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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

50 msec (90%) and 100 msec (10%) respectively, and they were in pseudorandom order. During testing, online ERP averages to standard and deviant tones were also acquired to monitored signal quality and the number of sweeps free of gross artifacts (defined as ±100 μV across the 100–500 msec following stimuli). The whole session took approximately 30 min, and a minimum of 225 artifact-free deviant trials were collected.

2.4. Offline data processing for MMN

Data processing was performed offline with automated procedures using nasal tip as a reference in the analyses (Duncan et al., 2009; Light et al., 2010; Salisbury et al., 2017). Continuous recordings were mathematically corrected for eye movement artifacts using established methods (Semlitsch et al., 1986). Digital filtering with bandpass 1–40 Hz was utilized before segmentation and ocular artifact correction (Duncan et al., 2009). Continuous data were divided into epochs relative to the onset of stimuli (−100 to 500 msec), and centered at the mean of the prestimulus baseline. Following blink correction, epochs containing greater than ±50 μV in frontal recording sites (F3, F4, and Fz) were automatically rejected (Salisbury et al., 2002). The MMN were generated by subtracting event-related potentials in response to standard tones (50 msec) from the event-related potentials generated in response to the deviant tones (100 msec) from 135 to 205 msec mean amplitude (Rissling et al., 2010; Hsieh et al., 2012; Lin et al., 2012). The resultant MMN subtraction waveforms were lowpass filtered at 20 Hz (0 phase shift and 24 dB/octave roll off) to remove any residual high frequency artifact (Light and Braff, 2005). In order to compare MMN of the two groups, Fz was chosen for analysis because of maximal MMN waveform (Duncan et al. 2009).

2.5. MRI and FreeSurfer

The MRI scanners used in this study was 1.5 T Sonata (Siemens, Erlangen, Germany), with sequences 3D T1 Spoiled Gradient-echo (FLASH, TR = 8 ms, TE = 3.12 ms, flip angle = 12°, FOV = 200.0 × 200.0 mm, slice thickness = 0.9 mm, contiguous 0.9 mm sections, 256 × 256 matrix, NEX = 1, voxel size = 0.78 × 0.78 × 0.9 mm). The MRI scans were analyzed using the FreeSurfer software package (version 3.0.5). We analyzed and performed cortical reconstruction and volumetric segmentation using the FreeSurfer software package (version 5.1), which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). In brief, this software performed the processing automatically in multiple sequential steps, including performing 3-dimensional reconstruction from the volumetric high resolution T1 weighted images, using a hybrid watershed/surface deformation procedure to remove the non-brain tissue, transforming the images according to the Talairach atlas, segmenting the subcortical white matter and deep gray matter volumetric structures including the basal ganglion, hippocampus, amygdala, thalamus and ventricles, normalizing the signal intensity, processing tessellation of the gray matter/white matter boundary, automatically correcting the topology, and carrying surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders. The software works in two individual streams. In the cortical surface stream, the tools construct models of the boundary between the cortical gray matter and white matter, and also the cortical gray matter and the pial surface. Cortical thickness was calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface. The volume-based stream was designed to preprocess MRI volumes and label subcortical tissue classes. Both the cortical and the subcortical labeling used the same basic algorithm. The software defined the cortical surface based on average folding patterns mapped to a sphere and then this surface could be aligned with this atlas using a high-dimensional nonlinear registration algorithm. The spherical atlas naturally forms a coordinate system in which point-to-point correspondence between subjects can be achieved. After processing via FreeSurfer, visual inspection of the snapshots from the results was used to ensure that the non-brain areas had not been wrongly segmented as brain tissue. In this study, several candidate regions of MMN were selected and analyzed: bilateral hippocampus, bilateral superior temporal lobe, and bilateral inferior frontal lobe (including pars opercularis, pars orbitalis, pars triangularis in FreeSurfer). Data in other brain regions were analyzed only for exploratory purposes.

2.6. Statistical analysis

For continuous variables, the Shapiro-Wilk test was used for examining data normality. Independent *t* tests (for variables distributed normally) and chi square tests were used to compare the demographic data, MMN, and brain volumes of the control and schizophrenia groups. Correlation analysis (mainly Pearson's correlation analysis, and Spearman's correlation analysis for data not distributed normally) was performed to examine the relationship between MMN at Fz, demographic data, brain volumes, and PANSS scores (categorical variables were recoded into dummy variables). For the correlation between brain volumes and MMN at Fz, Bonferroni correction was used to correct the problem of multiple testing. Finally, multiple linear regression analysis (with enter method) was used to examine the correlated variables (including brain volumes and demographic data) of MMN at Fz while controlling for potential confounders.

