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Impaired mismatch negativity is associated with current functional status rather than genetic vulnerability to schizophrenia

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ABSTRACT

The aim of this study is to investigate whether mismatch negativity (MMN) is associated with functional status or is a state-independent trait for schizophrenia. We assessed MMN in 26 patients with schizophrenia, 20 healthy subjects with high genetic loading, and 48 healthy controls. Repeated measures analysis of variance and Pearson's correlations were used to test the hypothesis that MMN is not state-independent. We found a significant main effect of group, indicating differences in the peak amplitudes of the MMN among the three groups. Post-hoc analyses revealed that schizophrenia patients showed a significant reduction in the peak amplitude of MMN, but subjects at high genetic risk and healthy controls did not. Additionally, significant correlations between Global Assessment of Functioning scores and MMN peak amplitude at Fz and Cz were found in patients with schizophrenia. These findings suggest that MMN may reflect current functional status rather than a genetic risk for schizophrenia.

1. Introduction

Many patients with schizophrenia suffer from a wide variety of characteristic brain dysfunctions, especially within the cognitive domain. There is evidence that patients with schizophrenia and their biological relatives exhibit deficits in the areas of sustained attention, executive function, and working memory (Green et al., 1992; Goldman-Rakic, 1994; Kremen et al., 1994; Conklin et al., 2000). In addition to such higher cognitive dysfunctions, abnormalities in automatic pre-attentive processing are consistently reported in schizophrenia (Shelley et al., 1991; Javitt et al., 1993; Shutara et al., 1996; Umbricht and Krljes, 2005). An emerging view is that this dysfunction in automatic information processing may influence, at least in part, higher order cognitive functions and, in turn, contribute to psychosocial disabilities (Javitt et al., 1995; Rissling et al., 2010). Therefore, research focusing on pre-attentive information processing as a neurophysiological marker of abnormal brain function in schizophrenia has increased.

Mismatch negativity (MMN) is a negative component in the event-related potential (ERP) that is thought to represent pre-attentive information processes associated with the automatic detection of change (Naatanen et al., 2001). Impaired MMN in patients with schizophrenia has been well established by many previous studies (Shelley et al., 1991; Catts et al., 1995; Javitt et al., 2000; Michie et al., 2000; Umbricht and Krljes, 2005). Previous studies have also noted that impairments in MMN are correlated with the dysfunction in higher level cognitive processes, such as working memory and social cognition, seen in patients with schizophrenia (Toyomaki et al., 2008; Wynn et al., 2010; Sevik et al., 2011). Additionally, the relationship between reduction in MMN and poor functional status in patients with schizophrenia has been consistently observed in many studies (Light and Braff, 2005; Kawakubo and Kasai, 2006; Kiang et al., 2007). For example, Light and Braff (2005) reported that a higher level of MMN impairment is associated with lower scores on the Global Assessment of Functioning (GAF).

In the context of the recent increased interest in the early detection and prevention of psychosis, studies investigating impaired MMN in subjects with genetic high risk (GHR) as an endophenotype for schizophrenia have increased. GHR subjects represent an appropriate model with which to study genetic liability because they have not developed the prominent features of the disease but have a higher risk for schizophrenia than the general population (Jessen et al., 2001). Unlike the results concerning the MMN abnormality in patients with schizophrenia, however, results in subjects at GHR are inconsistent. Several family studies have reported that MMN is abnormal in unaffected first

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degree relatives of patients with schizophrenia (Jessen et al., 2001; Michie et al., 2002; Sevik et al., 2011), whereas other studies have not found any differences between individuals at GHR and healthy control (HC) subjects (Bramon et al., 2004; Magno et al., 2008). This inconsistency may be due to the fact that the subjects in the former studies did not have enough genetic loading (Jessen et al., 2001; Michie et al., 2002; Bramon et al., 2004; Magno et al., 2008; Sevik et al., 2011) or they had different functional status. For instance, two of the previous studies excluded subjects who had had previous psychotic episodes but did not present psychotic symptoms at the time of admission to the studies (Jessen et al., 2001; Michie et al., 2002). Another study eliminated subjects with psychosis according to DSM-IV criteria but included subjects with other psychiatric illnesses, such as major depressive disorder, panic disorder, and schizotypal personality disorder (Bramon et al., 2004). In terms of current psychiatric symptoms, only two studies used the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) or the Structured Clinical Interview for DSM-IV Non-Patient version (SCID-NP) to confirm that subjects at GHR were free of any psychiatric symptoms, although they did not measure prodromal symptoms (Magno et al., 2008; Sevik et al., 2011). Meanwhile, one of the Edinburgh cohort studies, in which subjects had high genetic loading for schizophrenia, reported that more than 40% of GHR subjects experience transient symptoms or a subsyndromal psychosis (Owens et al., 2005). This suggests that GHR subjects with subtle prodromal symptoms were likely to be included in previous studies, and these symptoms might have had an influence on the current functioning of these subjects. However, these previous studies did not adequately explore the relationship between MMN and the current functional status of those at GHR.

This study was conducted to evaluate whether MMN is a candidate marker of a genetic predisposition for schizophrenia by comparing the MMN amplitudes of patients with schizophrenia, healthy GHR subjects, and HC subjects. It was hypothesized that if MMN were associated with functional status rather than with genetic predisposition, this marker would not be impaired in well-functioning GHR subjects free of psychotic symptoms, including the prodromal syndrome. Therefore, GHR subjects with high genetic loading who were not seeking help, healthy, and without prodromal symptoms when screened by the Structured Interview for Prodromal Symptoms (SIPS) were included in the current study (Jung et al., 2010).

