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Differential relationship between mismatch negativity and cortical thickness of frontal cortices in schizophrenia

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Abstract

Differential relationship between magnetic counterpart of mismatch negativity and cortical thickness of frontal cortices in schizophrenia

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Introduction: Mismatch negativity (MMN) is thought to reflect pre-attentive, automatic auditory processing. Reduced MMN amplitude is among the most robust findings in schizophrenia research. MMN generators have been shown to be located in the temporal and frontal cortices, which are key areas in the pathophysiology of schizophrenia. This study investigated whether fronto-temporal cortical thickness was associated with reduced MMN current source density (CSD) strength in patients with schizophrenia.

Methods: In total, 16 schizophrenia patients and 18 healthy controls (HCs) were examined using magnetoencephalography while they performed a passive auditory oddball paradigm. All participants underwent a T1 structural magnetic resonance

imaging scan in a separate session. We evaluated fronto-temporal MMN CSD and cortical thickness, as well as their associations with each other and with clinical symptoms, and explored their utility as classifiers.

Results: Patients exhibited significantly reduced CSD strength in all temporal and frontal areas of interest relative to HCs. There was a positive correlation between CSD strength and cortical thickness in both the temporal and frontal areas in HCs. However, schizophrenia patients showed negative correlations between CSD strength and cortical thickness in the bilateral inferior frontal gyri. Additionally, we found positive correlations between frontal cortical thickness and negative and total scores on the Positive and Negative Syndrome Scale (PANSS).

Conclusions: Our findings provide evidence for deficient temporal and frontal MMN generators in schizophrenia patients, suggesting disruption of the structure-function relationship in this illness.

Keywords: schizophrenia, mismatch negativity, auditory processing, magnetoencephalography, cortical thickness

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Abbreviations

MMN, mismatch negativity

MMNm, magnetic mismatch negativity

CSD, current source density

MEG, magnetoencephalography

PANSS, Positive and Negative Syndrome Scale

MRI, magnetic resonance imaging

STG, superior temporal gyrus

TTG, transverse temporal gyrus

IFG, inferior frontal gyrus

MFG, middle frontal gyrus

Introduction

Schizophrenia is a debilitating illness with various manifestations of uncertain pathophysiological origins presented at its basis. Among these phenomena are early sensory processing and memory deficits (Javitt, 2009), which are thought to contribute to higher order cognitive dysfunction and psychosocial impairments (Javitt & Freedman, 2015; Kargel, Sartory, Kariofillis, Wiltfang, & Muller, 2014; Toyomaki et al., 2008). This has resulted in a multitude of schizophrenia research probing its underlying neural basis and mechanisms. Together with brain structure abnormalities, these characteristics are thought to be involved in the generation of clinical symptoms (Insel, 2010).

Auditory mismatch negativity (MMN) and its magnetic counterpart (MMNm) refer to the automatic brain response to a rare, unexpected stimulus within a sequence of otherwise regularly occurring standard stimuli. MMN has been considered a marker of pre-attentive, automatic auditory processing that underlies sensory and echoic memory (Bodatsch, Brockhaus-Dumke, Klosterkotter, & Ruhrmann, 2015; Damaso, Michie, & Todd, 2015); these processes are impaired in schizophrenia (Naatanen, Paavilainen, Rinne, & Alho, 2007). Previous studies have consistently shown reduced MMN amplitude in chronic schizophrenia patients (Erickson, Ruffle, & Gold, 2015), patients with recent-onset schizophrenia (Atkinson, Michie, & Schall, 2012; Hermens et al., 2010), and individuals at clinical high risk for the illness (Shin, Kim, et al., 2012; Solis-Vivanco et al., 2014).

The relative specificity of MMN impairment to schizophrenia suggests that it may serve as a potential biomarker, reflecting a central auditory deficit that is a characteristic of this disease (Light & Naatanen, 2013; Naatanen & Kahkonen, 2009).

Attempts to elucidate the underlying dynamic neural mechanisms underlying MMN have used current source density (CSD) analysis to identify the locations and relative magnitudes of current sources (Kamarajan, Pandey, Chorlian, & Porjesz, 2015). CSD studies have implicated superior temporal and frontal areas in MMN generation in both healthy subjects and schizophrenia patients, with the latter group exhibiting reduced intensities in these regions (Fulham et al., 2014; Naatanen & Alho, 1995; H. Takahashi et al., 2013). Such findings are consistent with the superior temporal and frontal underactivation reported in schizophrenia patients by a study using an auditory MMN paradigm that relied on functional magnetic resonance imaging (fMRI) (Gaebler et al., 2015).

Some studies have suggested that gray matter abnormalities in fronto-temporal areas could constrain MMN CSD intensity, as MMN response is thought to be produced by the neuronal aggregates of its cortical sources of activity. For example, both Salisbury, Kuroki, Kasai, Shenton, and McCarley (2007) and Rasser et al. (2011) reported a positive relationship between MMN amplitude using EEG and gray matter volume in schizophrenia. However, these studies utilized a single, fronto-central EEG electrode (Fz) to measure MMN. The relationship between gray matter changes and MMN amplitude reductions in patients could be better

characterized if the two measures were spatially aligned. That is, gray matter in the auditory cortex should be correlated with the temporal MMN, whereas frontal gray matter could be correlated to the frontal source of MMN. Analysis of the signals at the source level would provide improved indications of the activity distribution, as well as the perturbations of such, at the cortical level. In this respect, CSD transforms, especially with the spatial localization advantage of magnetoencephalography (MEG) compared with EEG, may provide improved estimates of the MMN activity distribution (Cuffin & Cohen, 1979).

Furthermore, classification methods have been used with various features, such as gray matter volume and cortical thickness, to discriminate between different participant groups. A classifier takes values of features during the training phase to predict which class a new sample belongs to (Pereira, Mitchell, & Botvinick, 2009), one example of which is done by the support vector machine (SVM) classification approach. Previous studies have reported better classification through SVM than observation of differences between groups through more common approaches, such as voxel-based morphometry (Ecker et al., 2010). Using such methods may complement the analysis of feature differences, whether it be structural or functional, and provide support for a better understanding of potential relationships, as well as its representativeness of the samples.

