Neuromagnetic mismatch responses to auditory deviance during periods of threat and safe anticipation in patients with obsessive-compulsive disorder

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Directed by Professor Se Joo Kim

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<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Neuromagnetic mismatch responses to auditory deviance during periods of threat and safe anticipation in patients with obsessive-compulsive disorder

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Purpose: Compulsion is the most prominent feature of OCD (obsessive-compulsive disorder), a condition that causes distress and disability. Animal models of compulsion suggest that deviance detection contributes to the pathogenesis of OCD. Auditory mismatch negativity (MMN)/its magnetic counterpart (MMNm), is an electromagnetic brain response that reflects auditory deviance-detection. OCD is also characterized by harm avoidance and hypersensitivity to potential threats. MMN is known to be related to anxious reactivity and a state of anticipatory anxiety. Therefore, this study aimed to determine the effect of threat anticipation on MMNm in OCD patients and healthy controls.

Methods: 27 OCD patients and 19 controls were presented with a classical

oddball paradigm of interspersed repeated standard tone stimuli and unitary deviant tone stimuli. Auditory stimuli were presented under threat conditions, when participants were anticipating unpleasant electric shocks, and safe conditions when no shocks were anticipated. Magnetic data was collected with a 152-channel whole-head MEG system. Distributed source estimation was conducted across regions of interest (ROIs) of the brain.

Results: ROI analyses revealed greater activity in response to stimulus deviance in OCD patients in right lateral orbitofrontal cortex. ROI analysis showed an interaction effect between group and condition in the medial orbitofrontal cortex.

Conclusions: Our results support MMN response in lateral and medial orbitofrontal cortex as a potential biomarker of OCD.

Key words : obsessive-compulsive disorder, novelty detection, auditory oddball paradigm, mismatch negativity, threat anticipation, magnetoencephalography

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I. INTRODUCTION

Obsessive-compulsive disorder (OCD) is a common psychiatric condition that is characterized by obsession and compulsion.[1] Compulsive symptoms are the most prominent feature of OCD, which causes distress and disability.[2] Compulsion is repetitive ritualistic behavior and is defined by actions inappropriate to the situation that nevertheless persist and which often have undesirable results.[3] The most common compulsive symptom is checking behavior to ensure no harm has occurred (e.g. checking the safety of the stove, doors, windows).[4] There are theories that explain the mechanism of symptom formation of compulsion. In cognitive theory, checking compulsion occurs when people feel unsure whether a perceived threat has been reduced or removed, especially for those with an inappropriately elevated sense of responsibility for harm prevention[2]. Animal models of compulsion suggest that novelty detection or, in other words, deviance detection contributes to the pathogenesis of OCD by

activating anxiety and checking of the dangerous situation.[5] According to this animal model, deviance detection and related anxiety-induced behaviors correspond to the checking behavior of OCD patients.[5] In humans, auditory deviance detection is thought to be reflected in a neurophysiological brain response called the mismatch negativity (MMN) – an event-related potential (ERP).[6]

ERP is a small, time-locked electrical current generated in the brain in response to specific stimuli or events.[7] Excited neurons in brain areas generate an electromagnetic field which can be recorded by electroencephalography(EEG) and magnetoencephalography (MEG). MEG and EEG both have good temporal resolution, but MEG provides higher spatial resolution than EEG. ERP provides noninvasive and safe access to the neural correlates of mental processes.[8] ERPs can be elicited by sensory, motor, or cognitive events such as auditory tones.[7,8]

The MMN and its magnetoencephalographic equivalent (MMNm) may be elicited by the passive auditory oddball paradigm during which participants are exposed to a uniform and repetitive series of sounds (i.e., standard stimuli) with infrequent changes in the auditory event (i.e., deviant stimuli).[9] The MMN is revealed as a difference waveform which is obtained by subtracting the electromagnetic response to the standard stimuli from the electromagnetic response to the deviant stimuli.[10] This procedure elicits a large evoked brain activity that peaks between 100 and 200 ms after the onset of the stimulus and shows the strongest intensity in auditory and frontal cortex.[11-15] The auditory

mismatch response is known to be generated by a preattentive auditory novelty detection process in the temporal cortex and by a further conscious change detection process in the frontal area.[16-22] Although the frontal MMN process has been less studied than temporal process, the role of the frontal generator has recently received more attention. Given its automatic nature, it has been suggested that the frontal MMN is associated with involuntary switching of attention caused by auditory deviance.[23]

The MMN and MMNm have become popular tools for studying the neurobiological basis of various neuropsychiatric disorders.[24-26] In the area of neuropsychiatric disorders, the MMN of schizophrenia has been extensively studied, and a reduced MMN amplitude has been suggested as a potential biological marker.[6,11,27-31] Various psychiatric conditions such as Alzheimer's disease, mood disorders, and autism spectrum disorders have also been studied with regard to MMN.[32-36] As mentioned above, MMN could be helpful for understanding the pathophysiology of OCD. However, the number of studies that have investigated MMN in OCD is relatively small, and those few studies have produced contradictory results.[37,38] A recent study with EEG reported a greater MMN amplitude for adult OCD.[37] However, an EEG study of childhood OCD revealed no significant change in MMN.[38] These inconsistent results may due to the different brain developmental stages of subjects in the two studies. We therefore decided to recruit adult subjects to make our study comparable to the former study of adult OCD.[37] We further speculated that stressful or symptom-

provoking stimuli could help to elicit a different MMN response between healthy controls and patients with OCD.

