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Mismatch negativity is a stronger indicator of functional outcomes than neurocognition or theory of mind in patients with schizophrenia

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ABSTRACT

Objectives: Mismatch negativity (MMN) is known to be associated with neurocognition, social cognition, and functional outcomes. The present study explored the relationships of MMN with neurocognition, theory of mind, and functional outcomes in patients with schizophrenia, first-degree relatives of patients with schizophrenia, and healthy controls.

Methods: Twenty-five patients with schizophrenia, 21 first-degree relatives of patients with schizophrenia, and 29 healthy controls were recruited. We examined symptom severity, neurocognition, theory of mind, functional outcomes, and MMN.

Results: MMN amplitudes decreased in order of patients with schizophrenia, then first-degree relatives, then healthy controls. MMN amplitude was significantly correlated with measures of neurocognition, theory of mind, and functional outcome measurements in patients with schizophrenia. However, the most powerful correlations were those between MMN in the frontal region and measures of functional outcomes. The power and frequency of the correlations were weaker in first-degree relatives and healthy controls than in patients with schizophrenia. Hierarchical regression analysis revealed that functional outcomes (relative to measures of neurocognition and theory of mind) constituted the most powerful predictor of MMN.

Conclusions: Our results suggest that MMN reflects functional outcomes more efficiently than do measures of neurocognition and theory of mind in patients with schizophrenia.

1. Introduction

Mismatch negativity (MMN) is an automatically generated ERP component when a sequence of relatively uniform stimuli is interrupted by the infrequent presentation of deviant stimuli. MMN is thought to reflect an automatic measure of detection of perceptual change or a sensory prerequisite of cognition (Naatanen et al., 1978). MMN deficiency appears to be an index of cognitive decline, irrespective of the specific symptomatologies and etiologies of the involved disorders (Naatanen et al., 2012).

MMN deficits have been observed in patients with schizophrenia (Light and Braff, 2005a; Salisbury et al., 2002; Wynn et al., 2010). MMN has been known to be relatively uninfluenced by the effects of antipsychotic medication (Catts et al., 1995; Umbricht et al., 1998, 1999), and MMN deficit may reflect the progression of disease or premorbid neurocognitive impairment (Umbricht et al., 2006). Şevik et al. (2011) reported that patients with schizophrenia had similar MMN amplitudes to an age- and education-matched sibling group; however, they have lower MMN amplitudes than healthy controls. The major pathology of MMN deficit appears to originate from dysfunction of the N-methyl-D-aspartate (NMDA) receptor system (Javitt et al., 1996; Umbricht et al., 2002). NMDA-receptor-mediated glutamatergic dysfunction may well explain the pathology of both schizophrenia and other neuropsychiatric diseases (Umbricht et al., 2002), which explicitly reflect MMN deficits. Several groups have reported correlations between MMN and global social functioning in patients with chronic schizophrenia (Kawakubo and Kasai, 2006; Kiang et al., 2007; Light and Braff, 2005a; Rasser et al., 2011), and one study found a stable association over a 1-year period (Light and Braff, 2005b). Significant associations between MMN and Global Assessment of Functioning (GAF) scores have also been noted in healthy subjects (Light et al., 2007). The results of these studies imply that deficits in MMN can impact social functioning in the community.

Functional outcomes are important in schizophrenia research. Recent work has demonstrated that social cognition is a more important

Abbreviations: MMN, mismatch negativity; GAF, Global Assessment of Functioning; PANSS, Positive and Negative Syndrome Scale; BACS, Brief Assessment of Cognition in Schizophrenia; TMT-A & B, Trail Making Test-A & -B; ToM, theory of mind; K-SAS, Korean version of the Social Adjustment Scale; SFQ, Social Functioning Questionnaire; EEG, electroencephalogram; EOG, electrooculograms; ANOVA, analysis of variance.

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mediator of functional outcomes than is neurocognition in patients with schizophrenia (Bae et al., 2010; Brekke et al., 2005). Wynn et al. (2010) studied the relationship among MMN, social cognition, and functioning in patients with schizophrenia; they reported that MMN deficits had a downstream impact on higher-order social cognition and community functioning. However, no previous studies have completely explored the relationships among early auditory processing (MMN), neurocognition, social cognition, and functional outcomes in patients with schizophrenia and their first-degree relatives.

In the present study, we aimed to explore the relationships of MMN with neurocognition, social cognition, and functional outcomes in patients with schizophrenia, first-degree relatives of patients with schizophrenia, and healthy controls. The first-degree relatives were recruited because they represent a continuum between patients with schizophrenia and healthy controls. This will also aid our understanding of MMN differences in schizophrenia and first-degree relatives. We hypothesized that MMN amplitude, neurocognition, social cognition, and functional outcomes would be lowest in patients with schizophrenia, followed by first-degree relatives and healthy controls. In addition, we hypothesized that MMN would show a stronger relation with functional outcomes than with social cognition and neurocognition in patients with schizophrenia as well as first-degree relatives of patients with schizophrenia and healthy controls.