3. Results

Fourteen healthy adults and 36 schizophrenia patients were recruited into this study. The age and gender in the two groups were not statistically different (Table 1). The educational level in the schizophrenia group was significantly lower than the control group. The MMN amplitude was significantly higher in the control group than the schizophrenia group ($t = 2.603$, $p = 0.012$, Table 1). Detailed information about MMN is shown in Fig. 1. Grand average MMN waveform at each electrode is shown for the controls ($n = 14$; solid line) and schizophrenia patients ($n = 36$; dot dash line). The waveform reversed in polarity at the mastoid electrodes, which is typical for MMN. In terms of brain volumes, the following regions showed significantly higher values in the control group: left hippocampus, left pars triangularis, and right superior temporal gyrus (marginal significance in right hippocampus) (Table 1).

We performed correlation analysis of MMN with demographic data (Supplementary Table S1) and brain volumes (Table 2 and Supplementary Table S3) in schizophrenia and controls respectively. In the schizophrenia group, MMN was significantly correlated with age, left hippocampal and right pars opercularis volumes (locations of these brain regions are shown in Supplementary Fig. S1). The simple linear regression models of the left hippocampus, right pars opercularis and MMN are shown in Fig. 2. PANSS scores had no statistically significant correlations with MMN or brain volumes (Supplementary Table S2). In addition to the preselected brain regions, an exploratory, whole-brain analysis was conducted to examine correlations with MMN in areas beyond the a-priori regions of interest. Results showed that the correlations were weaker in other brain areas compared with left hippocampus and right pars opercularis.

Table 1
Demographic data, MMN and brain volume of the control and schizophrenia groups.

	Control group (N = 14) Mean (±SD)/Number (%)	Schizophrenia group (N = 36) Mean (±SD)/Number (%)	t	$\chi 2$	p value
Demographics					
Age (years old)	33.86 (±8.41)	37.78 (±10.67)	1.231		0.224
Gender (male)	6 (42.9%)	18 (50%)		0.206	0.757
Educational level (years)	16.79 (±3.19)	12.75 (±3.26)	3.950		<0.001***
Duration of illness (years)	–	13.17 (±9.89)	NA		NA
Equivalent dose of antipsychotics (mg/day)	–	335.65 (±257.16)	NA		NA
MMN					
Amplitude at Fz (μV)	−1.16 (±1.21)	−0.39 (±0.80)	2.603		0.012*
Number of total stimuli (standard + deviant)	2786(±404)	2858(±815)	−0.426		0.672
Number of accepted deviant stimuli for a grand average MMN	270(±36)	269(±71)	0.067		0.947
Percentage of rejected deviant stimuli (%)	2.74(±3.55)	5.51(±12.64)	−0.806		0.424
Brain volume, aseg (mm^3)					
Left hippocampus	4219.50 (±333.14)	3924.94 (±419.37)	2.350		0.023*
Right hippocampus	4308.93 (±283.80)	4065.78 (±421.68)	1.984		0.053
Brain volume, aparc (mm^3)					
Left pars opercularis volume	5127.07 (±1126.92)	4819.69 (±771.67)	1.106		0.274
Left pars orbitalis volume	2315.43 (±426.75)	2200.61 (±358.38)	0.964		0.340
Left pars triangularis volume	3934.00 (±645.78)	3444.36 (±664.43)	2.357		0.023*
Left superior temporal volume	12214.14 (±1429.06)	11699.06 (±1242.20)	1.262		0.213
Right pars opercularis volume	4366.00 (±753.46)	4041.94 (±719.09)	1.412		0.164
Right pars orbitalis volume	2849.79 (±414.60)	2649.75 (±410.87)	1.542		0.130
Right pars triangularis volume	4461.29 (±800.48)	4390.42 (±818.94)	0.276		0.783
Right superior temporal volume	11888.14 (±1138.26)	11053.92 (±1310.06)	2.092		0.042*

MMN, mismatch negativity; aparc, automatic cortical parcellation; aseg, automatic segmentation volume.
* $p < 0.05$.
*** $p < 0.001$.

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.clinph.2018.06.018.

