Neural Correlates of Error-Related Brain Activity in Obsessive-Compulsive Disorder

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Directed by Professor Chan-Hyung Kim

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This certifies that Doctoral Dissertation
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ABSTRACT

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Patients with obsessive–compulsive disorder (OCD) typically view perceived inadequacy or error in daily activities and often feel that compensatory action is needed to rid themselves of this perception. Enhanced error monitoring provides evidence for the fronto-striatal model of OCD, typically examined by measuring error-related negativity (ERN). This study examined ERN in OCD patients and compared it with that in healthy subjects through affective modulation induced by task-irrelevant emotional stimuli (fearful faces). A modified version of the flanker task with task-irrelevant emotional face stimuli was performed by 22 OCD patients and 22 healthy subjects while EEG signals were recorded from 65 electrodes. To quantify response-locked ERN, a mean amplitude of 20–120 msec post-response was computed. During trials with fearful face stimuli, the patients with OCD showed more significantly enhanced ERN amplitude than did the control. The difference between ERN following fearful and neutral face stimuli was larger in the OCD patients than in the control group. Across the entire sample, ERN following fearful and neutral face stimuli was reversely correlated with the responsibility subscore of the Dimensional Obsessive–Compulsive Scale. Only the OCD patients exhibited

significantly increased ERN amplitude under fearful face conditions compared with neutral face conditions. The ERN amplitude of the healthy control did not vary with emotional interference. The OCD patients exhibited significantly larger and correct-related negativity amplitudes than did the control in both fearful and neutral conditions. These data provide further support for the view that performance monitoring is overactive in OCD. These findings also suggest that emotional interference using emotionally valent facial images modulates performance monitoring processes in OCD. On the basis of ERN as a state affect-independent property, changes in performance monitoring associated with emotional interference suggest that affective function in the fronto-striatal network be considered in understanding the neural bases of OCD.

Key words: obsessive-compulsive disorder, error related negativity, event related potential, anterior cingulate cortex, emotional interference

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I. INTRODUCTION

Intrusive thoughts or concerns about safety, cleanliness, symmetry, sex, or violence and urges to count or check "to be sure" are commonly experienced by most people to one degree or another. Healthy adaptive human function requires an ability to regulate and control such intrusive thoughts, doubts, urges, and behaviors. Patients with obsessive–compulsive disorder (OCD), however, are unable to control their thoughts, feelings, and behaviors, thereby experiencing psychological distress. OCD is characterized by intrusive obsessions and repetitive compulsions that are time consuming and lead to significant functional impairments (DSM-IV[1] criteria). For patients who suffer from OCD, obsessions are experienced as unwanted recurrent and persistent thoughts, and compulsions are experienced as repetitive behaviors or mental acts that a person is compelled to perform. Patients typically view perceived inadequacy and error in everyday activities, followed by exaggerated concerns, for which ritualistic behavior can compensate. This phenomenology of OCD is characterized by one

perspective as the generation of inappropriate or hyperactive performance monitoring.[2]

1. Overactive error monitoring in obsessive–compulsive disorder

In terms of the neural substrates of OCD, neuroimaging studies[3-5] suggest abnormalities in the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and basal ganglia (BG), which are involved in the control, monitoring, and inhibition of behaviors and thoughts. The OFC and ACC are intimately connected to the BG via cortico-striato-thalamo-cortical loops. On the basis of converged findings of neuroscience research, a model that implicates disturbed cortico-striatal brain systems in the pathogenesis of the disorder has been developed;[6,7] this model is referred to as the fronto-striatal circuit of OCD Activity in the major nodes of this circuit is elevated at rest, accentuated during symptom provocation, and attenuated toward normal levels with successful treatment.[8,9]

The hypothesis on performance monitoring in OCD originated from the cybernetic model of obsessive–compulsive pathophysiology.[10] This hypothesis maintains that excessive or hyperactive error signals may be a common characteristic of OCD patients. Enhanced performance monitoring, particularly overactive error processing, provides evidence for the fronto-striatal model of OCD,[11] typically examined by measuring error-related brain activity. The exaggeration of this electrophysiological response, that is, error-related negativity (ERN),[12] is a frontally maximal negative deflection in the

response-locked event-related potential (ERP) that peaks within 100 ms after an incorrect response; such response can be induced by errors committed outside of conscious awareness.[13] Increased error-related brain activity in patients with OCD has been consistently demonstrated using event-related brain potentials[14-16] and functional magnetic resonance imaging.[17] Source localization[18] and functional neuroimaging studies[19,20] strongly suggest ACC as one of the principal generators of ERN and an important structure of an error detection system.

2. Theoretical explanation for error-related negativity

Extensive discussion has been devoted to the precise cognitive mechanisms that generate ERN. The principal theories that explain the functional significance of enhanced ERN suggest that such enhancement reflects the detection of a mismatch between the representations of actual and intended responses (mismatch theory),[21] conflict monitoring in the ACC arising from multiple simultaneously active response tendencies (conflict monitoring theory),[22] or the disinhibition of the dopaminergic innervations in the ACC, which signal events as worse than anticipated (reinforcement learning theory).[20] However, many instances of ACC activation during correct response trials contradict the first hypothesis because enhanced ERN should be observed only under incorrect responses. Low ERN-like amplitude is sometimes evident in correct response trials; this amplitude is called correct-related negativity (CRN).[23] Several studies[2,15] showed that subjects with OCD symptoms

exhibited enhanced CRN amplitudes, suggesting that people with OCD may engage in excessive performance monitoring during correct responses. Motivational significance theory[24] also suggests that ERN reflects error-detection that is used for motivational ends and that ERN amplitude is related to error significance.

