). Stimuli consisted of standard tones (1000 Hz, 50 ms; 90% of stimuli) and deviant tones (1000 Hz, 100 ms; 10% of stimuli). Another two-tone auditory oddball paradigm with 2000 stimuli was used for frequency MMN (fMMN), with 90% of stimuli consisting of standard tones (1000 Hz, 50 ms), while 10% of stimuli were deviant tones (1200 Hz, 50 ms). All the stimuli were at an 80 dB sound pressure level and 1 ms rise/fall time. Stimulus onset asynchrony was 500 ms. The order of the oddball paradigms were counter-balanced across participants. Tones were presented binaurally through earphones while participants watched a silent cartoon.

2.3. Electroencephalography recording and analyses

We used a 64-channel Geodesic EEG System (Electrical Geodesics Inc., Eugene, OR) to obtain EEG data. Electrodes were referenced to the vertex, and impedances were kept below 50 kΩ. The sampling rate was 500 Hz. The analog filter bandpass was set at 0.1–100 Hz.

Table 1
Demographics of participants at baseline.

	FEP	UHR	HC	Statistics
N (sex ratio M/F)[a]	14 (11/3)	16 (7/9)	16 (9/7)	$\chi^2 = 3.8$, df = 2, $p = 0.15$
Age (years)[b]	22.6 (5.4)	20.6 (3.7)	22.3 (4.0)	$F_{2,43} = 0.87$, $p = 0.43$
Education (years)[b]	13.9 (1.6)	13.3 (2.7)	14.4 (1.4)	$F_{2,43} = 0.98$, $p = 0.39$
Premorbid IQ[b]	108 (9.4)	107 (8.1)	111 (8.6)	$F_{2,43} = 0.88$, $p = 0.42$
DUP (weeks)	23.1 (36.5)			
DOI (weeks)	37.9 (37.6)			
Follow-up period (days)[b]	709 (424)	464 (115)	1071 (692)	$F_{2,43} = 6.60$, $\underline{p = 0.003}$

All values are shown as mean (standard deviation). Underline indicates $p < 0.05$.
Abbreviations: FEP, first-episode psychosis; UHR, ultra-high risk; HC, healthy control; IQ, intelligence quotient; DUP, duration of untreated psychosis; DOI, duration of illness.
[a] Chi-square test.
[b] One-way ANOVA.

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