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Aberrant temporal behavior of mismatch negativity generators in schizophrenia patients and subjects at clinical high risk for psychosis

Minah Kim [a], Kang Ik Kevin Cho [b], Youngwoo Bryan Yoon [b], Tae Young Lee [c], Jun Soo Kwon [a,b,d,*]

[a] Department of Psychiatry, Seoul National University College of Medicine, Seoul, Republic of Korea
[b] Department of Brain and Cognitive Science, Seoul National University College of Natural Science, Seoul, Republic of Korea
[c] Department of Neuropsychiatry, Seoul National University Hospital, Seoul, Republic of Korea
[d] Institute of Human Behavioral Medicine, SNU-MRC, Seoul, Republic of Korea

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HIGHLIGHTS

- Schizophrenia patients and clinical high risk subjects show decreased mismatch negativity (MMN) strength in frontal and temporal cortices.
- Disconnection between MMN-related brain regions exists even prior to psychosis onset.
- Aberrant MMN generator activity might be related to schizophrenia pathophysiology.

ABSTRACT

Objective: Although disconnection syndrome has been considered a core pathophysiologic mechanism of schizophrenia, little is known about the temporal behavior of mismatch negativity (MMN) generators in individuals with schizophrenia or clinical high risk (CHR) for psychosis.
Methods: MMN was assessed in 29 schizophrenia patients, 40 CHR subjects, and 47 healthy controls (HCs). Individual realistic head models and the minimum L2 norm algorithm were used to generate a current source density (CSD) model of MMN. The strength and time course of MMN CSD activity were calculated separately for the frontal and temporal cortices and were compared across brain regions and groups.
Results: Schizophrenia patients and CHR subjects displayed lower MMN CSD strength than HCs in both the temporal and frontal cortices. We found a significant time delay in MMN generator activity in the frontal cortex relative to that in the temporal cortex in HCs. However, the sequential temporo-frontal activities of MMN generators were disrupted in both the schizophrenia and CHR groups.
Conclusions: Impairments and altered temporal behavior of MMN multiple generators were observed even in individuals at risk for psychosis.
Significance: These findings suggest that aberrant MMN generator activity might be helpful in revealing the pathophysiology of schizophrenia.

1. Introduction

Mismatch negativity (MMN) is an event-related potential (ERP) component that represents pre-attentive auditory information processing (Naatanen et al., 2001). Since MMN was thought to be produced by two sequential processes (auditory sensory change detection and involuntary switching of attention), multiple MMN generators were suggested primarily in the temporal and frontal cortices (Naatanen and Michie, 1979). This suggestion was supported by MMN findings from patients with frontal lesions and intracranial recording (Alho et al., 1994; Liasis et al., 2001; Rosburg et al., 2005). Studies using distributed source analysis also reported that MMN generators were located in both the frontal and temporal cortices (Giard et al., 1990; Jemel et al., 2002) and that frontal generator activity peaked after temporal generator activity in healthy subjects (Fulham et al., 2014; Rinne et al., 2000). Successive functional magnetic resonance imaging (fMRI) findings

* Corresponding author at: Department of Psychiatry, Seoul National University College of Medicine, 101 Daehak-no, Chongno-gu, Seoul 03080, Republic of Korea. Fax: +82 2 747 9063.
E-mail address: kwonjs@snu.ac.kr (J.S. Kwon).

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provided several suggestions of frontal cortex contributions to the MMN mechanism, which indicated temporo-frontal sequential activity of MMN generators in healthy volunteers (Doeller et al., 2003; Opitz et al., 2002; Rinne et al., 2005). These findings suggest that the separate temporal behavior of discrete MMN generators may serve as an indicator of functional connectivity between related brain regions at the pre-attentive level.

Structural and functional disconnection between brain regions has been suggested as a core pathophysiologic mechanism of schizophrenia; the resulting disorder has been termed disconnection syndrome (Friston, 1999; Friston and Frith, 1995). Reduced white matter volume and integrity in schizophrenia patients were found in widespread regions (Bora et al., 2011; Lee et al., 2013; Wheeler and Voineskos, 2014). In subjects at clinical high risk (CHR) for psychosis, structural connectivity was disrupted, although less prominently than in schizophrenia patients, and was associated with the transition to an overt psychotic disorder (Carletti et al., 2012; von Hohenberg et al., 2014; Ziermans et al., 2012). In addition, previous fMRI studies revealed functional disconnection between the temporal and frontal cortices during the performance of executive function tasks among schizophrenia patients and CHR individuals (Benetti et al., 2009; Crossley et al., 2009). Recently, Gaebler et al. reported fMRI results showing that the sensory processing deficit of schizophrenia patients during an auditory mismatch task was related to disrupted connectivity between the temporal and prefrontal cortices (Gaebler et al., 2015). However, the temporal behavior of discrete MMN generators assessed via electroencephalography (EEG), which has the great advantage of millisecond-order time resolution, has not yet been sufficiently studied in patients with schizophrenia.