3. Error-related negativity as a candidate endophenotype

Endophenotypes are unobservable measurable components that mediate relationships between distal genotypes and behavioral phenotypes.[25] ERN is considered a potentially suitable OCD endophenotype because it fulfills the criteria[25] for the identification of markers in psychiatric genetics. The criteria suggested are as follows: (1) it is associated with OCD in that increased ERN amplitudes have been repeatedly shown in patients who suffer from this condition; (2) it is substantially heritable, as indicated by a study on 12-year-old twins found to have genetic factors account for 45% and 60% of ERN [26] (3) enhanced ERN amplitude may serve as a trait marker because it remains constant as a function of decreased OCD symptoms in pediatric OCD patients who are administered pharmacologic treatment;[27] (4) in an ERP investigation, increased error-related brain potentials similar to those of OCD patients were observed in their asymptomatic first-degree relatives.[28,29] The results of these studies on ERN and OCD suggest that enhanced error-related brain activity represents a candidate neurocognitive endophenotype for OCD. Further studies are required to determine whether enhanced ERN amplitude mediates the

genetic risk for clinical phenotypes or whether it indicates only risk associated with some genes shared by OCD and other disorders.

4. Effects of affective state or emotion on error monitoring

Although a predominantly cognitive view of action monitoring has received much support, recent works suggest that such theoretical models may provide an incomplete picture of the ERN, because they do not account for affective aspects. For example, ERN increases when errors are monetarily valuable or personally significant.[30,31] A study on OCD patients[16] showed that error-related brain activity cannot be enhanced further with experimentally induced high error significance. Nevertheless, research on the relationship between affective states and the neural indices of error monitoring have provided mixed results. Several studies[32,33] suggest that after affective distress inducement, ERN remains unaltered and that individuals are oriented less toward errors. These findings are consistent with results[34] on ERN being related to trait measures, such as behavioral shame and agreeableness, but not to affective states, including depression, anger, and tension. Task performance feedback is also unassociated with changes in performance monitoring indices.[35,36] By contrast, changes in affect stimulated by emotionally valent images alter the neural indices of performance monitoring. Larson et al.[37] presented a flanker stimulus superimposed on neutral, unpleasant, or pleasant pictures taken from the International Affective Picture System (IAPS). In contrast to what has been observed with longer lasting affective states, the findings of the study indicate

more negative ERN amplitude for pleasant than neutral and unpleasant background pictures. Another report[38] demonstrated decreased-amplitude ERN following exposure to positive video clips relative to exposure to neutral video clips. By contrast, Wisewede et al.[39] showed that unpleasant IAPS pictures that precede a performance error more strongly increased ERN amplitude than did neutral and pleasant IAPS pictures.

With the use of emotionally valent faces in the context of facial expressions, more strongly enhanced ERN amplitudes were derived during evaluations on negative expressions than those on pleasant expressions in healthy participants.[40] However, this study required explicit processing of negative emotional information, such as that carried out in Simon tasks. To better elucidate how general alterations in ERN in OCD patients arise, a helpful approach is to disentangle the cognitive task at hand from emotional stimuli. In the present study, I used ERPs to investigate how incidental, task-irrelevant, emotional interference affects the ERN and neural mechanisms that govern the attention-demanding cognitive tasks performed by OCD patients.

Despite clues to its affective qualities, the purely cognitive perspectives of the ERN still very much prevail. Thus, more work is needed to understand how negative affects directly contribute to the amplitude of the ERN.[41] To the best of our knowledge, no ERN study on OCD patients has adopted affective modulation or emotional interference. Because emotional reactivity in OCD patients are pronounced as they process fearful faces,[42] I modified a previous version of the flanker task[43] that features fearful versus neutral faces as

irrelevant emotional distracters. I used a stimuli set of fearful or neutral facial expressions as basis in hypothesizing that ERN in OCD patients is greater than that in healthy controls, even under emotional interference. I predicted enhanced-response CRN in OCD patients, regardless of emotional stimulus. Another hypothesis that I formulated was an increase in ERN amplitude in performance errors following the presentation of fearful face stimuli to OCD patients. I elucidated the relationship between the ERN and other clinical correlates of the participants.

II. METHODS

1. Participants and clinical assessments

A total of 22 OCD patients and 22 healthy comparison subjects were recruited. All the participants, aged 18–65 years, were examined by trained clinicians using DSM-IV-TR[1] criteria; no history of head trauma or neurological disease was reported. The participants were then individually matched in terms of age, gender, and years of education (Table 1). The patients were recruited from the outpatient unit of Severance Mental Health Hospital, and evaluated as satisfying the DSM-IV criteria for OCD. The healthy comparison subjects were recruited through a local advertisement. They reported no family history of OCD and no past or present signs of psychiatric disease.

The psychopathological symptoms of the patients with OCD were assessed by a psychiatrist using the Yale-Brown Obsessive–Compulsive Scale (Y-BOCS),[44] Hamilton Anxiety Scale (HAM-A),[45] and Hamilton Rating Scale for Depression (HAM-D).[46] Other clinical symptoms were measured for all the participants with self-report questionnaires, such as Obsessive Compulsive Inventory-Revised (OCI-R),[47] Dimensional Obsessive-Compulsive Scale (DOCS),[48] Beck Depression Inventory (BDI),[49] State-Trait Anxiety Inventory (STAI),[50] Obsessive-Compulsive Trait Core Dimensions Questionnaire (OC-TCDQ),[51] Symmetry, Ordering and Arranging Questionnaire (SOAQ),[52] and Toronto Alexithymia Scale (TAS).[53]

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

	OCD patients (N = 22)		Healthy controls (N = 22)		t/ χ^2	p-value
Age (years)	33.1	± 10.6	34.6	± 8.6	0.500	0.620
Sex					0.910	0.763
Male	11	(50.0)	10	(45.5)		
Female	11	(50.0)	12	(54.5)		
Education (years)	14.8	± 1.4	15.9	± 2.1	1.944	0.055
Age at onset (years)	21.0	± 6.1				
Medication status[a]						
Antidepressants	22	(100)				
Benzodiazepine	16	(73)				
Antipsychotics	7	(32)				

Values are mean±standard deviation or n (%); [a]antidepressants include clomipramine, fluoxetine, escitalopram, duloxetine, sertraline, and buproprion.