This study investigated pre-attentive auditory processing disruptions at the reported sources of MMN(m), both temporal and frontal, using CSD methods of source analysis on MEG data in both patients with schizophrenia and healthy

controls (HCs). We were interested in investigating whether the MMNm CSD intensities of fronto-temporal areas were associated with the cortical thickness of their corresponding brain regions and with clinical symptoms. This is an important question because alterations in fronto-temporal cortical thickness have been consistently found in, and even before the onset of, schizophrenia (Jung et al., 2011; Zhang et al., 2015). Moreover, using SVM classification methods, the utility and accuracy of these features as classifiers were of interest. We hypothesized that reduced MMNm source intensity would be reflected in fronto-temporal cortical thinning in schizophrenia patients. Furthermore, we expected to observe relationships of source intensity and/or cortical thickness with clinical symptom scale scores.

Methods

Participants

Sixteen patients with schizophrenia were recruited, and their diagnoses were confirmed based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First MB, 1996). At the time of this study, all patients except one were receiving atypical antipsychotic medication, with a mean dosage equivalent to 16.44 mg of olanzapine (range: 2.50 to 26.64 mg). The patients were clinically stable at the time of data collection. Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987), and estimated intelligence quotient (IQ) scores were obtained using an abbreviated version of the Korean-Wechsler Adult Intelligence Scale (K-WAIS) (Kim & Lee, 1995). Eighteen HCs were recruited from among the general population through Internet advertisements. They were screened using the SCID-I Non-patient Edition (SCID-NP) to exclude subjects with past or current Axis I diagnoses or any first- to second-degree biological relative(s) with a psychiatric disorder.

The exclusion criteria for all subjects included a lifetime diagnosis of substance abuse or dependence, any neurological disorder (including head injury), evidence of medical illness with documented cognitive sequelae, sensory impairments, intellectual disability (IQ < 75), and professional musical training in the last 5 years (Brattico et al., 2009). Data from 11 of the schizophrenia patients and 18 HCs were used in our previous study that tested a different hypothesis from

our current one (Shin, Kim, et al., 2012). Written informed consent was obtained from the participants themselves or from their parents (for those under 18 years of age). The Institutional Review Board of Seoul National University Hospital approved this study.

Task paradigm

We used a passive auditory oddball task in which subjects were instructed to focus on finding characters (i.e. Wally and his friends) in a series of pictures, which were presented through an LCD projector located 1.5 m in front of the subject. While directing their attention to this visual task, a total of 1200 pseudorandom series of 1,000 Hz (80 dB, 10 ms rise/fall) tones differing in duration were presented through tubular insert earphones by the STIM2 system (Compumedics Neuroscan, El Paso, TX, USA). The block consisted of 982 frequent standard stimuli that were 50 ms in duration (81.8% of the total stimuli) and 218 infrequent deviant stimuli that were 100 ms in duration (18.2% of the total stimuli), with stimulus onset asynchrony of 300 ms. A diagram of the paradigm is provided in Figure 1.

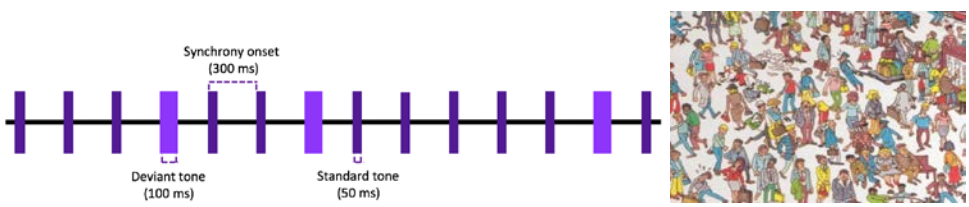


Figure 1. Passive auditory oddball paradigm with Where's Wally distraction task.

MEG recording and structural MRI data acquisition

While performing the task paradigm, MEG data were acquired using a whole-head 306 channel system (Elekta Neuromag Oy, Helsinki, Finland) with a sampling rate of 1,000 Hz in an electromagnetically shielded room at the MEG center located in Seoul National University Hospital. Previous to the session, the anatomical landmarks of each subject were recorded and adjusted to three fiducial locations, which include the naison, the left pre-auricular point, and the right pre-auricular point. Furthermore, we performed 3D digitization (FASTRAK, Polhemus, Colchester, VT, USA) in order to align the MEG and magnetic resonance imaging (MRI) systems. An online band-pass filter of 0.1 to 200 Hz was applied during the recording. Eye blinks and eye movement were monitored through electrodes attached near the outer canthus and below the left eye.

Structural brain images were obtained in the axial plane using a 1.5-T MRI scanner (Avanto, Siemens, Erlangen, Germany). The MRI parameters consisted of an epoch time/repetition time ratio of 4.76/1,160 ms, flip angle of 15°, field of view of 230 mm, and voxel size of $0.45 \times 0.45 \times 0.9$ mm^3.

MEG data pre-processing

A Maxwell filter was used to minimize external noise, such as environmental and biological artifacts, in the MEG data (Taulu, Simola, & Kajola, 2005). Similar to previous MEG studies of auditory change detection (Hsiao, Wu, Ho, & Lin, 2009;

Shin, Kim, et al., 2012), we used 204 gradiometers in our analysis, as magnetometers are considered to be more sensitive to noise artifacts (Hamalainen, 1992). Data analysis was performed with Curry software 7.0 (Compumedics Neuroscan), with a low pass filter of 40 Hz to exclude high frequency noise. We visually inspected all data to exclude ocular artifacts, irrelevant noise, and muscle-related activity. Following inspection, epochs of each stimulus were extracted from 100 ms preceding to 300 ms following stimulus onset. We performed baseline correction using the pre-stimulus interval from -100 to 0 ms. At minimum, 110 epochs remained for the deviant stimuli (HC: 200.7 ± 23.7; patients: 173.1 ± 30.6). The number of trials in each group was considered to be sufficient. Epochs of the standard and deviant stimuli were averaged separately in each individual. The average of the standard stimuli was then subtracted from that of the deviant stimuli in order to obtain MMNm in a time window from 130 to 250 ms after stimulus-onset.