An impaired MMN response has been consistently reported in schizophrenia patients, suggesting its relationship with the pathophysiology of the disorder (Umbricht and Krljes, 2005). A reduced MMN amplitude in CHR individuals has also been reported, although this finding is not as consistent as in patients with schizophrenia (Bodatsch et al., 2015; Shin et al., 2009). Associations of reduced MMN amplitude with higher-order cognitive deficits and poor functional status were suggested in schizophrenia patients (Kim et al., 2014; Wynn et al., 2010). In CHR subjects, it has been shown that MMN amplitude effectively predicts the transition from a CHR status to overt psychosis and the time to psychosis onset (Bodatsch et al., 2015, 2011; Perez et al., 2014). Recent current source density (CSD) analyses showed that schizophrenia patients displayed MMN generator impairments in widespread brain regions (Miyanishi et al., 2013; Takahashi et al., 2013), but CSD analysis of CHR individuals has not yet been presented. Regarding the separate temporal behavior of discrete MMN generators, only one study reported delayed MMN CSD activation between primary and secondary auditory cortices in schizophrenia (Fulham et al., 2014). However, due to the high variability of CSD onset latencies in the frontal lobe, the delay in frontal cortex CSD activation relative to temporal cortex CSD activation was excluded from analysis in that study.

In this study, we aimed to demonstrate disruptions in functional connectivity at the pre-attentive level in patients with schizophrenia and individuals at CHR for psychosis using MMN CSD analysis. We first hypothesized that MMN CSD strength was reduced in both the schizophrenia and CHR groups compared to the healthy control (HC) group not only in the temporal cortex but also in the frontal cortex. Second, we sought to confirm the findings of previous studies that HC subjects would show sequential temporo-frontal activation of discrete MMN generators, but aberrant temporal behavior of frontal and temporal MMN generators was expected in schizophrenia patients and CHR individuals.

2. Methods

2.1. Participants and clinical assessments

Twenty-nine patients with schizophrenia, 40 individuals at CHR for psychosis, and 47 HC subjects participated in this study. Study participants were recruited via the Seoul Youth Clinic (www.youthclinic.org), a center for early detection and intervention of people at high risk for psychosis (Kwon et al., 2012). The diagnosis of schizophrenia was confirmed using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Axis I Disorders (SCID-I), and the severity of psychotic symptoms was measured using the Positive and Negative Syndrome Scale (PANSS). The CHR subjects met at least 1-of the following 3 criteria of the Structured Interview for Prodromal Symptoms (SIPS) (Miller et al., 2002): attenuated positive symptoms (APS), brief intermittent psychotic symptoms (BIPS), and genetic risk with deterioration (GRD). Prodromal psychotic symptoms were assessed in CHR individuals using the validated Korean version of the SIPS (Jung et al., 2010). In both the schizophrenia and CHR groups, the Global Assessment of Functioning (GAF), Hamilton rating scale for anxiety (HAM-A) and depression (HAM-D) were used to assess general functioning, anxiety, and depressive symptoms. Intelligence quotient (IQ) was measured in all participants using the abbreviated version of the Korean-Wechsler Adult Intelligence Scale (Kim et al., 1994). The exclusion criteria included a lifetime diagnosis of substance abuse or dependence, neurological disease, significant head injury accompanied by loss of consciousness, medical illness with documented cognitive sequelae, sensory impairments, or intellectual disability (IQ < 70).

All of the participants fully understood the study procedure and provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and with the approval of the Institutional Review Board of Seoul National University Hospital.

2.2. EEG recordings and MRI acquisition

Subjects were instructed to find Wally from a “Where’s Wally?” picture book while ignoring acoustic stimuli. While subjects concentrated on the game, pseudorandom series of 1000-Hz (80-dB, 10-ms rise/fall) auditory stimuli were binaurally presented using a STIM2 sound generator (Compumedics, Charlotte, NC). The auditory oddball stimuli consisted of 982 (81.8%) standard stimuli lasting 50 ms and 218 (18.2%) deviant stimuli lasting 100 ms. The deviant stimuli were preceded by at least one standard stimuli and the inter-trial interval was 600 ms.

Before the data acquisition session, each subject’s anatomical landmarks and the scalp locations of each electrode were recorded with an Isotrak 3D digitizer (Polhemus, Colchester, VT). 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). The electrodes at the mastoid sites served as reference electrodes. The EEG data were digitized at a 1000-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 with a 3-T scanner (Siemens Magnetom Trio, Erlangen, Germany) using 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, FOV 250 mm, flip angle 9°, and 208 slices).