2. Experimental paradigm

A modified version of the flanker task with task-irrelevant emotional and neutral distracters (Figure 1) was presented to the participants by using Stim 2 software (Compumedics, Inc., El Paso, TX). The participants were instructed to respond with their left or right index finger in accordance with the direction of the target arrow, which was the center arrow in a set of arrows. Half of the trials were congruent (i.e., the target and flanker stimuli were pointed in the same direction), whereas the remaining were incongruent (i.e., the target and flanker stimuli were pointed in opposite directions).

Stimulus compatibility and direction pseudo-randomly varied across trials. The theory of embodying emotion[54] holds that the perception of emotional expressions elicits a re-experiencing of the relevant emotion in one's self. The faces with either neutral or emotional expressions were chosen as background stimuli. Face stimuli were obtained from the Korean Facial Expressions of Emotion[55], and converted into black and white images. Task-irrelevant pictures of neutral or emotional faces were presented before exposure to the target stimulus. The target flanker was surrounded by dashes only, and a blurred face was presented in the background to keep from stimulating a conflict. Example stimuli and the sequence of one trial are shown in Figure 1. Each trial began with durations varying from 100 to 400 ms of a fixation point ("+") to decrease eye movements, followed by an emotional or neutral face stimulus for 650 ms, and then a 350 ms presentation of the flanker stimulus, during which the face stimulus was blurred, and followed by an 850 ms for a response. Flanker stimuli

were presented at the location of the face's eyes, thereby compelling subjects to keep the face within the focus of attention. The experiment featured four primary conditions of interest, with combinations of congruent/incongruent flanker targets and emotional/neutral face stimuli. After each of the 180 trials, the participants were allowed a short break, with feedback presented. The feedback was intended to instruct the participants to more accurately respond when their error rates during the preceding block were >20%. When the error rates ranged from 10% to 20%, the participants were reminded to both quickly and accurately respond. When the error rates were <10%, they were instructed to respond at a faster pace. The 4 blocks of the 180 trials lasted approximately 25 minutes.

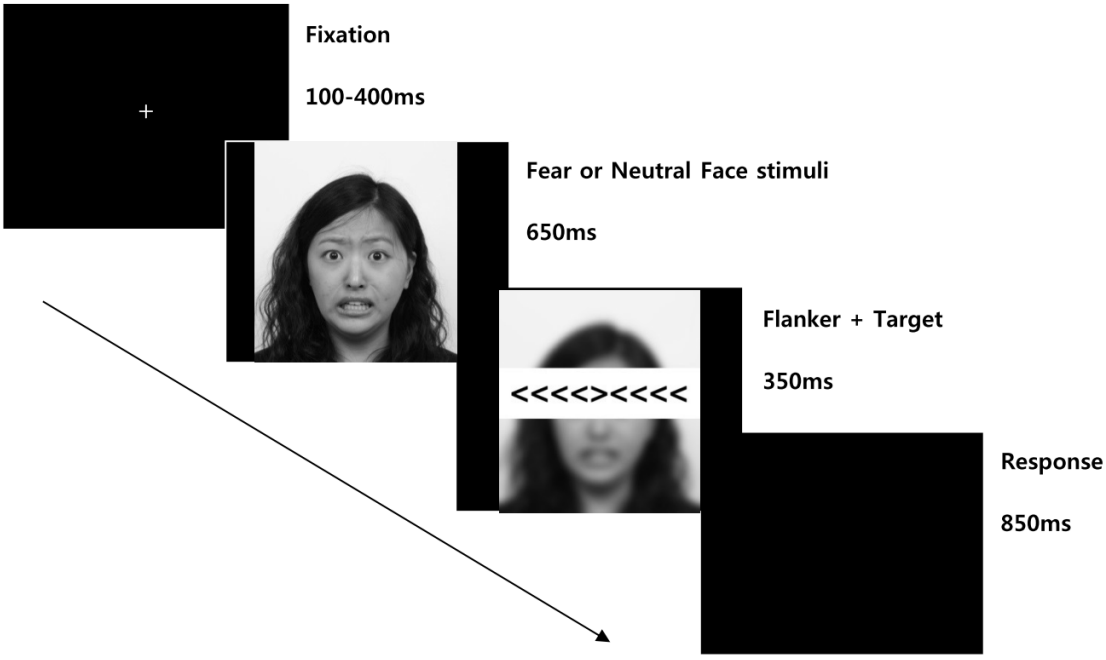

Figure 1. Illustration of the modified flanker task with emotional interference. The participants were instructed to respond to the target arrow with the index finger of their right or left hand as quickly and accurately as possible.

3. Electroencephalogram recording, data reduction, and analysis

Electroencephalogram (EEG) signals were recorded from 65 electrodes, including Cz as a recording reference. All electrode impedances were <5 kΩ. EEG activity was recorded with a sampling rate of 1000 Hz and filtered with a band pass of 0.015–100 Hz (SynAmpsII). The recordings were referenced to linked electrodes placed on the left and right mastoid processes. Eye blinks and movements were monitored by electrodes placed near the outer canthus and beneath the left eye.

Recording was performed in a dimly lit, quiet, and electrically shielded electroencephalography room. The subjects were seated in a comfortable reclining chair at an eye distance of 50 cm from the computer monitor (visual angle, 9°×12°). They were instructed to concentrate on the center of the monitor and avoid blinking as much as possible. The subjects' performance levels were monitored by a closed-circuit camera; the participants did not experience sleepiness during the experiments.