MMNm source analysis

Individual T1 images were normalized to the Talairach space, and were used to construct individual head models via the boundary element method head model for MEG. For each subject, the minimum norm method was implemented for source reconstruction. Through this method, current density distributions were extracted, with source locations constrained to each individual's cortex. The resulting

whole-brain CSD extractions included information from 18000 to 25000 locations (varying according to cortex size). The derived outcome was presented as an image of the CSD distribution on the cortex level and as a time series of numerical CSD intensity values at each coordinate location of extraction. Data on coordinates were utilized to divide the information by lobe, by matching each CSD time series to a named cortical location. Using the resulting information from the frontal and temporal lobes, maximum CSD intensities and their respective latencies were extracted bilaterally for areas in these cortices that have been implicated in MMN(m) in previous studies (Fulham et al., 2014; T. Takahashi et al., 2009). These areas include the superior temporal gyrus (STG), transverse temporal gyrus (TTG), inferior frontal gyrus (IFG), and middle frontal gyrus (MFG). Thus, a total of 8 maximum CSD intensities and latencies, 4 per hemisphere, were extracted for each individual.

MRI data analyses

The FreeSurfer software package v.5.3.0 (http://surfer.nmr.mgh.harvard.edu) was used for automated reconstruction of a three-dimensional model of the cortical surface, tissue segmentation, and parcellation of anatomical structures. Parcellations matched the anatomical regions prescribed by the Destrieux atlas (Destrieux, Fischl, Dale, & Halgren, 2010), from which cortical thickness measures were extracted. The cortical thickness values for the fronto-temporal

regions implicated in MMNm, on each hemisphere, was extracted. Spatial smoothing of the maps was performed using a Gaussian kernel of full-width half-maximum 10 mm.

Statistical analyses

Differences between groups with respect to demographic and clinical characteristics were examined using independent sample t-tests in SPSS software (version 21.0; SPSS Inc., Chicago, IL, USA). A repeated-measures analysis of covariance (ANCOVA), with group as a between-subjects factor, region and hemisphere as the within-subjects factors, and age as a covariate, was performed to assess MMNm CSD intensities. To further analyze significant effects of group, differences in the MMNm CSDs of each region, and the corresponding latencies, were assessed through ANCOVA with age included as a covariate. A similar repeated measures ANCOVA was performed for cortical thickness, with sex as an additional covariate. Finally, the relationships among the CSD intensities of fronto-temporal regions, the cortical thickness of their respective regions, and clinical variables were observed by within-group analyses using Spearman's correlation coefficient.

Classification through SVM

A non-linear SVM with a Gaussian radial basis function (RBF) kernel (sigma = 0.5, c = 1) was utilized for training and classification procedures using the Matlab software package (ver. R2016b; MathWorks, Natick, MA) on CSD intensities and cortical thickness measures. During the training procedure, we used the N-fold (with our N = 4) cross-validation procedure, in which the data was randomly divided into N folds. A repetition of training using N-1 folds, with the remaining used for testing, was performed N times, until all folds had been used for testing. At each testing point, classification accuracy was calculated by the proportion of samples that were classified correctly into its respective group. Sensitivity and specificity measures were also calculated, with sensitivity being the number of true positives divided by the sum of true positives and false negatives, and with specificity being the number of true negatives divided by the sum of true negatives and false positives. Here, we defined the patient group as the target group being classified, i.e., the “positives”, and the healthy controls as the “negatives”.

Results

Demographic and clinical characteristics

Data for demographic and clinical characteristics are presented in Table 1. There were no significant differences in sex, age, years of education, handedness, parental socioeconomic status, or IQ between the two groups.

Table 1. Demographic and clinical characteristics of schizophrenia patients and healthy controls.

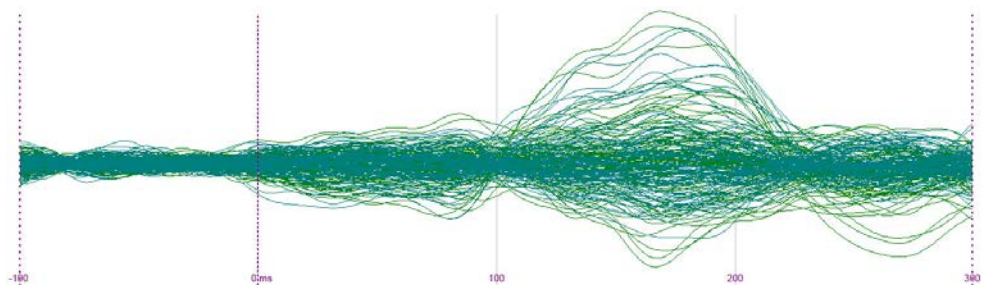
	HC (n = 18)	**SPR (n = 16)**	**Analysis**	
	Mean ± SD	Mean ± SD	t / χ^2	p
Sex (M/F)	12/6	11/5	0.017	.897
Age (y)	22.00 ± 2.11	23.75 ± 4.04	9.160	.135
Education (y)	14.17 ± 1.10	13.44 ± 2.78	11.883	.338
Handedness (R/L)	17/1	15/1	0.007	.932
SES	2.67 ± 0.49	2.69 ± 1.25	0.063	.951
IQ	108.83 ± 17.42	100.50 ± 5.99	14.972	.070
PANSS				
Positive	-	12.50 ± 4.44	-	-
Negative	-	15.75 ± 5.39	-	-
General	-	27.50 ± 7.43	-	-
Total	-	55.75 ± 14.23	-	-
Duration of Illness (y)	-	7.75 ± 3.28	-	-

Note: HC, healthy controls; SPR, schizophrenia; SES, Hollingshead socioeconomic status (1 = highest, 5 = lowest); IQ, intelligence quotient; PANSS, Positive and Negative Syndrome Scale.

MMNm CSD results

Butterfly plots of the grand average MMNm difference waveform and CSD intensity distributions for each group are provided in Figure 2 and Figure 3, respectively.