Patients with OCD are characterized by behavioral avoidance of unpredictable threats or harmful situations.[39] Elevated anxiety and harm avoidance has been reported in OCD patients and their first degree relatives.[40] Current neurobiological models of OCD indicate that dysfunction in the orbitofrontal cortex (OFC) and connected structures contributes to the pathology of OCD.[41] Abnormally enhanced activations within the orbitofronto-striatal circuit have been found to mediate OCD patients' exaggerated concern with potential threat.[42,43] Moreover, it has been suggested that MMN may be related to anxious reactivity and a state of anticipatory anxiety.[9] Existing studies have revealed that MMN amplitude is associated with anxiety-related temperaments such as hypervigilance and harm avoidance.[44,45] A recent study revealed heightened responses to stimulus deviance during a state of anticipatory anxiety in the known locations of MMN/MMNm generators in healthy adults.[9] Therefore, probing the effect of such stimuli on MMN in OCD may be informative in revealing the neurophysiological characteristics of OCD.

Our aim was to explore the preattentive auditory deviance detection process as reflected in MMNm in OCD and the effect of threat anticipation on this process. We addressed these questions by exposing OCD patients and healthy controls to an auditory oddball paradigm under threat conditions, when they were anticipating aversive electric shocks, and during a safe period. Because the

clinical features of OCD suggest that OCD is related to deviance detection, we predicted that the response to deviant auditory stimuli relative to standard stimuli would be enhanced in OCD patients compared to healthy controls. We also hypothesized that, under threat conditions, OCD subjects would display altered neuromagnetic mismatch responses.

II. MATERIALS AND METHODS

1. Participants

A total of 27 OCD patients and 19 control subjects participated in MEG recording. All OCD subjects and control subjects were male and right handed. Handedness was assessed with the Edinburgh Handedness Inventory.[46] The primary diagnosis of OCD and other psychiatric comorbidities were determined by the patient version of the Structured Clinical Interview for the DSM-IV (SCID-IV),[47] conducted by a trained psychiatrist. Healthy control subjects likewise underwent SCID-IV and were required to be free of a history of psychiatric illness during their lifetime. Exclusion criteria for OCD patients demanded the absence of significant medical or neurologic illness and any other Axis I disorders except for comorbid major depressive disorder. Exclusion criteria for all participants included evidence of medical illness, lifetime diagnosis of neurological disease or head injury, sensory impairment, and intellectual disability. All participants gave written informed consent in

accordance with procedures approved by the Severance Hospital Institutional Review Board.

2. Clinical assessments

To assess OCD symptoms, we administered the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS).[48] To access state and trait anxiety, we used the State-Trait Anxiety Inventory (STAI).[49]

3. Design and procedure

The entire experiment was undertaken in a MEG-scanner. Individual pain thresholds to electric stimuli were measured before the actual experiment started. The shock intensity threshold was set to a moderately uncomfortable but not painful level.

At the start of experiment, subjects were informed that 1–5 electric shocks during the entire experiment would be received unexpectedly at any time during a threat period and that shocks would never be delivered during the a period.

All subjects participated in 2 runs of the experiment with a 15-second resting period between runs. In each run of 10 blocks, 5 blocks were threat conditions and the other 5 blocks were safe conditions. Under threat conditions, participants were threatened with electric shocks during each block by the

visually presented message “beware stimuli”. Safe condition blocks, when participants were safe from shocks, were accompanied by the visual message of “no stimuli”. During each run, threat and safe blocks were arranged in an alternating sequence. The first run was started with threat conditions and the second with safe conditions.

In each 30-second block of trials, a sequence of auditory stimuli was presented. Sound stimuli were generated with a STIM2 system (Compumedics Neuroscan, USA). Two types of pure tones were presented binaurally: a standard tone (1000 Hz) with a probability of 80% (frequent) and deviant tones (1500 Hz) with a probability of 20% (rare). Each stimulus was presented for 50ms, with a stimulus being presented every 480 – 520ms. During each block, 60 stimuli were presented.

Electric shocks were delivered by electrodes attached to the right wrist by a constant current stimulator. The electric stimuli were delivered at the end of the last threat period in the first run and the first threat block in the second run. At the end of the experiment, subjects reported anxiety by means of the visual analogue scale (VAS; 0–10, no anxiety–highly anxious) during threat and safe conditions.