The EEGs were analyzed on an offline basis. Salient noises originating from electroencephalography were removed by inspection. The continuous EEG signals were digitally filtered with a low-pass filter of 40 Hz. To control for eye movement artifacts, trials were adjusted by regression from electrooculograms.[56] Data were average referenced offline. Stimulus-locked epochs with a duration of 750 ms, including a 100-ms pre-response interval, were extracted. Response-locked epochs with a duration of 850 ms, including a

200-ms pre-response interval, were extracted. Epochs containing voltages that exceed a standard deviation of 75 μV between consecutive data points were excluded from further analysis. The pre-stimulus interval from –100 to 0 ms prior to the stimuli served as a baseline for stimulus-locked ERPs. The pre-response interval from –150 to –50 ms prior to response served as a baseline for response-locked ERPs. To quantify response-related negativities, the differences between the most negative peaks occurring from 20 to 120 ms post-response were computed.

Several ERP components, such as P100, N170, N250 and P300 have been identified as associated with early and late cognitive processes during face perception. The behavioral tasks used in this study were not designed to induce active appreciation of emotional faces. Therefore, P100, which is related to early visual processing of domain-general and low-level stimulus features, was analyzed for the face stimuli-locked ERPs in this study. The occipital P100 is characterized by a positive peak at occipital scalp sites around 75 – 135 ms and is supported by its face sensitivity.[87.88]

4. Statistical analysis

The chi-square test and independent t-test were used to assess demographic variables and clinical symptom scores. Repeated-measures ANOVAs were calculated with the between-subject factor—group (OCD vs. control)—and the within-subject factor—response type (correct, error) or stimulus type (fearful vs. neutral). For all repeated-measures analyses, p-values were corrected with the

Greenhouse–Geisser procedure. Pearson's coefficient of correlation were calculated to examine association between the amplitudes at electrodes and clinical variables. Statistical significance was set at a threshold of $P < 0.05$. SPSS version 17.0 was used for statistical analyses.

III. RESULTS

1. Sample characteristics

Table 1 shows the demographic and clinical measures for the OCD patients and healthy subjects. The groups did not differ in terms of age and gender. As expected, however, they significantly differed with regard to symptom severity scores (Table 2). The patient group showed significantly elevated levels of obsessive and compulsive symptoms, anxiety, depression, and alexithymic tendency.

Table 2. Clinical characteristics of OCD patients and healthy controls

	OCD patients		Healthy controls		t	*p*-value
	Mean	SD	Mean	SD		
OCI-R (total)	25.39	8.76	9.77	5.80	6.762	<0.001
DOCS-Contamination	6.06	6.25	2.41	2.13	2.572	0.028
DOCS-Responsibility	7.39	6.54	1.55	1.95	3.993	<0.001
DOCS-Unacceptable Thoughts	9.17	6.42	1.91	2.00	5.031	<0.001
DOCS- Symmetry	2.89	3.07	1.23	1.63	2.432	0.020
BDI	20.11	10.12	5.32	4.05	6.188	<0.001
STAI-S	57.53	11.12	38.77	8.48	5.884	<0.001
STAI-T	58.11	11.12	36.55	7.84	7.251	<0.001
OC-TCDQ-IC	19.24	6.38	8.86	5.50	5.452	<0.001
OC-TCDQ-HA	20.11	9.31	6.68	5.03	5.733	<0.001
SOAQ	23.56	18.80	16.36	12.257	1.457	0.153
TAS (total)	45.68	12.70	31.82	7.27	4.370	<0.001
Y-BOCS	26.11	7.47	-	-	-	-
HAM-A	16.06	7.75	-	-	-	-
HAM-D	19.11	7.75	-	-	-	-

OCI-R, Obsessive–Compulsive Inventory-Revised; DOCS, Dimensional Obsessive–Compulsive Scale; BDI, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory; OC-TCDQ, Obsessive–Compulsive Trait Core Dimensions Questionnaire; IC, Incompleteness Subscale; HA, Harm Avoidance Subscale; SOAQ, Symmetry, Ordering, and Arranging Questionnaire; TAS, Toronto Alexithymia Scale; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; HAM-A, Hamilton Anxiety Scale ; HAM-D, Hamilton Rating Scale for Depression

2. Behavioral results for the modified flanker task

Descriptive statistics for the reaction times and accuracy rates of both groups are presented in Table 3. For reaction times, neither group main effect nor emotion by group, correctness by group, or three-way interaction exhibited significance. The participants committed more errors in response to incongruent flankers ($F = 41.007$, $p < 0.001$). The $2 \times 2 \times 2$ repeated-measures ANOVA with accuracy revealed a significant level of interaction effects of congruency × group ($F = 4.651$, $p = 0.037$) and a trend level of interaction in congruency × emotion ($F = 4.648$, $p = 0.052$). There was no significant group difference in reaction time and error rate for both fearful and neutral conditions.

Table 3. Behavioral data of OCD patients and healthy controls

	OCD patients	Healthy controls	t	*p*-value
	Reaction time (SD), msec			
Fearful				
Error	437.17 (137.34)	401.66 (90.89)	0.997	0.325
Correct	422.74 (95.81)	410.07 (65.01)	0.505	0.616
Neutral				
Error	426.09 (130.41)	401.74 (92.58)	0.703	0.486
Correct	423.22 (95.10)	408.85 (63.14)	0.582	0.564
	Accuracy (SD)			
Fearful				
Congruent	0.939 (0.047)	0.917 (0.082)	1.101	0.278
Incongruent	0.788 (0.186)	0.829 (0.116)	-0.877	0.386
Neutral				
Congruent	0.931 (0.083)	0.897 (0.091)	1.330	0.191
Incongruent	0.793 (0.178)	0.834 (0.104)	-0.918	0.364

Values are mean or standard deviation; t, t-test

3. Event-related potential data

A. Stimulus-locked event-related potentials

Figure 2 shows a clear early emotional effect began at 100 ms (P100)[57], best observed on the parieto-occipital electrodes (POz). The peak P100 amplitudes and latencies for face presentation at POz are presented in Table 4. For both peak amplitudes and latencies, the main effect of emotion and emotion by study group interaction were nonsignificant ($p > 0.05$). The mean peak P100 amplitudes were relatively higher in patients with OCD, but the difference between the groups was nonsignificant (Figure 2).