We further examined the relationship between MMN and demographic data, left hippocampus and right pars opercularis using multiple linear regression analysis (Table 3). For schizophrenia, left hippocampus had the most robust predictive meaning for MMN (beta = −0.404, p = 0.041, R^2 = 0.451). When pooling all subjects (healthy controls and schizophrenia), left hippocampal volume and group * left hippocampal volume showed significant association with MMN at Fz (Table 3).

4. Discussion

There are three major findings in this study: (1) MMN and left hippocampal volume were significantly different in schizophrenia patients and healthy controls; (2) MMN was significantly correlated with left hippocampus and right pars opercularis volumes, and with age in schizophrenia; and (3) left hippocampal volume remained significantly correlated with MMN in schizophrenia after accounting for potential confounding variables.

Studies exploring gray matter volume in schizophrenia patients using region of interest (ROI) measurement (Tamnes et al. 2013) or voxel-based morphometry (VBM) have found smaller volumes in the frontal lobe, temporal lobe, hippocampus, cingulate cortex, corpus callosum and thalamic and caudate nucleus, and larger volumes in the lateral ventricle and third ventricle (Lawrie and Abukmeil, 1998; Niu et al., 2004; Ellison-Wright et al., 2008; Fornito et al., 2009; Collinson et al., 2014). In the present study, schizophrenia patients were found to have smaller left hippocampus and left pars triangularis using semi-automated processing software, finding that is consistent with previous reports derived from ROI and VBM (Wright et al., 2000; Iwashiro et al., 2012). With regard to MMN amplitude, concordant with previous literature, a significant MMN deficiency for duration deviants was found in schizophrenia compared to the controls (Umbricht and Krljes, 2005; Nagai et al., 2013a; Solis-Vivanco et al., 2014). In addition, significant correlations between MMN and volumes of hippocampus and frontal lobe were observed in schizophrenia, corroborating with findings in previous studies (Salisbury et al., 2007; Rasser et al., 2011). Because MMN elicitation depends on discrimination between deviant stimuli and the memory representation of the preceding typical stimuli (Naatanen et al., 2005, 2007), a possible explanation for the divergent patterns of the MMN-brain volume correlation in schizophrenia is the altered functional connectivity associated with auditory processing (Liemburg et al., 2012; Oertel-Knochel et al., 2013). However, a direct investigation of the mechanism underlying observed correlation was beyond the scope of current study.

While previous studies demonstrated associations between MMN and reduced auditory cortex volume in schizophrenia (Yamasue et al., 2004, Salisbury et al., 2007), the current study found significant correlations between MMN to duration deviants and volumes of the left hippocampus and right pars opercularis. Our findings are similar to one study which proposed the associations between MMN and gray matter volume was not confined to the auditory cortex but extended into superior frontal gyrus and frontal-orbital gyrus; though both duration and frequency deviants were adopted in that study (Rasser et al., 2011). The associations between MMN and brain regions beyond auditory cortex further suggest presence of widespread neurophysiological dysfunction underlying MMN reduction in schizophrenia. However, we did not find association between MMN to duration deviants and the auditory cortex (e.g., superior temporal gyrus) as reported in previous research (Rasser et al., 2011). Several factors may contribute to varying findings of the MMN-brain volume association in different studies. For example, age-related change in MMN response has been reported (Todd et al., 2008). Compared to previous reports, participants in the present study were older and had a longer mean duration of illness. Furthermore, different neuroimaging techniques and analytic models may also contribute to the discrepancy of brain volume-MMN association (Schall et al., 2003).

Multiple linear regression analysis in the current study revealed that left hippocampus had robust correlation with MMN in