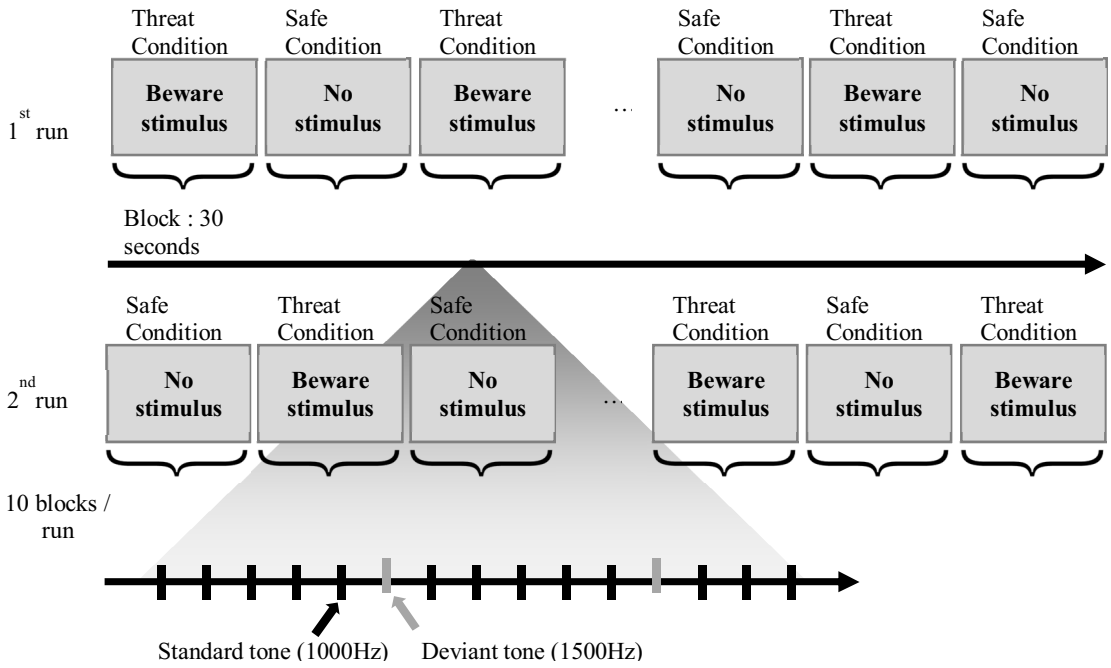

Figure 1. Schematic diagrams of auditory oddball paradigm under threat and safe condition.

4. MEG measurement and preprocessing

Magnetic field signals were acquired inside a magnetically shielded room at a sampling frequency of 1000 Hz by means of a whole head MEG system with 152 axial first-order gradiometers (KRISS, Daejeon, Korea). Head position relative to the sensor array was recorded with four additional head position indicator coils using a 3D head digitization system (Polhemus Fastra) that was attached to the scalp before MEG recording.

As a preprocessing step, a number of bad channels were identified by visual inspection and excluded for each individual. In addition to the visual inspection, the Brainstorm detection functionality was used to detect movement-related (1-7 Hz) and muscle- and sensor-related (40-240 Hz) contamination. After the exclusion of bad segments, artifact-free peri-stimulus periods between -100 and 400 ms were defined as epochs. In particular, only standard stimuli preceding deviant stimuli were deemed 'Standard' stimuli in contrast to 'Deviant' stimuli. For each stimulus (Standard or Deviant) and each experimental condition (Safe or Threat), the same number of epoch trials were averaged with a baseline of 100 ms before stimulus onset. Thereafter, the classical MMN response was determined by the subtraction of the sensor response to the Standard stimuli from those to Deviant stimuli. MMN responses were acquired respectively during Safe and Threat conditions in each individual and for Standard and Deviant stimuli. The mismatch field amplitude was defined as the maximal deflection of the

difference waveform, which occurred approximately 100 to 200 ms after stimulus onset.

5. MEG source estimation

In order to conduct the source modelling, an overlapping sphere model, which derives from a forward model the strength of a set of electric dipoles (15000 vertices) located at the cortical surface, was applied in Brainstorm. By using this method, a homogeneous sphere was refined by fitting one local sphere for each sensor.

In order to estimate distributed source activities, a single noise covariance matrix was also calculated within the baseline periods for all possible trials for each individual respectively.

Given the lack of individual anatomies from magnetic resonance imaging (MRI) data, the forward model was based on the template anatomy (Colin27), which was used as the common brain. Minimum Norm Estimation (MNE) using a standardized level of activation relative to the noise level (dSPM) was used in source estimation. Source orientations in a normal direction to the cortical surface were favored by weighting the transverse currents by a factor of 0.2. Depth-weighting was used to reduce the bias towards superficial sources. Noise covariance level was regularized with a factor of 0.1 at a signal-to-noise ratio of 3.0.

After reconstructing the distributed source modelling, the 148 atlas-based cortical parcellation (Destrieux), which is implemented in Brainstorm, was applied in order to obtain the representative source response of regions of interest (ROIs). In each ROI, principal component analysis (PCA) was applied to the set of sources (vertex), and the first component from PCA was determined as the response of the source scouts, which represent the regions of interest in Brainstorm jargon.

6. Selection of region of interest

We analyzed cortical activation using pre-defined regions of interest (ROIs). The same set of ROIs were applied for all subjects. The definition of the ROIs was based on the assumption that generators of MMN/MMNm would be located in the temporal and frontal area. The superior temporal gyrus (STG) was selected as the temporal ROI was because most previous MMN studies have localized the primary sources of MMN in STGA. The frontal ROI was selected on the basis that the inferior frontal cortex and orbitofrontal cortex have consistently been reported in by previous studies [50]. The specific location of the frontal ROI was defined by the inferior frontal cortex (IFC) and the medial and lateral orbitofrontal cortex (mOFC, lOFC)[51,52].