Table 4. Condition-wise peak P100 amplitudes and latencies for face presentation at POz for the participants.

	OCD patients	Healthy controls	t	*p*-value
Peak amplitudes (SD), μV				
Fearful	4.95 (5.51)	3.63 (4.92)	0.821	0.519
Neutral	4.98 (5.30)	3.91 (4.89)	0.674	0.506
Latencies (SD), ms				
Fearful	98.85 (9.85)	96.77 (15.95)	0.502	0.619
Neutral	97.40 (11.83)	97.82 (19.15)	-0.099	0.921

Values are mean or standard deviation; t, t-test

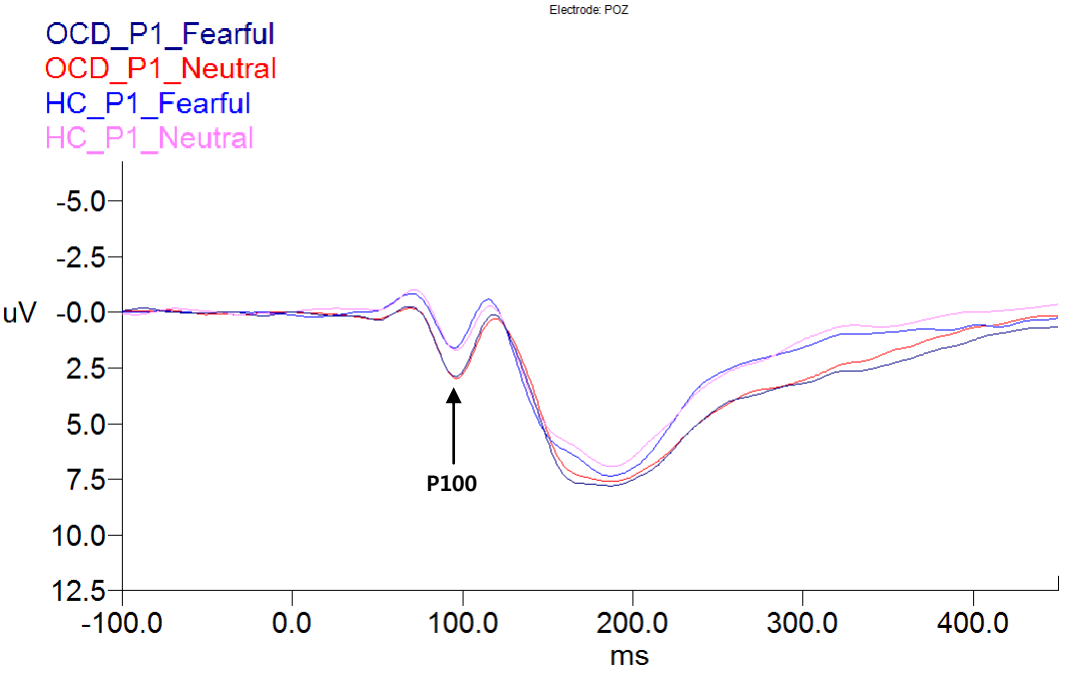

Figure 2. Grand averages of P100 components at POz for fearful and neutral faces from obsessive–compulsive disorder and healthy participants.

B. Response-locked event-related potentials

Both the groups showed more pronounced negativities under erroneous than under correct responses, as reflected by a significant main effect of response type ($F = 78.972$, $p < 0.001$). The 2 × 2 × 2 (correctness × emotion × group) repeated-measures ANOVA with mean amplitude at FCz showed significant interaction effects of emotion × group ($F = 6.868$, $p = 0.012$) and correctness × facial expression × group ($F = 12.237$, $p = 0.020$). The grand mean ERP waveforms are shown in Figure 3. The 2 × 2 repeated-measures ANOVA for each group showed that ERN amplitude was larger during trials with fearful face expressions than during trials with neutral face stimuli in the patients with OCD (correctness × emotion, $F = 11.130$, $p = 0.003$). On the contrary, the healthy control exhibited no interaction between response type and stimulus type ($F = 1.668$, $p = 0.459$). The t-tests (Table 5) revealed that ERN amplitude with fearful face stimuli for the OCD patients was significantly higher than that for the healthy control ($t = 2.292$, $p = 0.028$). These differences are evident in figure 4. In figure 5, the topographic maps for fearful and neutral conditions are shown for both groups in the 50-90 ms window with a fronto-central maximum. In addition, the CRN amplitudes under fearful ($t = 2.150$, $p = 0.039$) and neutral ($t = 2.050$, $p = 0.048$) facial expression for the OCD patients were significantly higher than that for the healthy control. The difference between ERN in fearful and neutral facial expression was larger in the OCD than in the control group ($t = 2.790$, $p = 0.007$).

Table 5. Event-related negativity potential data of OCD patients and healthy controls

	Mean amplitude (SD)		t	*p*-value
	OCD patients	Healthy controls		
ERN, FCz (μV)				
Fearful	–4.05 (4.44)	–1.03 (3.67)	2.292	0.028
Neutral	–2.61 (3.23)	–1.99 (2.70)	0.160	0.874
Δ(Fearful–Neutral)	–1.44 (2.33)	0.96 (3.42)	2.790	0.007
CRN, FCz (μV)				
Fearful	2.37 (3.83)	5.74 (5.55)	2.150	0.039
Neutral	2.21 (3.85)	5.17 (5.66)	2.050	0.048
Δ(Fearful–Neutral)	0.24 (0.56)	0.35 (1.15)	0.352	0.727

t, t-test; ERN, Error-related negativity; CRN, Correct response negativity; Δ refers to trials with fearful face stimuli minus trials with neutral face stimuli in the time window of the ERN.