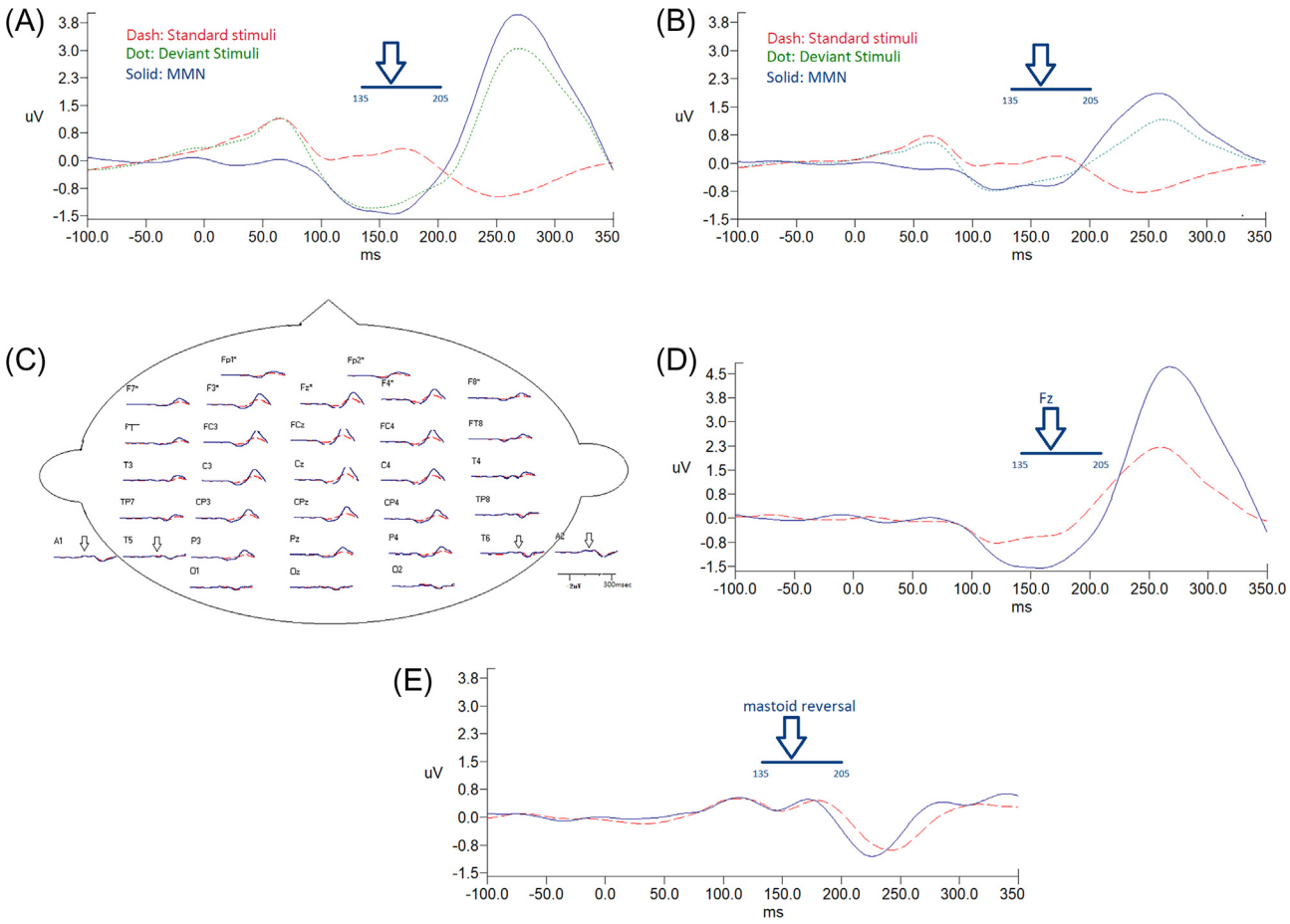

Fig. 1. Grand average mismatch negativity waveforms, followed by P3a, in both groups. MMN was calculated from mean amplitude of 135–205 msec (indicated by the arrow) in Fz electrode. (A) A close-up of grand average waveform at electrode Fz for control subjects. Standard stimuli (dash line), deviant stimuli (dot line), and the difference waveform MMN (solid line) were shown. (B) A close-up of grand average waveform at electrode Fz for schizophrenia patients. Standard stimuli (dash line), deviant stimuli (dot line), and the difference waveform MMN (solid line) were shown. (C) Grand average mismatch negativity waveform at each electrode shown for control subjects (n = 14; solid line) and schizophrenia patients (n = 36; dash line). Arrows indicated the waveform reversed in polarity at the mastoid electrodes, which is typical for MMN. (D) Comparison of MMN waveforms between control subjects (solid line) and schizophrenia patients (dash line) at electrode Fz. MMN was calculated from mean amplitude of 135–205 msec. (E) Comparison of MMN waveforms between control subjects (solid line) and schizophrenia patients (dash line) at electrode T6 (close to right mastoid process). The arrow indicated the waveform reversed in polarity at the mastoid electrodes, which is typical for MMN.

Table 2
Correlation between MMN and brain volumes in the control and schizophrenia groups.

