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Association between mismatch negativity and voxel-based brain volume in schizophrenia

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HIGHLIGHTS

- Mismatch negativity (MMN) amplitudes were significantly lower in schizophrenia patients than healthy controls.
- The volume of left hippocampus is correlated with MMN in schizophrenia patients.
- Hippocampal volume is related with MMN in schizophrenia patients after controlling for confounders.

ABSTRACT

Objective: This study aimed to investigate the association between mismatch negativity (MMN) and volumes of several brain regions measured using a semi-automated method in patients with schizophrenia and healthy controls.
Methods: MMN in response to duration deviants and magnetic resonance imaging were acquired from 36 schizophrenia patients and 14 healthy controls. FreeSurfer was used for volumetric analysis. MMN amplitudes, brain volumes and their association were compared between schizophrenia and controls. Correlation analysis and multiple linear regression analysis were used to examine the correlated variables of MMN.
Results: MMN amplitude was significantly lower in the schizophrenia group. In schizophrenia, MMN was positively correlated with age and negatively correlated with left hippocampal and right pars opercularis volumes. The association between left hippocampal volume and MMN in schizophrenia remained significant after controlling for potential confounders.
Conclusions: Smaller hippocampal volume may play a role in the abnormal manifestation of MMN in schizophrenia.
Significance: The significant association between MMN and left hippocampal volume may suggest unique neurobiological contribution of hippocampus in auditory processing in schizophrenia.

1. Introduction

Mismatch negativity (MMN), a type of event-related potential (ERP), is generated when a discernable change occurs in a series of repetitive standard stimuli (Naatanen et al., 1978). MMN represents the pre-attentive process of auditory discrimination and is associated with the function of auditory memory and involuntary attention shifting (Naatanen and Michie, 1979; Javitt et al., 1995; Naatanen et al., 2007). MMN deficit is extensively observed in schizophrenia patients (Shelley et al., 1991; Javitt et al., 1993; Umbricht and Krljes, 2005). By administering different auditory oddball paradigms (such as sounds with distinct duration, frequency, or intensity), research has revealed MMN to be related

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to the diagnosis of schizophrenia and a few functional indexes in schizophrenic patients, such as social cognition and independent living capability (Light and Braff, 2005; Wynn et al., 2010; Haigh et al., 2017). Conversely, duration of illness has been found unrelated to MMN deficit in a recent meta-analysis (Erickson et al., 2016). MMN deficit in response to duration deviants is stable in chronic schizophrenia patients; collectively, with the similar finding in first-degree relatives, it is considered as a candidate for endophenotype of schizophrenia (Michie et al., 2002; Turetsky et al., 2007; Rissling et al., 2010; Nagai et al., 2013b, 2013a; Umbricht et al., 2006; Solis-Vivanco et al., 2014).

Structural abnormalities in several brain regions have been found to be associated with schizophrenia (Shenton et al., 2001; Brent et al., 2013). A previous review reported structural differences in the left medial temporal lobe and left superior temporal gyrus in schizophrenia (Honea et al., 2005) and in areas that contribute to MMN generation (Alho, 1995). Furthermore, it was found that decreased MMN amplitude to frequency deviants is correlated with reduced gray matter volume of the left Heschl's gyrus in schizophrenia (Salisbury et al., 2007). As a candidate endophenotype of schizophrenia, the relationship between MMN and brain volumes is an interesting topic, for it may provide more understanding of the interrelatedness of structural and functional changes pertaining to the disease. Previous studies mainly focused on superior temporal and inferior frontal lobe involvement in MMN generation and auditory deviant processing (Wible et al., 2001; Schall et al., 2003; Rasser et al., 2011). Although it has been reported that mismatch activation could be detected in hippocampal areas at 350 msec with intracranially-placed electrodes (Rosburg et al., 2007), whether hippocampal activity could affect scalp-recorded MMN is less studied.

Previous studies exploring structural brain abnormalities in schizophrenia have adopted manual tracing procedures to delineate regional brain volumes. This approach has a major dependency on raters and a potential risk of rater bias. In recent years, semi-automated volumetric parcellation methods have been developed and utilized in schizophrenia research (Fischl, 2012; van Erp et al., 2014; Arnold et al., 2015). Automated measurements are more efficient, reproducible and useful for larger samples. Volume estimations from semi-automated approaches were found to have strong correlation with manual tracing, suggesting a satisfying validity (Morey et al., 2009; Arnold et al., 2015).