(a)



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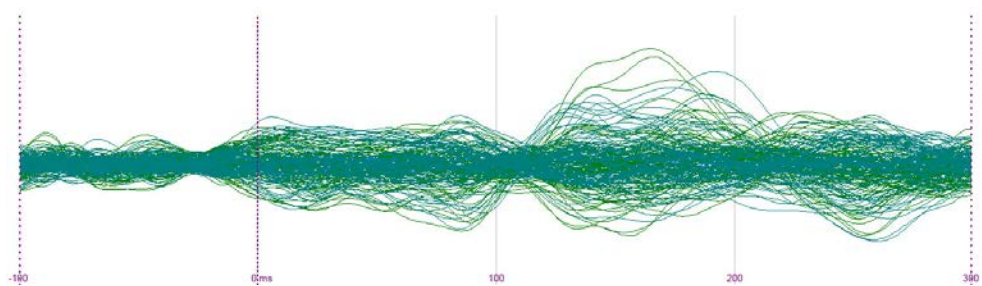
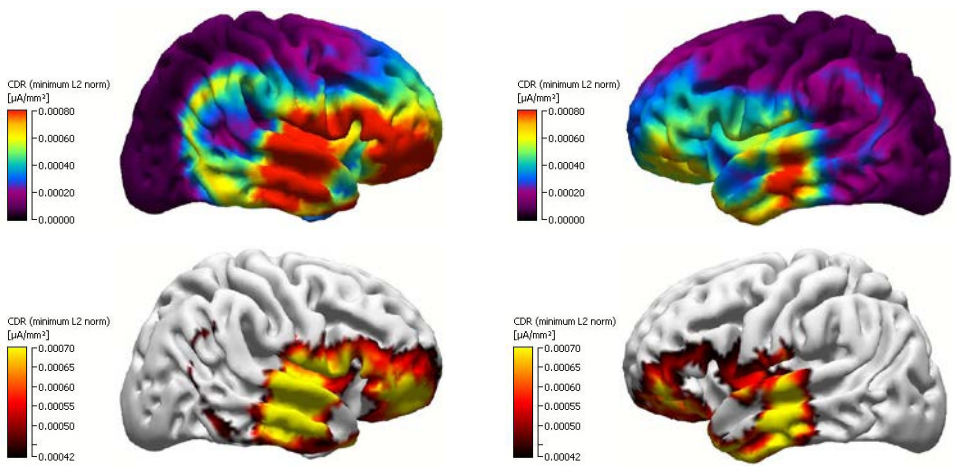


Figure 2. Butterfly plot of the grand average difference waveforms of the magnetic counterpart of mismatch negativity (MMNm) for 204 gradiometers, from 100 ms pre- to 300 ms post-stimulus onset. (a) Healthy controls. (b) Schizophrenia patients.

(a)



(b)

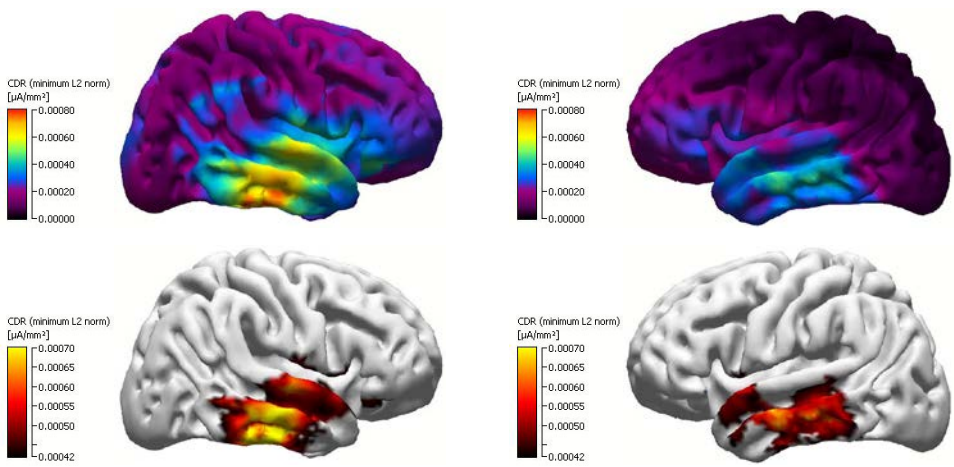


Figure 3. Two different surface views of current source density (CSD) intensities on standard Montreal Neurological Institute (MNI) space in a time window of 130 to 250 ms following the onset of the auditory stimulus. The initial views are of whole-brain CSD distributions in each hemisphere, highlighting the heightened CSD intensities in regions most pertinent to MMNm. The secondary views focus on these temporal and frontal regions involved by clipping below 60 %. Note that the scales have been optimized for visualization of differences between the groups, and that intensities may exceed the maximum value displayed on the scale. (a) Healthy controls. (b) Schizophrenia patients.

Table 2. Mean location coordinates for peak CSD in temporal and frontal areas of interest.

		x	y	z
STG (BA 22[a])				
Schizophrenia	L	-61 ± 6	-22 ± 18	3 ± 10
	R	62 ± 4	-22 ± 14	3 ± 10
HCs	L	-62 ± 6	-20 ± 14	1 ± 9
	R	62 ± 3	-19 ± 13	4 ± 8
TTG (BA 42[b])				
Schizophrenia	L	-60 ±3	-15 ± 5	11 ± 1
	R	60 ± 4	-17 ± 10	10 ± 6
HCs	L	-59 ± 4	-15 ± 10	11 ± 1
	R	61 ± 3	-16 ± 4	11 ± 2
IFG (BA 44/47[c])				
Schizophrenia	L	-46 ± 11	17 ± 12	8 ± 17
	R	52 ± 9	8 ± 6	18 ± 15
HCs	L	-42 ± 14	17 ± 8	-2 ± 18
	R	52 ± 6	11 ± 8	12 ± 15
MFG (BA 46[d])				
Schizophrenia	L	-38 ± 12	24 ± 15	24 ± 23
	R	42 ± 9	24 ± 16	24 ± 19
HCs	L	-38 ± 12	27 ± 9	15 ± 23
	R	46 ± 7	16 ± 16	29 ± 19

Note: HC: healthy control; STG: superior temporal gyrus; TTG: transverse temporal gyrus; IFG: inferior frontal gyrus; MFG: middle frontal gyrus; BA: Brodmann area.