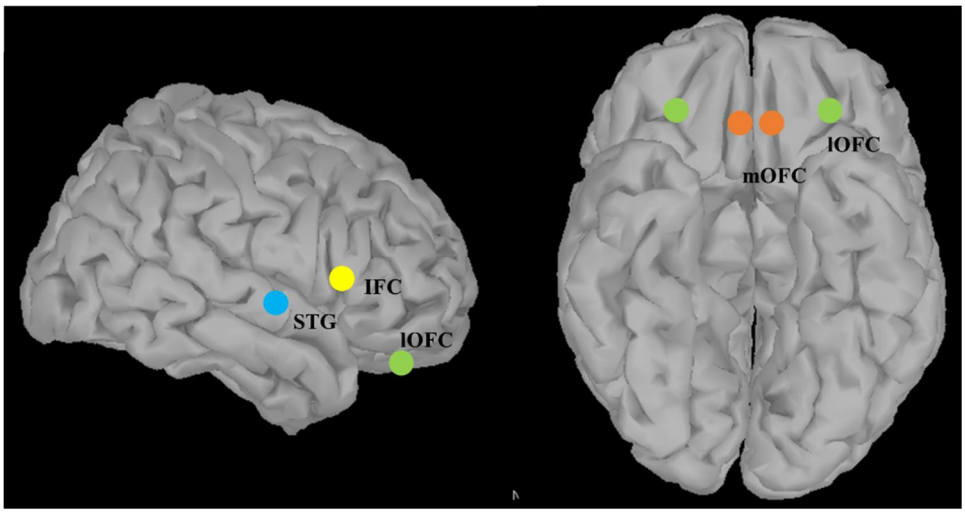

Figure 2. Selection of regions of interest on Colin27 brain template. STG, Superior Temporal Gyrus; IFG, Inferior Frontal Cortex; lOFC, Lateral Orbitofrontal Cortex; mOFC, Medial Orbitofrontal Cortex

A source-waveform for each group and condition was obtained within each ROI. For each ROI waveform, in each condition, we found the individual peak magnitude within the predefined time window and performed statistical analysis.

7. Statistical analysis

Demographic characteristics and self-reported scales were compared across groups using the t-test. For each ROI, we conducted the separate repeated measures ANOVA with group as between-subject factor and condition as within-subject factor in order to obtain the relevant source location which explains the group/condition effect. Spearman's correlation analysis was used to estimate the correlation between source strength and clinical scales. Statistical analysis was performed with the help of R software (version 3.2.2) and SPSS.

III. RESULTS

1. Sample characteristics

Demographic and clinical characteristics of the participants are presented in Table 1. A total of 27 OCD patients and 19 control subjects underwent testing. There were no significant differences in age between OCD patients and healthy controls. Patients with OCD presented within the range of moderate illness. Eighteen patients were taking medication. All of them were

medicated with serotonin reuptake inhibitor (SSRI), eight patients were taking benzodiazepines, and six patients were taking antipsychotics.

Table 1. Demographic and Clinical Characteristics of OCD and Healthy Control Subjects

	NC (n = 19)	OCD (n = 27)	
	Mean ± SD	Mean ± SD	p
Age (Years)[a]	22.74 ± 2.45	24.23 ± 3.28	0.103
State Anxiety[a]	42.63 ± 11.84	44.78 ± 26.21	0.741
Trait Anxiety[a]	43.89 ± 12.58	56.48 ± 17.97	0.012
Y-BOCS-T		22 ± 9.62	
Y-BOCS-O		11.46 ± 3.87	
Y-BOCS-C		10.27 ± 5.85	

NC, normal control; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; Y-BOCS-T, total score of Y-BOCS; Y-BOCS-O, obsession score of Y-BOCS;Y-BOCS-C, compulsion score of Y-BOCS
a. Independent samples two-tailed t-test.

2. Cortical responses

Figure 3 shows topographic maps of the grand-averaged MMNm signals and grand-averaged waveforms recorded by the MEG sensor in each group and under both conditions. As shown by the grand-averaged waveforms, clear deflections were observed for both groups and conditions. Figure 4 provides spatiotemporal cortical source maps that show that the superior temporal cortex was activated from approximately 130ms.