2. Methods

2.1. Participants

This study included 26 patients with schizophrenia, 20 subjects at GHR, and 48 HC subjects (Table 1). Patients with schizophrenia and subjects at GHR were recruited from the inpatient and outpatient clinics of the Department of Psychiatry of Seoul National University Hospital and the Seoul Youth Clinic, a center for the prospective, longitudinal investigation of people at high risk for psychosis that was established in Seoul, Korea, in November 2004 (Kim et al., 2012). HC subjects were recruited via advertisements placed on the Internet and in the outpatient office. Patients with schizophrenia were diagnosed with the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Axis I disorders (SCID-I). A GHR subject was defined as an unaffected family member who had at least one first degree relative with schizophrenia and one or more affected third degree relatives. Patients with schizophrenia and GHR subjects were assessed using the Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), and GAF upon admission into the study. Additionally, prodromal symptoms were assessed in GHR subjects using the SIPS. GHR subjects with SIPS scores exceeding a certain threshold were judged as having both a genetic and a clinical high risk and were excluded from this study. HC subjects were included when they reported no past or current Axis I diagnoses and no first to third degree biological relatives with any major psychiatric disorder. HC subjects were assessed and declared free of any psychiatric disorders or symptoms following screening with the SCID-NP. The IQ of all participants was measured with the abbreviated form of the Korean Wechsler Adult Intelligence Scale (K-WAIS). Exclusion criteria for all participants included a lifetime diagnosis of substance abuse or dependence or neurological disease or head injury, evidence of medical illness with documented cognitive sequelae, sensory impairments, or intellectual disability (IQ < 70).

The Institutional Review Board of 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.

2.2. Stimuli and task

Participants were given the visual task of finding a specific character, Wally, in a picture book to divert their attention from acoustic stimuli; this paradigm was used in a previous study from our laboratory (Shin et al., 2012). The acoustic stimuli were presented using tubular insert earphones with the STIM2 system (Neuroscan, E1 Paso, TX) and comprised two experimental blocks. Each block consisted of a pseudo-random series of 1000-Hz (80-dB, 10-ms rise/fall) tones that could be differentiated by duration. A total of 1200 stimuli were presented in a fixed order to all subjects; 982 (81.8%) were frequent standard stimuli lasting 50 ms, and 218 (18.2%) were infrequent deviant stimuli lasting 100 ms. The stimulus onset asynchrony was 300 ms.

2.3. Data acquisition

Continuous electroencephalographic (EEG) recording was acquired using a Neuroscan 128 Channel Synamps system with 64 scalp electrodes based on the 10–20 international system; electrodes at each mastoid site served as reference electrodes. The EEG was digitized at a 1000-Hz sampling rate with an analog filter from 0.05 Hz to 100 Hz. Eye-movement artifacts were monitored by recording the vertical and horizontal electro-oculogram by placing electrodes below and on the outer canthus of the left eye. The resistance at all electrode sites was below 5 kΩ.

2.4. Event-related potential analysis

Data were analyzed using Neuroscan version 4.5 software. Acquired recordings were visually inspected to remove trials with large eye movements or any other artifacts, epoched to 100-ms pre-stimulus and 300-ms post-stimulus, and then baseline-corrected using the pre-stimulus interval. Individual epochs were rejected if the EEG amplitude exceeded $\pm 100\,\mu V$, and a second manual inspection was performed after the automated artifact rejection to discard trials with remaining artifacts. ERPs were averaged separately for standard and deviant stimuli, baseline-corrected again using the pre-stimulus interval, and band-pass filtered between 0.1 Hz and 30 Hz. The MMN was extracted separately for each subject by subtracting the ERPs elicited by standard stimuli from those elicited by deviant stimuli. The peak amplitude and latency of the MMN were determined as the most negative peak between 130 ms and 250 ms of the subtracted waveform using a peak detection method.

2.5. Statistical analysis

The demographic and clinical characteristics of the subjects were examined using one-way analysis of variance (ANOVA), independent sample *t*-tests, or Welch's test if the variances were not equal; a chi-square analysis or Fisher's exact test was used for categorical data. A repeated-measures ANOVA with age as a covariate was performed to assess group differences in MMN amplitudes and latencies at eight central line electrode sites. Covariates such as years of education and IQ were disregarded because these factors are intrinsic features of the illness. Moreover, the findings of a 2005 meta-analysis reporting that no specific factor was significantly associated with MMN deficits support our decision not to examine the effects of years of education and IQ on MMN (Umbricht and Krljes, 2005). A simple contrast test was used to identify differences between groups. Additionally, ANOVA with Tukey's post-hoc multiple-comparison test was performed for each electrode site to reveal local group differences. Pearson's correlations were used to assess the relationship of MMN peak amplitude to PANSS, BPRS, and GAF scores in patients with schizophrenia and subjects at GHR. The correlation between SIPS and MMN amplitude was also analyzed in GHR subjects. *P*-values < 0.05 were considered statistically significant. The SPSS software version 21 was used for statistical analysis.

3. Results

3.1. Characteristics of subjects

We found no significant group differences according to sex, years of education, or handedness. However, the three groups differed with regard to age ($F_{2,91}=3.737$, $p=0.028$) and IQ