[a] BA 22: lateral and caudal part of STG; considered to contain Wernicke's area.

[b] BA 42: transverse temporal area, also known as Heschl's gyrus; primary auditory cortex thought to span this area.

[c] BA 44/47: opercular and orbital part of IFG; part of Broca's area.

[d] BA 46: middle frontal area; roughly corresponds with the dorsolateral prefrontal cortex.

The mean coordinates for the location of peak intensity for the regions of interest are presented in Table 2. Repeated measures ANCOVA, with hemisphere and region as within-group factors, group as a between-subjects factor, and age as a covariate, showed a significant main effect of group ($F_{1,31}$ = 9.48, p = .004) for MMNm CSD intensities. We also found a significant group by region interaction ($F_{3,29}$ = 4.70, p = .009), with a larger difference between temporal and frontal region CSDs for HCs versus schizophrenia patients.

In a follow-up ANCOVA, we observed significant group differences in CSD values for all four, bilateral, frontal and temporal regions of interest. As observed in Table 3, schizophrenia patients showed significantly attenuated CSD intensities in the bilateral STG (left, $F_{1,31}$ = 8.35, p = .007; right, $F_{1,31}$ = 9.56, p = .004) and bilateral TTG (left, $F_{1,31}$ = 8.00, p = .008; right, $F_{1,31}$ = 9.13, p = .005). Similarly, the patient group had lower CSD intensities in the bilateral IFG (left, $F_{1,31}$ = 6.93, p = .013; right, $F_{1,31}$ = 5.04, p = .032) and bilateral MFG (left, $F_{1,31}$ = 6.07, p = .020; right, $F_{1,31}$ = 4.94, p = .034). Group differences in these areas are visualized in Figure 4. There were no significant group differences in the latencies corresponding to the temporal and frontal CSD intensities.

Table 3. Peak MMNm CSD intensities and respective latency values in temporal and frontal areas of interest, with age included as a covariate, in the healthy control and schizophrenia groups.

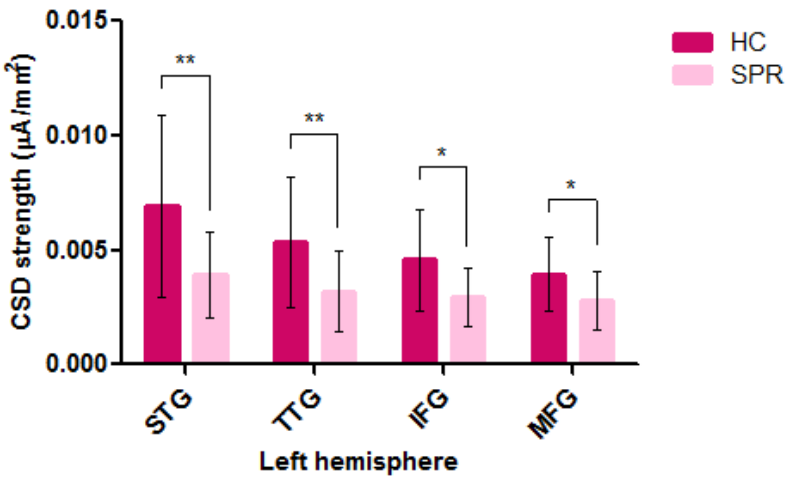
	HC (m ± SD)	SPR (m ± SD)	*F*(1,31)	*p*
CSDs (μA/mm²)				
Left				
STG	.00694 ± .00397	.00393 ± .00188	8.348	.007**
TTG	.00531 ± .00284	.00319 ± .00174	8.003	.008**
IFG	.00455 ± .00224	.00292 ± .00127	6.932	.013*
MFG	.00394 ± .00163	.00277 ± .00129	6.069	.020*
Right				
STG	.00926 ± .00500	.00510 ± .00210	9.563	.004**
TTG	.00760 ± .00409	.00419 ± .00195	9.129	.005**
IFG	.00611 ± .00356	.00395 ± .00171	5.035	.032*
MFG	.00493 ± .00252	.00330 ± .00134	4.939	.034*
Latencies (ms)				
Left				
STG	185.08 ± 30.50	191.32 ± 39.04	0.677	.417
TTG	189.52 ± 31.99	198.06 ± 40.70	0.696	.410
IFG	191.02 ± 38.74	177.16 ± 38.12	1.003	.324
MFG	193.18 ± 38.98	179.16 ± 40.60	0.837	.367
Right				
STG	174.78 ± 29.92	194.50 ± 35.80	2.162	.152
TTG	182.15 ± 36.87	182.84 ± 35.88	0.268	.608
IFG	181.66 ± 31.85	189.44 ± 37.83	0.642	.429
MFG	186.88 ± 36.51	193.00 ± 26.28	0.705	.408

Note: HC, healthy controls; SPR, schizophrenia; CSD, current source density; STG, superior temporal gyrus; TTG, transverse temporal gyrus; IFG, inferior frontal gyrus; MFG, middle frontal gyrus

* $p < .05$

** $p < .01$

(a)



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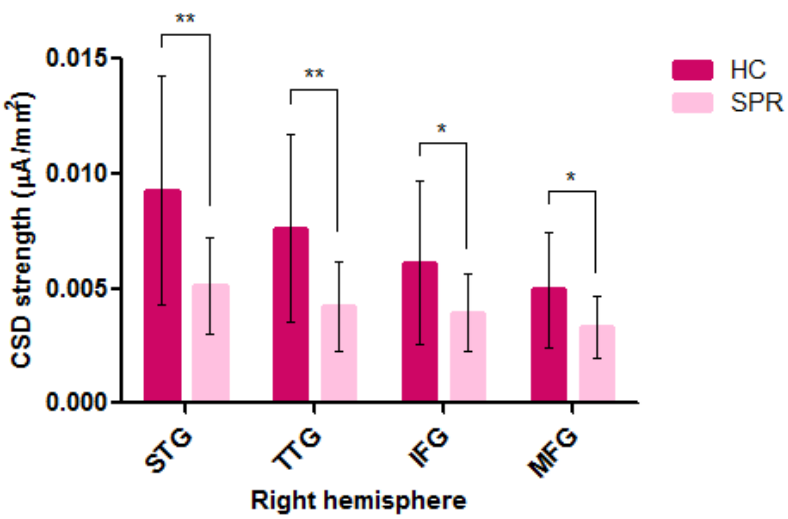

Figure 4. Peak MMNm CSD intensities of significant areas in both hemispheres in the healthy controls and schizophrenia patients. (a) Left hemisphere. (b) Right hemisphere. Error bars represent standard deviation. "*", $p < .05$; "**", $p < .01$.