2. Methods

2.1. Participants

Patients with schizophrenia (n = 25, 13 female), first-degree relatives of patients with schizophrenia (n = 21, 16 female), and healthy controls (n = 29, 13 female) were recruited from the Psychiatry Department of Inje University Ilsan Paik Hospital, Korea. Patients with schizophrenia were diagnosed according to the criteria set forth in the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) Axis I Psychiatric Disorders (First and Gibbon, 1997a). Their psychiatric symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). None of the patients had mental retardation or a history of central nervous system disease, alcohol or drug abuse, electroconvulsive therapy, or head injury with loss of consciousness. All patients were in stable condition and taking atypical antipsychotics (olanzapine, n = 11; risperidone, n = 14).

First-degree relatives and healthy controls were recruited through posters displayed in the hospital and advertisements in local newspapers. An initial screening interview was conducted by a board-certified psychiatrist in order to exclude subjects with identifiable psychiatric disorders or histories of head injury or neurological disorders. The first-degree relatives were siblings, parents, or children of people with schizophrenia; they were excluded if they had any personal history of psychiatric disease. Ten of the first-degree relatives were relatives of the patients in this sample, and 11 were not. Healthy controls were excluded if they had any personal history of psychiatric disease or family history of psychiatric illness. Potential healthy control subjects were interviewed using the Structured Clinical Interview for DSM-IV Axis II Disorders (First and Gibbon, 1997b) and excluded if they had any of paranoid, schizoid, or schizotypal personality disorders. All Structured Clinical Interviews and PANSS administrations were conducted by two psychiatry residents (KS and KSL); the interrater reliability value was 0.76.

All subjects' normal hearing ability was confirmed by the 512-Hz tuning fork test (Burkey et al., 1998), and all were identified as right-handed, as they responded that they used that hand for writing and other precise motor skills. All subjects signed a written informed consent form approved by the Institutional Review Board of Inje University Ilsan Paik Hospital prior to participation in the study.

There were no significant between-group differences in terms of gender distribution or education (Table 1). However, the first-degree relatives were older than the patients with schizophrenia or healthy controls.

2.2. Neurocognition

2.2.1. Verbal fluency test — animal

In this test, subjects state the names of as many animals as possible within 60 s. This evaluates verbal production and semantic memory abilities. This test was adapted from the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004).

2.2.2. Symbol coding

Patients were given 90 s to write the numerals 1–9 to match symbols on a response sheet as quickly as possible to evaluate their capacity for psychomotor speed. Possible scores on this measure range 0–110. This task was adapted from the BACS (Keefe et al., 2004).

2.2.3. Trail Making Test-A & -B (TMT-A & TMT-B)

In the TMT-A, subjects are asked to draw lines sequentially, connecting 25 consecutive, encircled numbers distributed across a sheet of paper within 360 s. In the TMT-B, subjects are instructed to draw lines alternating between numbers and Korean letters within 300 s (Seo et al., 2006). The TMT-A and TMT-B are scored according to the time taken to complete the task. The TMT-A mainly evaluates visual attention, while the TMT-B evaluates executive functioning. Longer time scores indicate worse performance.

2.3. Theory of mind (ToM)

2.3.1. Cartoon test

We used the modified version of the cartoon test (Oh et al., 2005), the original version of which was developed by Sarfati et al. (1997). Subjects see four consecutive panels of a cartoon and are asked to determine the most appropriate still cut to place next. This test evaluates the ability to understand social context. This measure comprises 30 items; the total possible score is 30.

2.3.2. False belief task

This test was developed to assess the ability to imagine other people's false beliefs in a specific situation described in a story. We used four short stories including first-order (Wimmer and Perner, 1983) and second-order false belief tasks (Perner and Wimmer, 1985), each of which asks about two stories.

Table 1
Demographic data and symptom ratings of patients with schizophrenia.

	Patients with schizophrenia (n = 25)	First-degree relatives (n = 21)	Healthy control subjects (n = 29)	*F*-test
Sex (male/female)	12/13	5/16	16/13	2.62
Age (years)	35.72 (11.33)	52.86 (13.16)	30.21 (11.17)	23.34***
Education (years)	12.20 (3.35)	13.05 (3.99)	14.48 (4.31)	2.33
Number of hospitalizations	3.5 (2.5)			
Dosage of medication (CPZ equivalent, mg)	482 (170)			
PANSS score				
Positive	19.60 (6.54)			
Negative	22.20 (5.37)			
General	38.08 (10.19)			
Total	79.68 (12.73)			

PANSS: Positive and Negative Syndrome Scale.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.