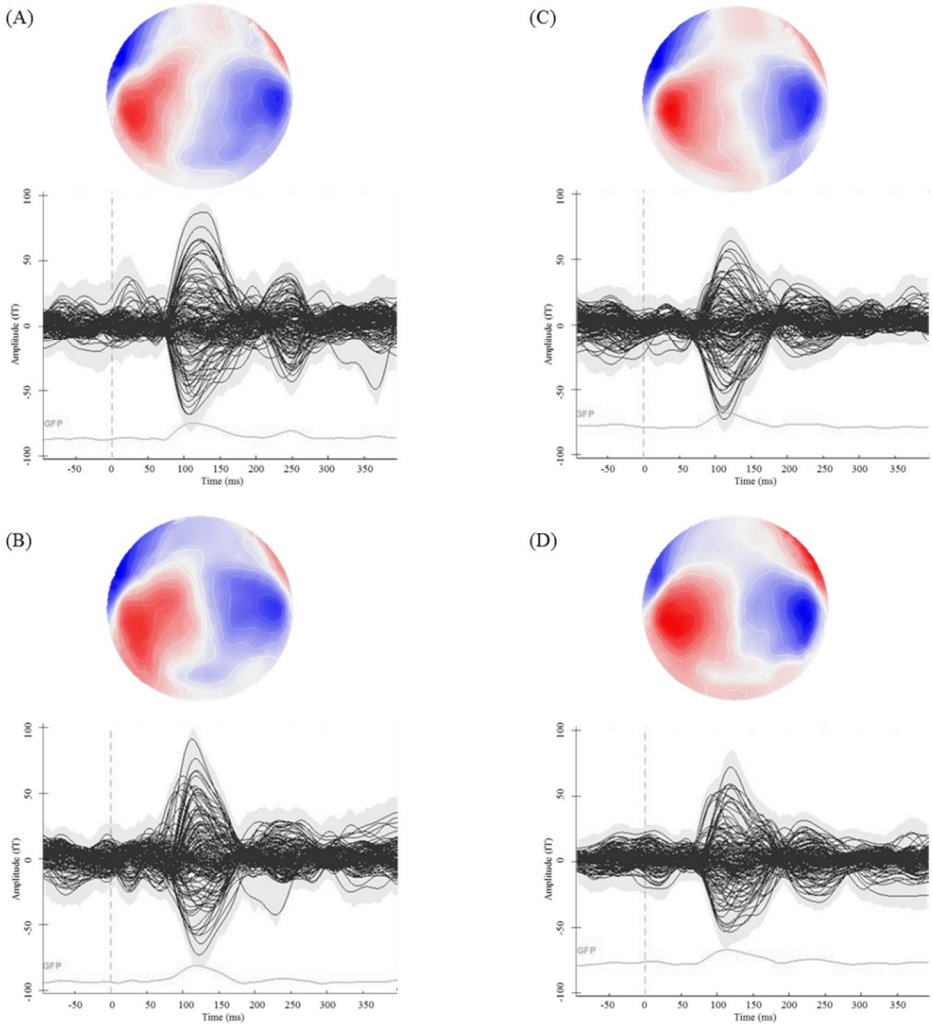

Figure 3. Topographic distributions of grand-averaged magnetic mismatch negativity (MMNm) signals (the upper part) and grand-averaged waveforms of MMNm (the lower part). (A) Normal control in safe condition. (B) Normal control in threat condition. (C) OCD in safe condition. (D) OCD in threat condition.

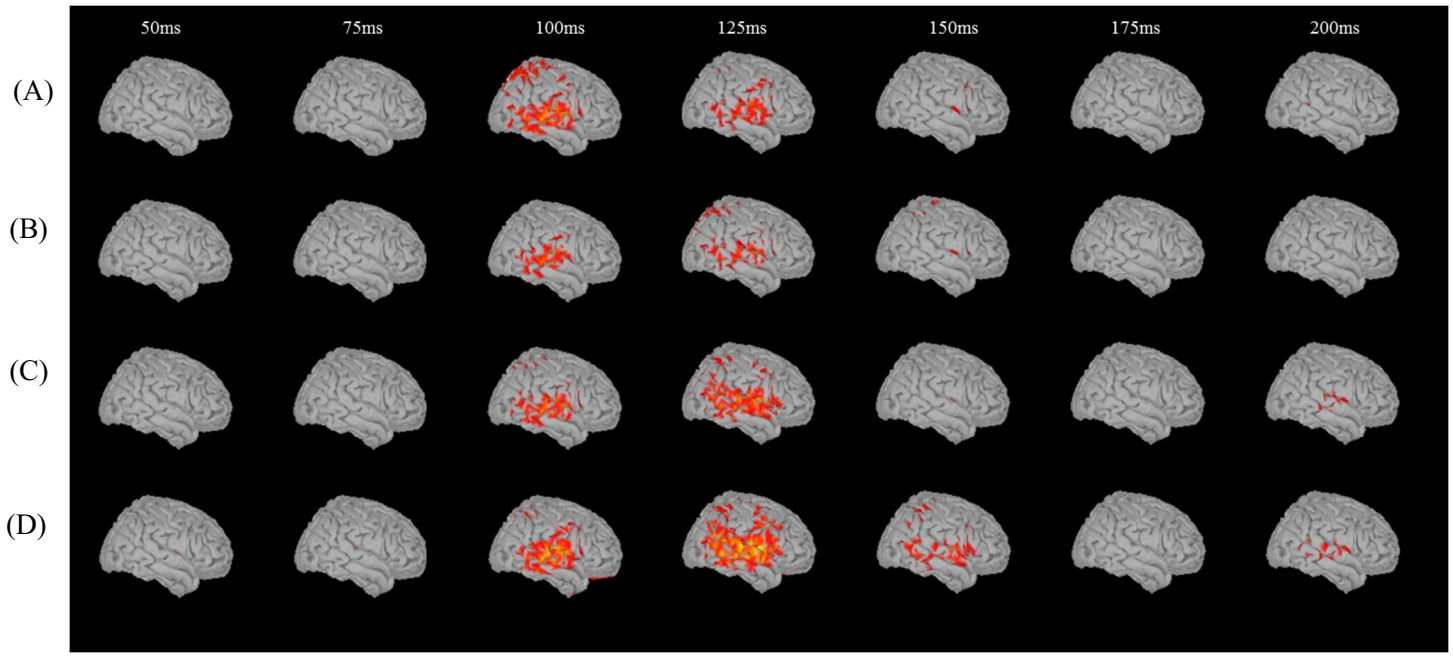

Figure4. Spatiotemporal dynamics of dSPM of MMNm responses. (A) Normal control in safe condition. (B) Normal control in threat condition. (C) OCD in safe condition. (D) OCD in threat condition.