Cortical thickness results

According to a repeated measures ANCOVA of cortical thickness treating region and hemisphere as within-group factors, group as a between-subjects factor, and age and sex as covariates, there were no significant interactions or main effects of group ($F_{1,30}$ = 0.133, p = .718), region ($F_{1,30}$ = 2.095, p = .123), or hemisphere ($F_{1,30}$ = 0.604, p = .443).

Correlations among CSD, cortical thickness, and PANSS scores

Scatterplots of the relationship between CSD and cortical thickness are provided in Figure 5. In temporal regions, no significant correlations were observed between CSD and cortical thickness in schizophrenia patients. In contrast, HCs showed significant positive correlations between the cortical thickness of the left planum temporale and the CSD of the left STG and TTG (ρ = 0.53, p = .023 and ρ = 0.47, p = .047 respectively). In frontal regions, the bilateral IFG CSD and the cortical thickness of the bilateral IFG (pars opercularis) were negatively correlated in the schizophrenia patient group (left, ρ = -0.50, p = .049; right, ρ = -0.59, p = .016). In HCs, a significant correlation was observed between the cortical thickness and the CSD of the left MFG (ρ = 0.53, p = .024).

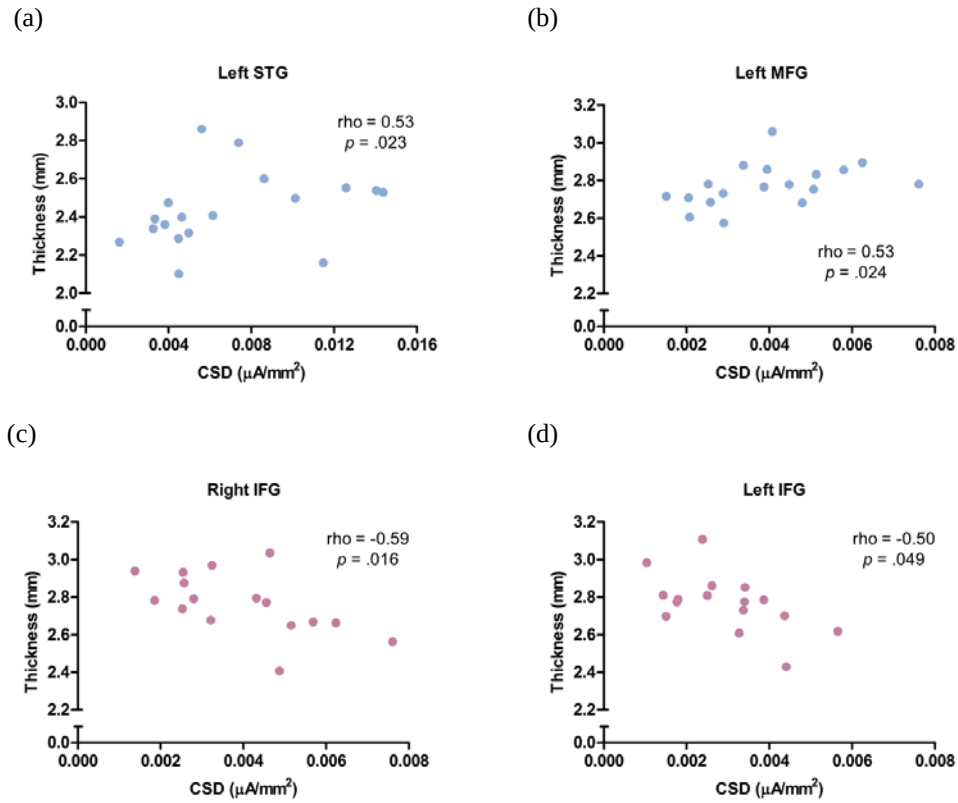

Figure 5. Scatterplots of CSD and cortical thickness for schizophrenia patients (in pink) and healthy controls (HCs: in blue). (a) Left superior temporal gyrus (STG) CSD and cortical thickness in HCs. (b) Left middle frontal gyrus (MFG) CSD and cortical thickness in HCs. (c) Right inferior frontal gyrus (IFG) CSD and cortical thickness in schizophrenia patients. (d) Left IFG CSD and cortical thickness in schizophrenia patients. Cortical thickness in the IFG was observed in the pars opercularis region (Brodmann area 44) in particular.

We observed no significant correlations between MMNm CSD intensities and any of the PANSS subscores in the schizophrenia group. Concerning cortical thickness, as illustrated in Figure 6, the patient group showed a significant positive correlation between the left IFG and PANSS negative symptom score ($\rho = 0.60$, p

= .014). Furthermore, the cortical thickness of the right IFG also had a significant positive relationship with the PANSS total score (ρ = 0.54, *p* = .032).

