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Association between mismatch negativity and global functioning is specific to duration deviance in early stages of psychosis

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ABSTRACT

Background: Mismatch negativity (MMN) is a candidate biomarker for early stages of psychosis. Although an association among duration MMN (dMMN), cognitive deficits, and functional outcome in chronic schizophrenia has been shown by a large-scale study, the effects of deviant type and clinical stages have not been investigated.
Methods: We investigated the relationships among dMMN, frequency MMN (fMMN), global functioning, and cognitive function in early stages of psychosis. The participants included 26 individuals with recent-onset schizophrenia (ROSZ), 30 individuals with ultra-high risk (UHR), and 20 healthy controls.
Results: The correlational analyses revealed that dMMN amplitude, which was impaired in the ROSZ group compared to the healthy controls, correlated with global functioning (Global Assessment of Functioning-Functioning scale) in the ROSZ ($r = -0.45$) and UHR ($r = -0.37$) groups. The amplitude of fMMN, which did not differ among the groups, correlated with working memory ($r = -0.57$) only in the ROSZ group. The path analyses indicated that dMMN had a direct effect on global functioning in the ROSZ and UHR groups while fMMN had a direct effect on working memory only in the ROSZ group.
Conclusions: Our findings suggested that the association between MMN and global functioning was specific to the duration deviant and was already present in early stages of psychosis. These findings confirm the usefulness of dMMN as a biological marker of early psychosis to guide treatment interventions.

1. Introduction

Mismatch negativity (MMN) is an event-related potential that is considered a promising candidate biomarker of psychosis (Light and Näätänen, 2013; Light and Swerdlow, 2015; Näätänen et al., 2015; Näätänen et al., 2016). MMN can be elicited in passive listening situations in an auditory oddball paradigm in response to duration deviants (duration MMN: dMMN) and frequency deviants (frequency MMN: fMMN). Many original investigations and subsequent meta-analyses have demonstrated that MMN amplitudes are reduced in schizophrenia (Catts et al., 1995; Erickson et al., 2016; Haigh et al., 2017; Javitt et al., 1993; Light and Braff, 2005; Shelley et al., 1991; Umbricht and Krljes, 2005). Impaired MMN amplitudes are thought to reflect the dysfunction of *N*-methyl-D-aspartate receptors (NMDA-Rs) in patients with psychosis because NMDA-R antagonists reduce MMN amplitudes (Javitt et al., 1996; Umbricht et al., 2000). Recent studies have suggested that MMN is a useful biomarker for the development of new treatments (Javitt, 2015; Javitt et al., 2008; Nagai et al., 2013a) and to monitor treatment response in patients with psychosis (Lavoie et al., 2008; Light and Swerdlow, 2015)

One reason that MMN is expected to be used as a biomarker for new treatments is its association with cognition and functional outcome. Previous studies have reported that dMMN is associated with executive function (Toyomaki et al., 2008); social cognition (Wynn et al., 2010); daily functioning, including work and independent living (Friedman et al., 2012; Wynn et al., 2010); and global functioning (Jahshan et al., 2012; Kawakubo and Kasai, 2006; Kiang et al., 2007; Kim et al., 2014; Lee et al., 2014; Light and Braff, 2005) and that fMMN is associated with working memory (Kargel et al., 2014). These findings suggest that new treatments that enhance MMN may improve the functional outcomes of patients with psychosis.

Recent schizophrenia research has focused on the early stages of psychosis because its early detection and intervention might improve the functional outcomes of patients with psychotic disorders

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(McGorry et al., 2014; Owen et al., 2016; van Os and Kapur, 2009). Previous studies have reported that dMMN is associated with working memory (Kaur et al., 2011; Miyanishi et al., 2013) and functional outcome (Carrion et al., 2015) in early stages of psychosis. These findings suggest that MMN may serve as a biomarker for early psychosis to guide treatment interventions.

An important issue to investigate is how MMN is associated with cognition and functional outcome in psychosis. Because cognitive deficits affect functional outcome in schizophrenia (Green, 1996), the association between MMN and functional outcome may be mediated by cognition. Actually, Thomas et al. (2017) showed that dMMN affects functional outcome through cognitive deficits in a large number of individuals with chronic schizophrenia. However, to the best of the authors' knowledge, no studies have investigated the associations between MMN and both cognition and functional outcome in early stages of psychosis.

Another important issue concerns the effects of deviant types. Previous studies have revealed that dMMN amplitudes are significantly impaired in individuals with first-episode schizophrenia (FES) and in those with ultra-high risk (UHR) compared to healthy controls (HCs) (Nagai et al., 2013a; Nagai et al., 2013b). In contrast, fMMN amplitudes are not impaired in FES or UHR (Nagai et al., 2013a; Nagai et al., 2013b). A recent meta-analysis also reported amplitude reductions of dMMN but not fMMN in FES (Haigh et al., 2017). These findings suggest that dMMN and fMMN may associate differently with cognition and functional outcome in early stages of psychosis. However, no studies have comprehensively investigated the associations among dMMN/fMMN, neurocognition, and global functioning during early stages of psychosis.

Therefore, in this study, we measured both dMMN and fMMN and concurrently assessed cognition and global functioning in individuals with recent-onset schizophrenia (ROSZ) and UHR to investigate the associations among these neurophysiological, neuropsychological, and social outcome indices in early clinical stages of psychosis.