Tabe 2. Magnetic field responses to deviant auditory stimuli in the safe and threat condition of OCD patients and health comparison subjects measured with MEG

Region of Interest	NC (N = 19)				OCD Patients (N = 27)				Group by Condition interaction		Main Effect of Group		Main Effect of Condition	
	Safe		Threat		Safe		Threat							
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p-value	F	p-value	F	p-value
Left STG	29.1	12.4	29.8	13.8	31.7	21.3	32.1	19.2	0.35	0.559	0.68	0.415	0.00	0.981
Right STG	30.9	14.2	32.0	15.9	41.1	21.4	36.0	21.4	2.32	0.135	0.05	0.823	3.32	0.075
Left IFG	24.5	10.6	27.6	12.0	28.7	13.9	29.4	12.0	0.45	0.506	1.16	0.287	0.31	0.581
Right IFG	24.3	8.6	24.1	10.3	26.6	14.3	26.9	15.6	0.02	0.895	1.20	0.280	0.11	0.743
Left lOFC	47.5	24.0	45.9	22.1	59.7	32.5	54.5	21.5	0.49	0.487	2.42	0.127	1.31	0.259
Right lOFC	46.3	20.6	35.3	12.4	52.2	19.7	55.8	27.9	3.39	0.072	7.67	0.008	0.00	0.964
Left mOFC	26.3	11.8	21.4	10.0	30.5	14.7	28.5	12.7	0.10	0.753	3.24	0.079	1.94	0.170
Right mOFC	30.9	14.4	21.2	7.0	33.3	13.4	35.2	16.3	4.60	0.038*	0.41	0.528	0.81	0.374

NC, normal control; STG, Superior Temporal Gyrus; IFG, Inferior Frontal Cortex; lOFC, Lateral Orbitofrontal Cortex; mOFC, Medial Orbitofrontal Cortex

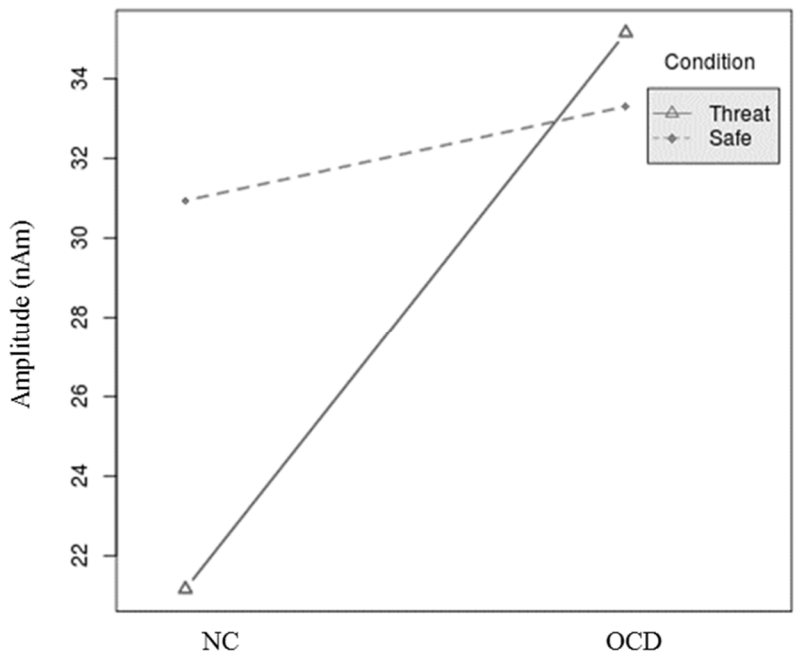

Figure 5. Effects of condition on mismatch negativity in OCD and control subjects. NC, normal control.

3. Source analysis

The source strength of each ROI is presented in Table 2. There was a significant main effect by group in the right lateral OFC [$F(1,44) = 8.61$, $p = 0.005$]. In the right medial OFC, there was an interaction between group and conditions [$F(1,44) = 4.60$, $p = 0.038$] (Figure 5).There was no simple effect by

group or conditions in medial OFC. We performed further separate analyses for both conditions. Under safe conditions, group differences were not significant, however, under threat conditions, group differences were significant (Safe: $t = 0.572$, $p = 0.570$, Threat: $t = 3.502$, $p = 0.001$).

Associations between YBOCS score and mean amplitude were analyzed in OCD patients (Table 3). There was no significant association between YBOCS scores and MMN amplitude under both conditions.