The current study aimed to: (1) compare MMN and brain volumes of the healthy controls and schizophrenia patients; and (2) examine the correlation between MMN and preselected brain regions in the schizophrenia group. We hypothesized that MMN was associated with volumes of brain regions such as the hippocampus, the superior temporal gyrus or the inferior frontal gyrus in patients with schizophrenia.

2. Materials and methods

2.1. Participants

Thirty-six clinically stable patients meeting the DSM-IV criteria of schizophrenia and 14 healthy controls with no family history of psychotic disorders were recruited for the current study. The subjects overlapped with the participants in our previous study (Lin et al., 2012). Schizophrenia diagnosis was based on the Chinese version of the Diagnostic Interview for Genetic Study (DIGS) by board-certified psychiatrists. Any subject with documented intellectual disability, hearing impairment, epilepsy, other neurological disorders or head injury was excluded. Schizophrenia patients within diagnostic entities such as schizoaffective disorder, bipolar affective disorder, organic mental disorder or substance-related mental disorder were also excluded. Subjects with no medication adjustment and no changes in psychopathology over the past 3 months were defined as clinically stable. In addition, psychopathology of the schizophrenia subjects was evaluated by their treating psychiatrists using the Positive and Negative Syndrome Scale (PANSS). All psychiatrists received training in using the PANSS to increase diagnostic reliability.

Demographic characteristics and clinical variables including age, smoking status, amount of tobacco consumption, duration of illness and antipsychotic medications were obtained by interview and medical records. The dose of antipsychotics was converted into the equivalent dose of chlorpromazine (chlorpromazine 100 mg/day = haloperidol 2 mg/day = risperidone 2 mg/day = olanzapine 5 mg/day = quetiapine 75 mg/day = aripiprazole 7.5 mg/day = clozapine 50 mg/day = sulpiride 200 mg/day = amisulpride 200 mg/day) according to previous reports (Woods, 2003, Andreasen et al., 2010).

This study was approved by the National Taiwan University Hospital Institute Review Board. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All participants provided written informed consent before their participation.

2.2. Testing environment and MMN recording

Participants' MMN responses were tested in a sound attenuating, electrically shielded booth. The hearing test was performed before MMN recording. Participants were seated in a comfortable recliner and instructed to relax with their eyes opened and to focus on the video monitor (MMN session). The stimuli were generated by and data was recorded by a Neuroscan [Neuroscan, El Paso, Tex.] STIM and ACQUIRE system. Electrodes were used at up to 32 recording sites utilizing Neuroscan QuikCaps. As recommended by the QuikCap website, all electrodes were placed according to the International 10–20 electrode placement standard). Auditory stimuli were presented to subjects binaurally via foam insert earphones.

During the MMN session, subjects were closely observed through a one-way mirror or video monitor. They were monitored visually and by EEG for signs of sleep or slow wave activity which, if present, prompted the experimenter to speak briefly with the subject.

Electrodes placed at the tip of the nose and at Fpz served as the reference and ground, respectively. Four additional electrodes placed above and below the left eye and at the outer canthi of both eyes are used for monitoring blinks and eye movements. All impedances were below 5 kΩ. Signals were digitized at a rate of 1 kHz with system acquisition filter settings of 0.5–100 Hz, with no 60 Hz notch filter. Electroencephalography and stimulus markers were recorded continuously, while subjects were instructed to minimize eye movements and muscle artifacts during the recording.

2.3. MMN session

ERP data were collected while participants viewed a benign cartoon film with the cartoon soundtrack turned off and replaced by the experimental tones. There were no tasks performed during the test, but all subjects were asked to pay attention to the silent cartoon before the experiment. To minimize eye movement, the film was presented at eye level on a 19-in. LCD monitor screen.

Stimuli were presented at a fixed 500 msec onset-to-onset asynchrony. All stimuli were 80 dB, 1000 Hz tones with 1 msec rise-fall time. Duration of standard and deviant tones were