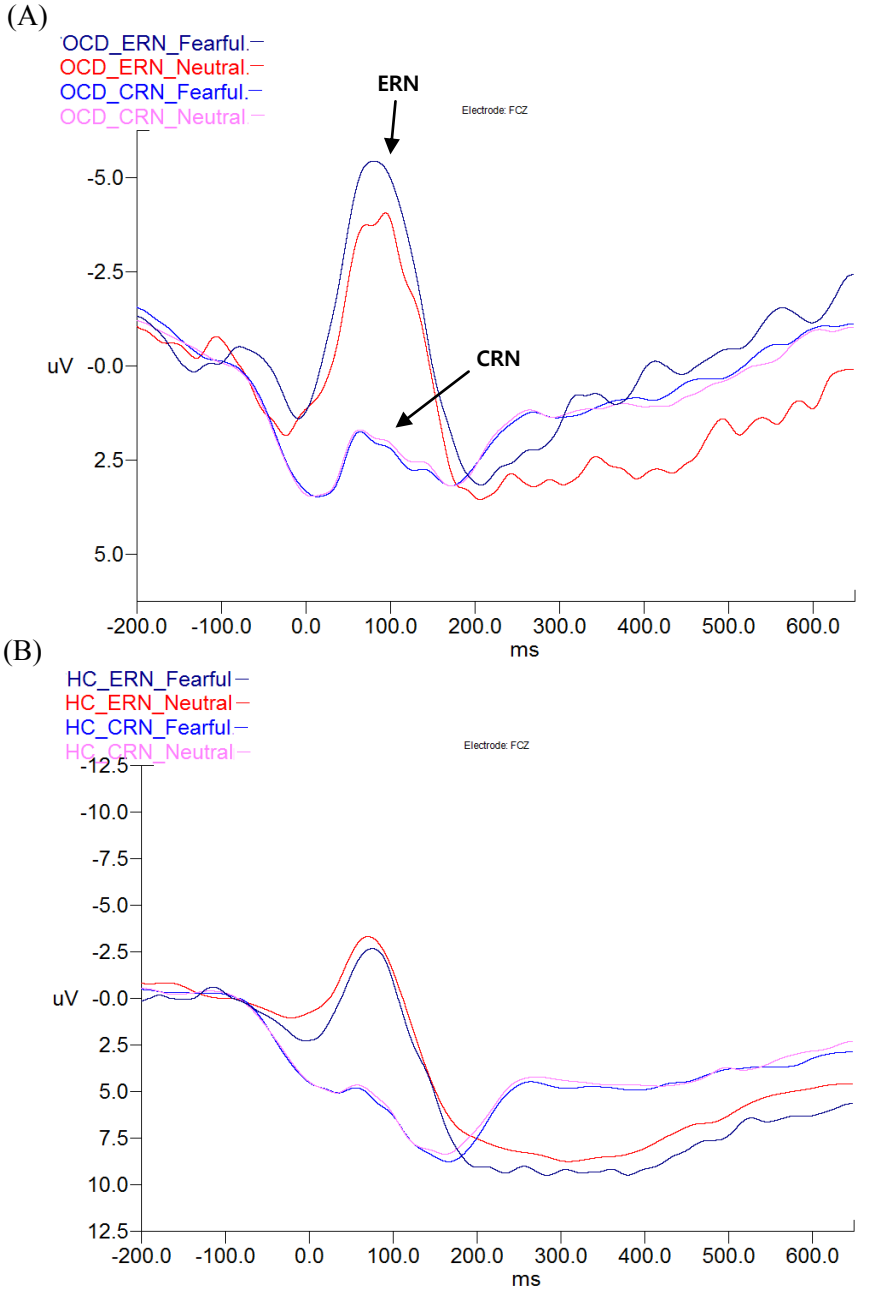

Figure 3. Grand averages of response-locked event-related potentials recorded at FCz for correct response and error trials for (A) obsessive–compulsive disorder and (B) healthy participants.