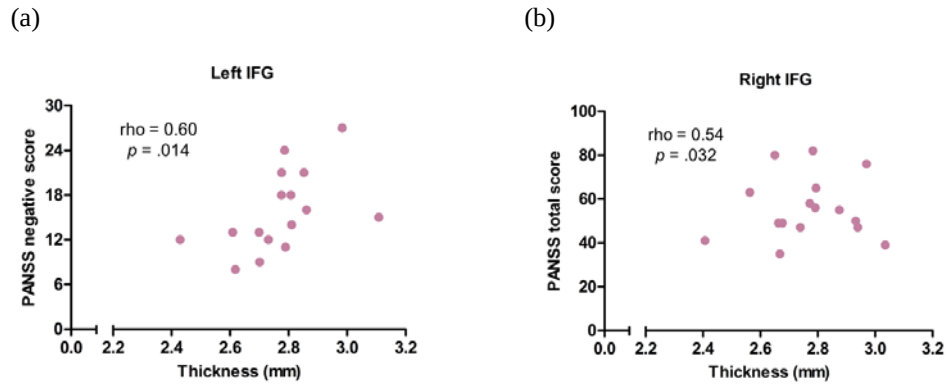

Figure 6. Scatterplots of inferior frontal gyrus (IFG) cortical thickness and Positive and Negative Syndrome Scale (PANSS) for schizophrenia patients. (a) Left IFG cortical thickness and PANSS negative scores in schizophrenia patients. (b) Right IFG cortical thickness and PANSS total scores in schizophrenia patients. Cortical thickness in the IFG was observed in the pars opercularis region in particular.

Classification results

The region showing the highest classification accuracy was the right STG, in which patients were distinguished from HCs with a mean accuracy of 73.96% (sensitivity = 74.17%; specificity = 72.50%) using CSD intensities and cortical thickness measures. The bilateral TTG followed, with an accuracy of 64.58% in the right TTG (sensitivity = 55.42%; specificity = 73.75%) and 62.15% in the left TTG (sensitivity = 64.17%; specificity = 61.25%). The left STG, as well as frontal areas, showed mean accuracies between 50% and 60%.

Discussion

Summary of results

The present study examined whether deficits in MMNm generation in schizophrenia patients were related to cortical thickness. To this end, we investigated the CSD intensities at, and the cortical thickness of, MMNm generator-relevant fronto-temporal locations and examined the relationships among them. Patients exhibited diminished CSD intensities in all temporal and frontal regions relative to HCs. However, we found no significant between-group difference in cortical thickness. In HCs, there were positive relationships between cortical thickness measures and CSD intensity in the STG and MFG. That is, lower CSD values were associated with cortical thinning in both temporal and frontal areas. In contrast, no such significant relationships were seen in the temporal areas of schizophrenia patients; instead, negative correlations were observed in the bilateral IFG. Furthermore, the cortical thickness of the IFG was positively correlated with PANSS negative and total scores. Through a classifier, the right STG, followed by the bilateral TTG, showed the highest mean classification accuracy among our regions of interest in classifying patients from HCs. To the best of our knowledge, this is the first study to investigate CSD intensities at MMN(m)-related cortical locations in addition to the association of CSD intensity with the cortical thickness of each respective region.

We found that, compared with HCs, schizophrenia patients displayed attenuated CSD intensities in fronto-temporal areas implicated in MMNm generation. This is consistent with the robust finding of MMN attenuation in schizophrenia shown by a number of previous studies (Gaebler et al., 2015). Although temporal auditory areas have been shown to be involved primarily in the generation of MMN, frontal activity may also contribute to MMN generation (Miyanishi, Sumiyoshi, Higuchi, Seo, & Suzuki, 2013; Tse, Rinne, Ng, & Penney, 2013). Consistent with these reports, our results suggest that temporal regions play a key role in MMN(m) deficits observed in schizophrenia patients. Moreover, we also detected frontal attenuations during MMNm responses in the patient group, corroborating the involvement, albeit in the form of a deficiency, of the frontal lobe in pre-attentive auditory processing (Erickson et al., 2015; Ranlund et al., 2016).

In terms of cortical thickness, we did not find a significant between-group difference. Brain anatomical aberrancies have been consistently observed in schizophrenia patients, both with or without medication (Jung et al., 2011; Nenadic, Yotter, Sauer, & Gaser, 2015; Schultz et al., 2010; Zhang et al., 2015). Possible mechanisms underlying structural changes in schizophrenia include pruning in the early stages of disease development that continues up to illness onset, as well as pruning that occurs after disease onset with reduced neuroplasticity (Andreasen et al., 2011). This may explain previous null findings regarding the frontal cortices (Wible et al., 1995), as well as brain changes that are observed in only a certain

subset of patients. Nonetheless, despite the brain volume reductions observed during the early stages of illness, evidence of cortical modulation as a result of treatment suggests the possibility that schizophrenia patients could recover cortical thickness (Goghari et al., 2013). The discrepancy between the results of Jung et al. (2011) and those of the present study may be explained by differences in mean durations of illness, sample sizes, and analytic methods. Consistent with this interpretation, a study on the N100 response and cortical thickness conducted by Shin, Jung, et al. (2012) also reported no significant difference in cortical thickness between schizophrenia patients and HCs.

We found positive correlations between MMNm CSD values and thickness measures in the STG and MFG in HCs, but no such a relationships were observed in the patient group. This is in contrast to studies by Salisbury et al. (2007) and Rasser et al. (2011), in which gray matter volumetric changes in temporal regions were correlated with MMN amplitudes in schizophrenia. This discrepancy may be due to differences in the methods used to measure both function and structure in our methods. The absence of such a correlation in our patient group may be attributable to our relatively small and heterogeneous study population. Nonetheless, one previous study reported a positive association between cortical thickness and auditory steady-state total power and inter-trial coherence in the STG of HCs but not of schizophrenia patients (Edgar et al., 2014), which accords with our findings in the STG. Hence, an alternative possibility is that different pathological sources may underlie gray matter loss and MMN attenuation in

patients with schizophrenia. In other words, gray matter loss and MMN attenuation may not co-exist in all (or in a majority of) patients, resulting in a non-significant correlation between the two measures. This structure-function issue in schizophrenia research is difficult to resolve (Cocchi et al., 2014), but future studies with various structural (gray matter volume and white matter integrity) and functional neuroimaging measures (MEG and fMRI) may aid in addressing this issue.