	MMN	
	Control group Correlation coefficient, r	Schizophrenia group Correlation coefficient, r
Brain volume, aseg		
Left hippocampus	0.496	−0.523*
Right hippocampus	0.302	−0.409
Brain volume, aparc		
Left pars opercularis volume	−0.029	−0.225
Left pars orbitalis volume	0.347	−0.237
Left pars triangularis volume	0.543	−0.283
Left superior temporal volume	0.519	0.005
Right pars opercularis volume	−0.068	−0.520*
Right pars orbitalis volume	0.196	−0.253
Right pars triangularis volume	0.597	−0.178
Right superior temporal volume	−0.056	−0.217

MMN, mismatch negativity; aparc, automatic cortical parcellation; aseg, automatic segmentation volume.
* $p < 0.005$ (after Bonferroni correction).

schizophrenia. Although recent ERP studies suggested involvement of hippocampus in auditory information processing (Boutros et al., 2005), few studies have examined functional significance of hippocampus in auditory stimulus discrimination. In animal studies, hippocampus was found to be involved in MMN generation (Csepe et al., 1987; Ruusuvirta et al., 2010; Ruusuvirta et al., 2013). Alterations in hippocampal structure and function have been extensively investigated in schizophrenia, including hippocampal volume reduction (van Erp et al., 2004; Velakoulis et al., 2006) and hippocampal-dependent cognitive deficits (Wilkins et al., 2013; Guo et al., 2014). The association between hippocampal volumes and impaired novel words detection in memory task has been reported in schizophrenia (Weiss et al., 2004). However, evidence supporting the association between MMN and hippocampus was lacking. Patients with hippocampal lesions or Alzheimer's disease did not show overt MMN deficiency (Alain et al., 1998; Baldeweg and Hirsch, 2015). Another study performed in epileptic patients found hippocampal activation at around 350 msec was elicited by both deviant stimuli and novel stimuli, whereas activation in rhinal cortex at around 200 msec was more specific to deviant stimuli (Rosburg et al., 2007). The

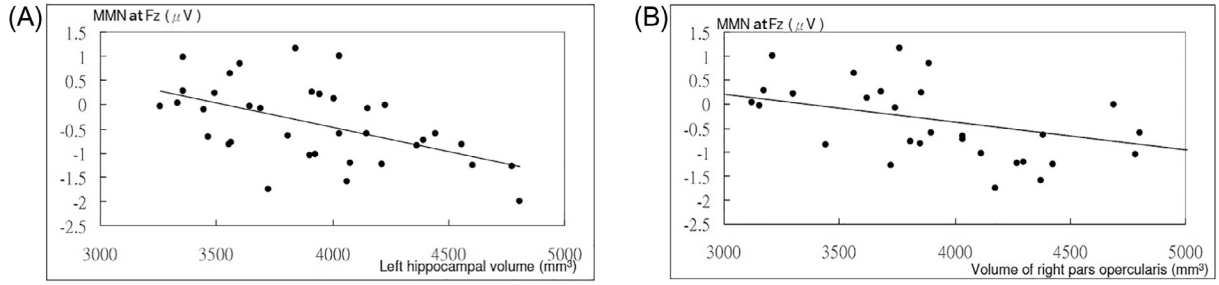

Fig. 2. Simple regression between MMN and brain volume of the schizophrenia group (A) Simple linear regression model between left hippocampal volume and MMN. β = −0.523, p = 0.001. (B) Simple linear regression model between right pars opercularis volume and MMN. β = −0.520, p = 0.001.

Table 3
Multiple linear regression model to MMN.

R^2	MMN at Fz, schizophrenia patients 0.451		MMN at Fz, controls 0.511		MMN at Fz, all subjects 0.502	
	β	*p* value	β	*p* value	β	*p* value
Age	0.199	0.438	0.057	0.849	0.047	0.719
Gender (male = 1, female = 2)	−0.253	0.100	−0.567	0.096	−0.309	0.012*
Duration of illness	−0.159	0.485	–	–	–	–
Equivalent dose of antipsychotics	0.027	0.878	–	–	–	–
Left hippocampus	−0.404	0.041*	0.368	0.262	1.742	0.003**
Right pars opercularis	−0.310	0.115	−0.457	0.156	−0.341	0.015*
Group (control = 0, schizophrenia = 1)	–	–	–	–	4.889	0.001**
Group * left hippocampus	–	–	–	–	−4.456	0.002**

MMN, mismatch negativity.
* p < 0.05.
** p < 0.01.

divergent findings (e.g. no MMN-hippocampus association in patients with Alzheimer's disease, and the association between MMN and hippocampus, rhinal cortex in patients with epilepsy) might be derived from different patient groups and different experimental settings. Therefore, further investigation into the interrelatedness between hippocampus and MMN in schizophrenia is needed.