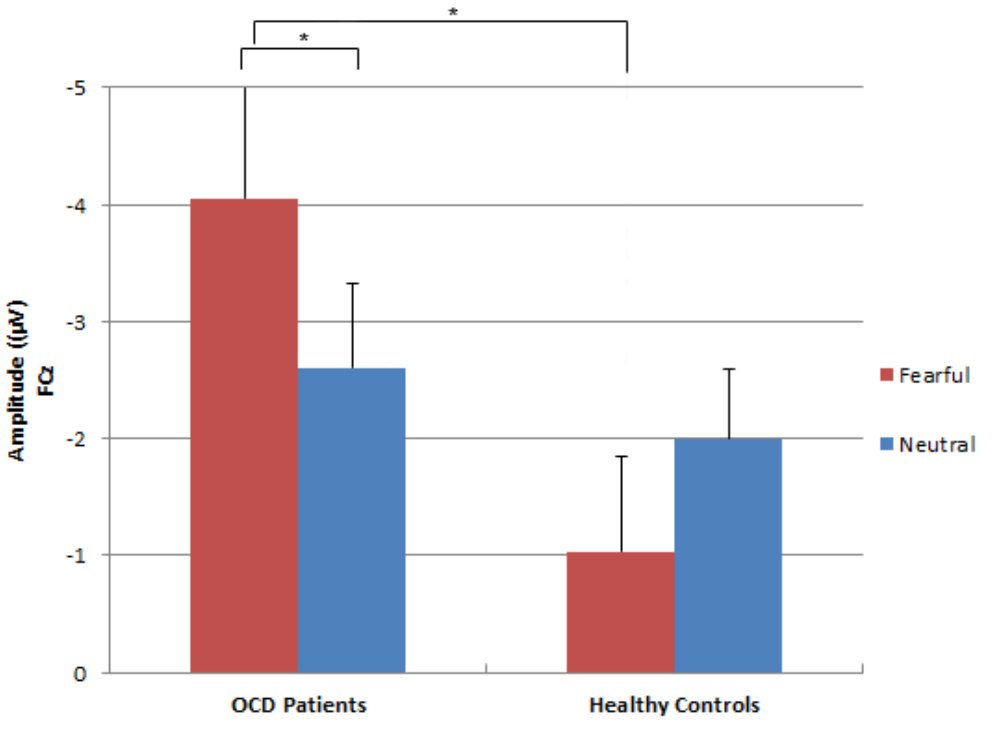

Figure 4. Mean amplitudes of the error-related negativities (bars represent standard errors) at electrode FCz (*: Significant finding at $P < 0.05$)

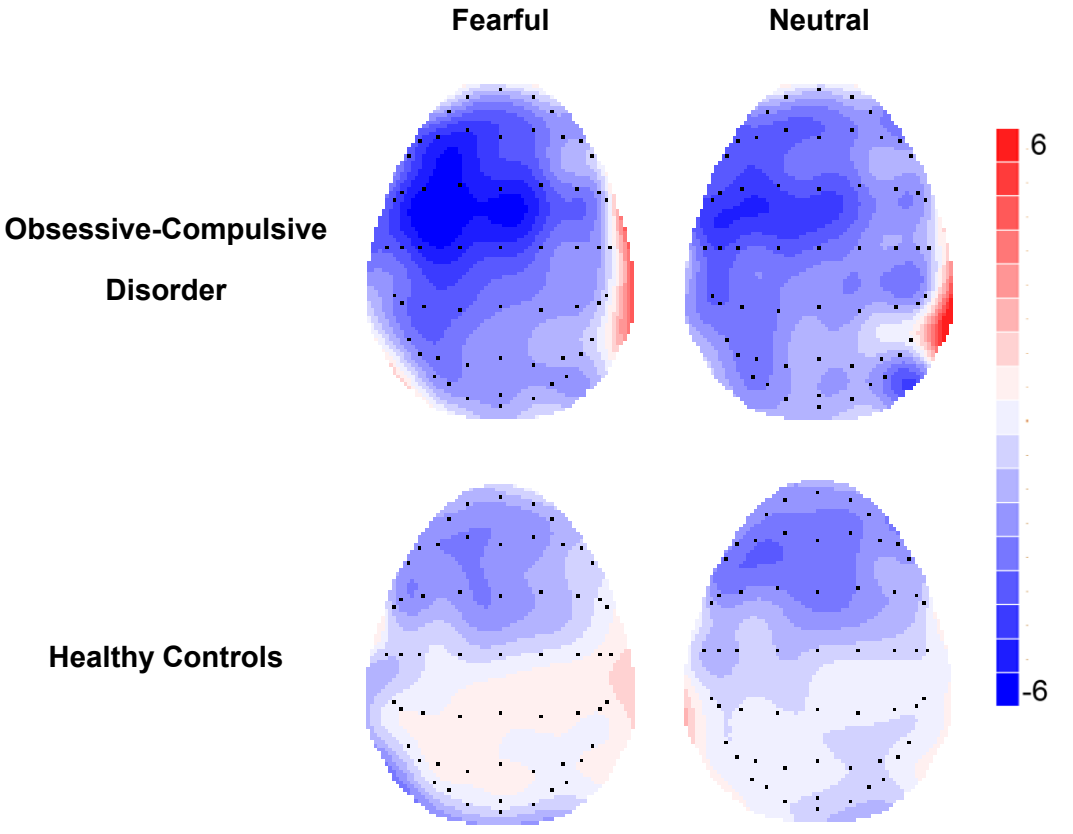

Figure 5. Scalp topographies of representing the error-related negativity (ERN) component in the 50-90 ms window after the commission of error responses.

4. Correlation analysis

Table 6 shows that across the entire sample, Correlations between ERN amplitudes in both conditions with symptom measures were computed. The ERN amplitude enhancement between fearful and neutral condition was significantly correlated with feeling of incompleteness (OC-TCDQ-IC: r=-0.339, p=0.025). All other correlations were not significant. In the OCD patients, there was no significant correlation between the clinical symptom scales (including HAM-A, HAM-D and Y-BOCS) and the any brain potentials

Table 6. Pearson correlation coefficients between mean amplitude of electrodes FCz and other variables for all the participants (N = 42).

Variable	ERN (Fearful)	ERN (Neutral)	ΔERN (Fearful–Neutral)
Age	–0.019	0.058	–0.080
OCI-R (total)	–0.173	0.020	–0.250
DOCS- Contamination	0.025	0.128	-0.080
DOCS- Responsibility	–0.165	–0.276	0.025
DOCS- Unacceptable Thoughts	–0.098	–0.074	–0.198
DOCS- Symmetry	–0.120	–0.033	–0.132
BDI	–0.080	0.426	0.090
STAI-S	–0.088	–0.137	–0.178
STAI-T	–0.115	–0.366	–0.206
OC-TCDQ-IC	–0.201	0.100	–0.359*
OC-TCDQ-HA	–0.074	0.090	–0.180
SOAQ	–0.068	0.143	–0.222
TAS	0.029	0.249	–0.188

OCI-R, Obsessive–Compulsive Inventory-Revised; DOCS, Dimensional Obsessive–Compulsive Scale; BDI, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory; OC-TCDQ, Obsessive-Compulsive Trait Core Dimensions Questionnaire; IC, Incompleteness Subscale; HA, Harm Avoidance Subscale; SOAQ, Symmetry, Ordering, and Arranging Questionnaire; TAS, Toronto Alexithymia Scale

*Correlation is significant at the 0.05 level (two-tailed).