Table 3. Correlation between neuromagnetic response and OC symptom severity

	Safe_peak			Threat_peak		
ROI	YBOCS-T	YBOCS-O	YBOCS-C	YBOCS-T	YBOCS-O	YBOCS-C
Left STG	-0.248	-0.160	-0.280	-0.141	-0.108	-0.143
Right STG	-0.195	-0.146	-0.196	-0.226	-0.156	-0.228
Left IFG	-0.052	-0.020	-0.075	-0.001	-0.069	0.003
Right IFG	0.154	0.114	0.168	-0.079	-0.090	-0.089
Left lOFC	-0.003	-0.022	0.007	0.149	0.106	0.098
Right lOFC	0.244	0.136	0.306	0.097	0.124	0.028
Left mOFC	0.015	-0.070	0.045	0.044	-0.007	-0.006
Right mOFC	0.105	-0.031	0.177	0.066	0.116	-0.014

STG, Superior Temporal Gyrus; IFG, Inferior Frontal Cortex; lOFC, Lateral Orbitofrontal Cortex; mOFC, Medial Orbitofrontal Cortex; YBOCS, Yale-Brown Obsessive Compulsive Scale; YBOCS-T, total score of YBOCS; YBOCS-O, obsession score of YBOCS;YBOCS-C, compulsion score of YBOCS

IV. DISCUSSION

To our knowledge, this is the first study to investigate MMN by MEG in OCD patients. We performed source level analysis using MEG data and therefore obtained better spatial resolution than would have been possible with sensor level analysis or EEG measures. This study is also the first to investigate the effect of threat anticipation on the MMN response in OCD. The main findings of this study provide evidence of the potential of MMN as neurophysiological marker of OCD, as well as of threat anticipation as modulator of MMN.

In subjects with OCD, we found a significantly increased MMN amplitude compared to control subjects in the right lateral OFC, which suggests that the right lateral orbitofrontal generator of MMN is hyperactive in OCD. This result is consistent with an existing EEG study that reported that OCD patients showed increased right frontal MMN.[37] The increased frontal MMN in OCD patients might reflect enhanced involuntary switching of attention caused by auditory change.[23] In line with this, a previous ERP study reported an increased P3 amplitude at frontal sensors in OCD, which reflects enhanced attention switching by auditory change.[53] The MMN-eliciting auditory changes also elicit a P3 response.[23] Therefore, the finding of increased P3 in OCD and our findings both support hyperactive auditory change detection processing of the frontal area in OCD. However, our results suggest that a mechanism of involuntary attention switching by deviant auditory stimuli in OCD exists as an earlier process than the

P3 response. It is also noticeable that the ROI showing an altered response, namely right OFC, is well known for showing structural and functional alterations in OCD in existing studies.

In the neurobiological model of OCD, a critical role has been assigned to the OFC.[54-56] In OCD, OFC hyperactivity during OC symptom provocation has been replicated several times with various functional imaging methods.[43,57-59] Furthermore, a recent fMRI study has provided evidence that the degree of connectivity of the OFC, medial prefrontal cortex, and the putamen, which are part of the cortico-striato-thalamic circuit, is increased in OCD and correlates with global OCD symptom severity.[60] Other functional imaging studies support the view that dysfunction of the cortico-striato-thalamic circuit leads to OCD.[42,61-64] Increased MMN in the orbitofrontal area in our results may reflect the altered function of this region in OCD. Therefore, our finding is in line with previous functional neuroimaging studies that have revealed altered orbitofrontal function in OCD. Increased MMN is regarded as increased cortical overactivity, which is supported by pharmacological studies.[65-68] Existing pharmacological studies show that the memory-trace formation underlying MMN depends on the activity of N-Methyl-D-aspartate (NMDA) receptors, which is essential to glutamatergic neurotransmission.[15,69-71] NMDA receptor antagonists such as ketamine have been reported to reduce the size of MMN.[31,70] Glutamatergic neurons are the most common excitatory neurons across the entire brain cortex and play an important role in cortico-striato-thalamic loops.[68] In OCD, the OFC has shown

susceptibility to variations in glutamatergic genes.[72] In line with those findings, there is converging evidence that glutamatergic dysfunction may contribute to the pathogenesis of OCD.[73] The most direct evidence for abnormal glutamatergic activity in OCD derives from elevated glutamate in the CSF in OCD. Several genes such as DLGAP, PTPRD, GRIN2B and GRIK2 which are involved in the glutamatergic neurotransmission system have been implicated in OCD.[65] A number of pharmacological studies of ketamine infusion in OCD patients have led to a clinically significant response.[74-76] Memantine, a noncompetitive antagonist of the NMDA receptor, also showed large and statistically significant treatment effects in OCD in recent studies.[77-79] The findings of these studies suggest that glutamatergic activity is increased in OCD. We therefore speculated that increased glutamatergic activity may underlie the increased MMN in OCD within OFC.

The OFC is known to be involved in many functions, including the learning of appropriate responses to reward and punishment, evaluation of the motivational significance of stimuli, and switching responses when it is advantageous to do so.[80-83] The orbitofrontal region is further divided into anatomically and cytoarchitecturally distinct regions, namely medial and lateral areas.[80] The lateral and medial regions of the OFC are known to have different patterns of connectivity, which suggests that the lateral and medial OFC have distinct functional roles.[84] The lateral OFC is connected to the caudate nucleus and participates in motor coordination.[80] The lateral OFC is also known to

subserve behavioral inhibition, response suppression, and setting appropriate behaviors under motivationally ambiguous conditions.[85] These functions are altered in OCD and attribute to symptom formation.[80] The lateral OFC, especially the right side has been reported to be impaired in OCD.[86] Therefore, our finding of a significant group effect in the right lateral OFC is consistent with existing literature.