We found no associations between MMN and gender, educational level, duration of illness, or medication in the schizophrenia group. However, MMN was significantly correlated with age. The effects of age on MMN have been investigated in previous studies. For example, Todd and colleagues (Todd et al., 2008) reported a significant age-related decline in amplitude of MMN to duration deviants in schizophrenia. Correlation between MMN to frequency deviants and age has also been reported (Rasser et al., 2011). In addition, as the volumes of certain brain areas change with human aging (Raz et al., 2005, Tamnes et al., 2013), age would be a confounding factor when interpreting the correlation between MMN and brain volume. However, in the current study, left hippocampal volume remained significantly associated with MMN after the age effect was controlled for. As such, the results indicate that the association of MMN to duration deviants with left hippocampal volume was independent of the effects of age and reflected the structural and functional interrelatedness. Furthermore, given the significant correlation of MMN with age and the unique correlation between MMN and left hippocampal volume, it is possible that left hippocampal brain volume serves a more sensitive indicator of aging than years of age per se. The non-significant association between age and MMN in the control group may be explained by young average age or narrow range of ages of our sample.

Current evidence regarding the correlation between clinical symptoms and changes in MMN are divergent (Umbricht and Krljes, 2005). Consistent with most of the prior literature, we did not find associations between MMN and positive or negative symptoms measured by PANSS (Naatanen and Kahkonen, 2009; Perez et al., 2014). However, it was proposed that MMN was influenced by current functional status, such as cognitive and social functioning, of patients with schizophrenia (Wynn et al., 2010, Kim et al., 2014). Therefore, further research is required to better understand the relationship between MMN attenuation, clinical symptoms and multiple domains of functioning in schizophrenia.

This study has several limitations. First, the study had relatively small sample size in both the control and schizophrenia groups (especially the control group), which may result in lack of statistical power and limit the generalizability of our results. However, we used split-half approach to examine our data, and the results seemed acceptable (Supplementary Table S4). Second, the present study examined only the associations between brain volume and duration-elicited MMN. Whether the findings could be replicated in MMN elicited by deviants with different sound properties (e.g. frequency, and intensity) awaits further investigation. Third, we used a semi-automated methodology to determine brain volumes. The technical limitation of automated parcellation of MRI should be considered (Murakami et al., 2011). FreeSurfer is extensively used in subcortical volume estimation and has a tendency toward overestimation (Morey et al., 2009; Schultz et al., 2010). Some parcellations in FreeSurfer are too wide-ranging to be meaningful. However, the high level of agreement between "gold-standard" manual tracing methods and FreeSurfer (van Erp et al., 2014) lends credibility to our finding of the significant correlation between left hippocampus volume and MMN. Fourth, the cross-sectional design of our study makes it hard to determine whether there is a causal relationship between MMN and brain volume; a definitive determination can only be made in a prospective design. The possibility that MMN and hippocampal volume were affected by another neurological factor cannot be excluded. Fifth, whether scalp EEG data

can reflect electrophysiological signals from hippocampus is controversial. However, even if the measured MMN was mainly originated from the cortex, it is still possible that the hippocampus has a modulating effect on cortical processing. Sixth, we did not have detailed medication data besides antipsychotics. Some benzodiazepines (such as lorazepam, clonazepam, estazolam) and anticholinergics (such as biperiden and trihexyphenidyl) were also taken by our schizophrenia patients. Therefore, the influence of medications on MMN cannot be excluded. Finally, previous studies found ERP findings changed when using different reference electrodes (Joyce and Rossion, 2005; Walker-Black and Stuart, 2008). Therefore, the effects of reference electrodes should be considered when interpreting our findings. However we found significant associations between MMN and left hippocampal volumes when using either nose tip or mastoid as reference (Supplementary Table S5). Changing reference electrode did not seem to affect our findings.

In summary, this is the first study to investigate the association between MMN and brain volumes using semi-automated parcellation and expands the reach of the current literature by showing the distinct patterns of associations in schizophrenia and healthy controls and the significant involvement of the left hippocampus in manifestations of MMN. The results encourage the use of automated parcellation volumetric approaches in schizophrenia research. Future studies investigating MMN to deviants with different sound properties and neuroanatomical changes in individuals with heterogeneous psychiatric diseases may provide more insight into the underlying neuropathological abnormalities.

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Conflict of interest

All authors declare no conflict of interest.

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