Furthermore, HCs showed positive relationships between thickness measures and CSD values in the MFG. By contrast, the schizophrenia patients showed the opposite pattern (i.e., increased cortical thickness associated with reduced MMN CSD intensities) in the bilateral IFG. In parallel with this finding of an association between increased thickness and reduced function, the patients showed a positive correlation between the cortical thickness in frontal regions and PANSS negative and total scores. Possible explanations for these results include inefficient global networks that fail to fully exploit the available resources, as well as abnormalities in neuronal pruning or migration that may contribute to the exacerbation of symptoms or functional deficiencies (Lacerda et al., 2007; Nesvag, Saetre, Lawyer, Jonsson, & Agartz, 2009; van den Heuvel et al., 2013; Volpe, Mucci, Quarantelli, Galderisi, & Maj, 2012). On the other hand, in cases where cortical thickness is not retained, potentially useful neural reserves may be recruited (including non-local resources) as a compensatory mechanism (Tan et al., 2006).

Although we expected to find correlations between CSD measures and PANSS scores, there were no significant associations between the two. Several studies have reported a non-significant association between clinical symptoms and MMN amplitude (Perez et al., 2014; Solis-Vivanco et al., 2014), whereas other studies reported that MMN was more strongly associated with functional outcome (Lee, Sung, Lee, Moon, & Kim, 2014). Further investigations of the potential relationship between clinical symptoms and MMN in larger and, preferably, unmedicated samples are warranted.

Using a SVM method for classification, we found that the right STG showed the highest mean accuracy among the features in our sample, followed by the bilateral TTG. With STG and TTG at the core of MMN studies (Javitt & Sweet, 2015), as well as schizophrenia studies in general, the MMN deficiencies we observe in patients, in conjunction with their cortical abnormalities, may have classification value, even though we did observe statistically significant group differences in cortical thickness between the two groups. The lower mean accuracies in frontal regions may be due to the smaller CSD intensity differences in the frontal areas, in comparison to temporal regions, which would make it difficult for accurate classification. However, it seems that future studies with a larger sample would aid in improving accuracy rates for all features.

Limitations

There are some issues to consider in interpreting the results of this study. Firstly, our study utilized a small sample of patients. It is possible that significant correlations were masked by the underrepresention of certain types of patients. Secondly, in our correlation analyses, we did not perform any statistical correction procedures to adjust for possible type I errors; thus, the results must be interpreted with caution. Nonetheless, they may provide a basis for generating new hypotheses pertaining to MMN(m) and gray matter abnormalities in schizophrenia. Thirdly, because of the small sample size and the number of cross-validations, the training data on which classification is learned was limited. With a larger sample size, the SVM training would be able to better characterize the features of the two groups during the training phase, with more cross-validations, to improve accuracy across regions. Finally, due to the use of a cross-sectional design, it is possible that the results may have differed if the study had been conducted during both earlier and later disease stages. Future MMNm studies including a larger sample, as well as longitudinal MRI and neurophysiological data, may be useful to further evaluate changes in the relationship between structure and function over time, as well as to improve the generalizability of the results

Conclusion

In conclusion, we found reduced MMNm CSD intensities in all temporal and frontal regions of interest in schizophrenia patients relative to HCs. Differences in the magnitude of the relationship between MMNm CSD intensities and cortical thickness between HCs and patients, as well as in the association between cortical thickness and symptom scores, may be due to abnormal neuronal pruning, aberrant global networks, and/or neuronal compensation. Future studies targeting MMN(m) mechanisms at both the neuronal and network level, in conjunction with SVM methods, would be useful to further explore and potentially utilize the robust finding of MMN deficits in relation to structural brain abnormalities in schizophrenia for classification.

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국문초록

연구배경: 조현병 환자들의 청각 기억 기능은 정상인과 비교 시 저하되어 있는 것으로 알려져 있다. 특히, 신경생리학적인 방법을 통해 볼 수 있는 사건관련전위 중 mismatch negativity (MMN)은 전주위적 청각기억기능을 관찰하며, 정상대조군과 비교 시 조현병 환자들은 저하된 MMN 을 보인다는 보고가 일관적으로 되어 왔다. MMN 을 발생 시키는 주요 신호원은 측두엽과 전두엽 영역으로 추정되고 있고, 이 영역들은 조현병에서 구조적 이상을 보이는 부위로 나타났다. 따라서, 본 연구는 조현병 환자들의 측두엽과 전두엽 신호원의 전류밀도 강도와 피질 두께의 상관관계를 분석하고자 한다.

연구방법: 본 연구는 16 명의 조현병 환자들과 18 명의 정상대조군을 대상으로 자동적 청각 주의를 관찰 할 수 있는 양자극 방안 (oddball paradigm)을 사용하여 뇌자도를 측정하였다. 또한, 대뇌피질 두께를 분석하기 위하여 자기공명 영상 기법으로 뇌구조 영상을 얻었다. 소스 분석을 통해 뇌자도 자료에서 측두엽과 전두엽 영역들의 전류밀도 강도를 추출하였고, 이를 피질 두께와 증상 척도 점수와의 상관관계를 조사하였으며 분류자로써의 가능성도 살펴 보았다.

연구결과: 예상대로 조현병 환자에서 양쪽 전두엽과 측두엽 영역들의 전류밀도 (current density) 강도 (intensity)가 정상대조군에 비해

감소되어 있는 것으로 나타났다. MMNm 전류밀도 강도와 대뇌피질 두께의 상관관계를 평가하였을 때, 정상인의 경우 전두엽과 측두엽 모두에서 대뇌피질이 두꺼울수록 전류밀도 강도가 유의하게 증가하는 양상이 관찰 되었다. 이런 반면, 환자군에서는 하전두이 영역의 전류밀도 강도와 대뇌피질 두께 사이에 음의 상관관계를 보였으며, 측두엽에서는 유의미한 상관을 관찰할 수 없었다. 또한, 조현병 환자의 하전두이 피질 두께와 증상 척도 점수 간의 양의 상관관계가 있는 것으로 나타났다.

결론: 본 연구는 MMNm 의 측두엽과 전두엽 신호원의 전류밀도 강도가 조현병에서 감소되어 있는 것을 보인다. 또한, 환자군에서 전두엽 신호원의 전류밀도 강도와 대뇌피질 두께의 상관관계가 정상인과 다르다는 것을 시사한다. 이를 통하여 조현병 환자의 뇌 구조와 기능의 관계가 변성 되어 있다는 가능성을 제안할 수 있다.

주요어: 조현병, mismatch negativity, 청각적처리, 뇌자도, 대뇌피질두께

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