The medial OFC meanwhile is connected to paralimbic, limbic and diencephalic structures (e.g., insula, amygdala, nucleus accumbens and hypothalamus).[80] The medial OFC subserves motivational evaluation, emotional response, and emotional regulation.[80,85] Some authors also suggest that the medial OFC is implicated in fear extinction and associated with the pathophysiology of anxiety.[85] In line with previous research, our ROI analyses revealed an interaction effect between group and conditions in the right medial OFC. More specifically, the difference between the two groups was significant under threat conditions. However, the patient group and control group did not exhibit a significant difference under safe conditions. In other words, participants with OCD showed an abnormal threat response in the medial OFC. Considering existing studies, the results of present study may reflect that abnormality in the medial OFC in OCD underlies abnormal MMN during threat anticipation in OCD. With regard to statistical analysis, we found no significant association between YBOCS score and MMN magnitude in each ROI in the OCD group. In particular, the right lateral and medial OFC, which showed different responses in the OCD and

control groups, did not show significant correlation with symptom severity. We therefore speculate that altered MMN response in OCD in right OFC could be a possible trait marker of OCD.

One potential limitation of this study is that the majority of OCD patients were taking medication. Therefore, we cannot rule out that medication has had an effect on our results. However, studies of dopaminergic, serotonergic, and GABA receptors in MMN generation are currently showing contradictory results, whereas there is broad agreement that glutamatergic agents influence MMN.[87-90] Therefore, we assumed that SSRIs, antipsychotics, and benzodiazepine would not substantially influence our results. Further studies involving drug naïve OCD patients may confirm this assumption. Another limitation is that our source analysis was confined to the surface. Therefore, we could not investigate deeper subcortical structures, such as the amygdala.

We have not determined whether altered MMN contributes to the pathophysiology of OCD or whether it is merely an epiphenomenon. However, our result supports the view that enhanced MMN could be an electrophysiological marker of OCD. Although speculative, our results draw a picture of the underlying mechanism of OCD. Namely, glutamatergic hyperactivity in OCD may influence the OFC, and hyperfunction within this region makes patients more sensitive to error signal or deviance detection.

V. CONCLUSION

We investigated auditory deviance processing in OCD patients under threat and safe conditions by MEG with source analysis. We found increased mismatch negativity response in the lateral OFC in OCD patients, regardless of the conditions. We also found mismatch response of the medial OFC is significantly different between groups under threat conditions. These findings suggest that hypersensitive deviance detection processing may constitute a potential intermediate phenotype of OCD. Our results support the view that altered mismatch response under potential threatening conditions may play an important role in the pathophysiology of OCD.

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ABSTRACT(IN KOREAN)

위협과 안전 조건에서의 청각적 변이자극에 대한 강박장애 환자의 mismatch 뇌자도 반응

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손 성 연

목적 : 강박행동은 강박장애의 가장 두드러지는 특징으로서, 심각한 고통과 장애를 초래한다. 강박행동의 동물 모델은 일탈된 자극에 대한 탐지가 강박장애의 병리기전에 기여하는 것으로 제시하고 있다. 사건 관련 전위 중의 하나인 mismatch negativity (MMN)는 일탈된 자극 탐지를 반영하는 뇌의 반응으로 알려져 있다. 한편, 강박장애 환자들은 위험 회피 성향과, 잠재적인 위협에 대한 과민감성을 특징으로 가진다. MMN은 불안 반응 및 예기불안 상태와도 관련이 있는 지표로 알려져 있다. 따라서 본 연구에서는 강박장애 환자와 정상대조군에서 위협에 대한 기대가 MMN에 미치는 영향을 알아보고자 하였다.

방법 : 27명의 강박장애 환자와 19명의 대조군에게 청각적 oddball 과제를 시행하였다. 수동적 청각 oddball 과제는 균일한 음높이의 표준자극(standard stimuli) 사이에 가끔씩 주어지는 다른 음높이의

일탈자극(deviant stimuli)에 피험자가 노출되는 과제이다. 청각자극은 불쾌한 전기자극이 주어질 것을 예상하고 있는 위험조건과 전기자극이 주어지지 않을 것으로 기대하는 안전조건에서 주어졌다. 152 채널의 뇌자도를 통해 자료를 수집하였고, 관심 영역에서의 신호원 세기를 측정하였다.

결과 : 관심 영역 분석을 통해 우측 가측 안와전두피질에서 강박장애 환자군이 대조군에 비해 유의하게 MMN 세기가 증가되어 있는 것을 관찰하였다. 관심 영역 분석을 통해 우측 내측 안와전두피에서 집단과 조건의 상호작용 효과가 유의한 것을 확인하였다.

결론 : 본 연구는 가측과 내측 안와전두피질에서의 MMN 반응이 강박장애 환자의 잠재적 생체지표가 될 수 있음을 시사한다.

핵심되는 말 : 강박장애, 청각적 oddball 과제, mismatch negativity, 위험 예상, 뇌자도