2. Methods

2.1. Subjects

Twenty-six individuals with ROSZ, 30 individuals with UHR, and 20 HCs participated in the current study (Table 1). We included individuals who participated in our previous studies ($n = 32$, Nagai et al., 2013b; $n = 35$, Koshiyama et al., in press; $n = 44$, Nagai et al., 2017). The methods of recruitment and inclusion and exclusion criteria are shown in Supplementary Table 1. We recruited the ROSZ and UHR individuals from outpatient and inpatient units at the University of Tokyo Hospital. We recruited HCs through advertisements at several universities in Tokyo. The inclusion criteria of ROSZ were diagnosis using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and the onset of continuous psychotic symptoms within the past 60 months. Of the 26 ROSZ individuals, 24 underwent electroencephalography (EEG) measurements for the biomarker assessments at time 1 of the Integrative Neuroimaging Studies for Schizophrenia Targeting Early Intervention and Prevention (IN-STEP) project (Koike et al., 2013) and satisfied the following criteria of FES: continuous psychotic symptoms within the past 60 months and no history of antipsychotic drug treatment for >16 cumulative weeks. The remaining two ROSZ individuals did not undergo EEG testing at time 1 but did their initial EEG testing during the follow-up period of the IN-STEP project. The inclusion criteria for UHR were identified by using the Structured Interview for Prodromal Symptoms (Kobayashi et al., 2007). We obtained written informed consent from each subject before their participation in the study. The Research Ethics Committee of the Faculty of Medicine of The University of Tokyo approved this study (approval Nos. 629 and 2226).

The premorbid intelligence quotient (IQ) was estimated for all participants using the Japanese version of the National Adult Reading Test (Matsuoka and Kim, 2006; Matsuoka et al., 2006). The clinical symptoms of the participants in the ROSZ and UHR groups were assessed using the Positive and Negative Syndrome Scale (Kay et al., 1987). Twenty-four patients with ROSZ and 16 individuals with UHR were taking antipsychotic medications, and their antipsychotic doses were converted to chlorpromazine equivalent doses (Inada and Inagaki, 2015).

2.2. Neuropsychological measures

A split version of the Global Assessment of Functioning (GAF) was used to assess symptom severity (GAF-S) and global functioning (GAF-F) in the ROSZ and UHR groups (Eguchi et al., 2015; Pedersen et al., 2007). We measured cognitive function using the Brief Assessment of Cognition in Schizophrenia (BACS) in all participants (Keefe et al., 2004). The BACS has six components: Verbal Memory, Working Memory, Motor Speed, Verbal Fluency, Attention, and Executive Function. For the BACS analyses, we used the z scores from each participant and calculated a composite score by averaging the z scores from six components.

2.3. Procedure and analyses of MMN

Procedure and analyses of MMN were conducted as previously described (Koshiyama et al., in press). We used a duration-deviant auditory oddball paradigm with 2000 stimuli to assess dMMN (standard tones: 1000 Hz, 50 ms, 90%; deviant tones: 1000 Hz, 100 ms, 10%) and a frequency-deviant auditory oddball paradigm with 2000 stimuli to assess fMMN (standard tones: 1000 Hz, 50 ms, 90%; deviant tones: 1200 Hz, 50 ms, 10%). The EEG data were collected with a 64-channel Geodesic EEG System (Electrical Geodesics, Inc., Eugene, OR). EEGLAB (Delorme and Makeig, 2004) was used to analyze the EEG data. For the MMN analysis, we used the mean MMN amplitudes from seven electrodes around the FCz. The dMMN amplitude was the mean voltage from 135 to 205 ms poststimulus. The fMMN amplitude was the mean voltage from 100 to 200 ms poststimulus.

2.4. Statistical analysis

SPSS (version 23.0.0.0, IBM Corp., Armonk, NY) and Amos (version 24.0.0.0, IBM Corp., Armonk, NY) were used for the statistical analyses. To compare the demographic data among the groups (ROSZ, UHR, and HC), we used χ^2 tests, one-way analyses of variance (ANOVAs), and independent *t*-tests. Posthoc tests with Bonferroni corrections were used in the comparisons between groups.

We separately calculated the Pearson correlation coefficients (r) between the MMN amplitudes and GAF scores in the ROSZ and UHR groups and between the MMN amplitudes and BACS scores in the ROSZ, UHR, and HC groups. The findings of Salisbury et al. (2017) of significant correlations of dMMN and fMMN with premorbid intellect suggested that premorbid intellect might affect MMN and its correlations with the GAF and BACS scores. Therefore, we calculated the Pearson correlation coefficients (r) for MMN amplitude and premorbid IQ separately for the ROSZ, UHR, and HC groups to evaluate the effects of premorbid IQ on the results. In addition, we calculated partial correlations and adjusted for antipsychotic dose to parse out the effects of antipsychotic medication on the main results of the associations between MMN amplitude and the GAF and BACS scores if there was a significant correlation with antipsychotic dose.

Structural equation modeling was used to investigate whether MMN directly affected global functioning or whether the effects of MMN on global functioning were mediated by cognition in early stages of psychosis. We used the GAF and BACS components that correlated significantly with MMN amplitude. The model goodness of fit was assessed using the goodness of fit index (GFI), root-mean-square error of approximation (RMSEA) (McDonald, 1989), and Akaike information criterion (AIC) (Akaike, 1974). All significance levels were set to $p < 0.05$.

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