IV. DISCUSSION

This study examined the psychophysiological indicators of performance monitoring in OCD patients and compared them with those of healthy comparison subjects under emotional interference. I found evidence of ERN amplitudes in all the participants; that is, ERN amplitude in performance errors was demonstrated after exposure to face stimuli. The posterior medial frontal/anterior cingulate cortex has been suggested as one of the principal generators of these components. The activity of the ACC is assumed to trigger the adjustment of cognitive control, which subsequently involves other brain regions (e.g., prefrontal cortex) to prevent future errors.[58] A persistently overactive performance monitoring system may therefore account for the need to control commonly observed actions and thoughts.

The patients with OCD showed higher ERN amplitude during trials with fearful face stimuli than did the controls In line with previous studies,[16,27,59,60] I derived evidence of enhanced ERN amplitudes in the OCD patients, reflecting overactive performance monitoring. Only the OCD patients exhibited significantly increased error-related brain activity under fearful face conditions; the subjects did not display such activity under compared with the neutral face conditions. The performance monitoring of the healthy controls did not vary with emotional interference. The absence of variations with error significance in the OCD patients was noted in previous research.[16] This phenomenon is attributed to a ceiling effect; that is, the OCD patients already reached the

maximum monitoring activity under standard conditions and were unable to further increase this activity with punishment feedback.[16] Taken together, these results indicate that in OCD patients, ERN amplitude is susceptible to manipulation via emotional interference and not by error significance. Given that fearful face stimuli may signal harm or a threat, they are of immediate importance to the wellbeing of an organism. These stimuli may therefore lead to more intense reactions from OCD patients. This finding suggests a neural mechanism, which recruits an extended ACC region that encompasses both attentional control and cognitive processing of emotions, such as the appraisal of fear responses.[61,62] The increased ERN for errors occurring after the presentation of fearful face stimuli may thus be viewed as an index of increased anterior cingulate activity in this condition. In OCD patients, therefore, the ACC may mediate compensatory cognitive processes during emotional interference. In addition to cortico-striatal circuitry, the critical involvement of the amygdala is suggested in the pathophysiology of OCD. Although controversial, recent studies have consistently shown that the presentation of negatively valenced stimuli (symptom related or unrelated) activate the amygdala in OCD.[42,63] In a functional imaging study[64] that used an experimental paradigm similar to that employed in the present work, images with fearful faces more frequently induced increased activation in the amygdala than did images with neutral faces. Several researchers support fronto-striato-limbic models of OCD[11,63,65] that involve amygdalo-cortical interactions. The amygdala is extensively connected, both anatomically and functionally, to the ACC.[66,67] Therefore, my study provides proposed features of OCD pathophysiology

beyond the classic parallel cortico-striatal pathways.

Although the OCD patients had numerically larger ERN amplitudes than did the healthy controls during the trials with neutral face stimuli, the difference was statistically nonsignificant. The subtle enhanced tendency of ERN with the neutral face stimuli of the healthy control compared with the fearful face stimuli prevented deviations in amplitude between the two groups. Similar findings in healthy subjects were derived by Larson et al.[37] and Wiswede et al.[39] on a second half trial. These findings can be partially explained by the reinforcement learning theory of ERN[20], which postulates that error processing is specifically heightened in the presence of a mismatch in reward signal. In my study, task-irrelevant face stimuli "prime" the subject to experience the appropriate affect. When neutral face stimuli are presented, which are relatively more positively valent than fearful face stimuli, a committing error, as a negative consequence, provides a greater number of mismatching contexts and increased ERN. These results further support the reinforcement learning–ERN model,[68] because the activity of the mesencephalic dopamine system increases toward appetitive and nonaversive stimuli and decreases toward attention-generating and aversive stimuli.[69] Wiswede et al.[39] suggested an alternative explanation that unpleasant background pictures may draw attention away from a target flanker and may have precluded an increase in ERN amplitude. I minimized this possibility by using blurred face stimuli in the background when the target flanker was presented (Figure 1).

It is important to note that in addition to the dopamine system, the locus ceruleus–noradrenaline system exerts a modulatory activity on the action

monitoring of ACC in humans.[70] The ACC has been viewed as playing a key role in the central autonomic system,[71,72] which is believed to regulate attentional, affective, and autonomic responses.[73] Noradrenergic neurotransmission seems to modulate information processing rather than reward processing by increasing the signal-to-noise ratio of relevant information.[74] The noradrenergic systems also appear to depend on the salience of the stimulus.[75] Previously, the stimulation of the noradrenergic system has been shown to enhance ERN amplitude action monitoring.[76] The noradrenergic effects of fearful face stimuli were demonstrated by the linear association between electrodermal activity and the increasing intensity of emotional stimuli with the use of fearful faces.[77] The higher arousal and noradrenergic function in OCD was demonstrated from studies with experimental animals[78] and humans.[79]

With regard to the question of how the interaction between affect and action monitoring on the ERN amplitude differs between OCD patients and healthy controls, I offer a possible explanation as follows. OCD patients are prone to be aroused by hypersensitive noradrenergic activation due to stimulation by fearful stimuli and are less moderated by affect-related changes in dysfunctional dopaminergic learning systems. In contrast, healthy controls are not sensitive to noradrenergic stimulation or influenced by intact dopaminergic activation coming from the mismatch between affective contexts with nonaversive stimuli and error consequences. The fact that no significant variation of ERN was reported between the standard condition and the punishment condition[16] may implicate the dysfunctional dopaminergic learning systems in OCD.

Nonetheless, my results should be interpreted with caution because

modulation by emotional interference in the healthy control was statistically nonsignificant. Further studies are necessary to determine the precise mechanisms underlying these effects.

Apart from ERN amplitudes, enhanced CRN amplitudes in OCD patients were revealed in the present study, as well as in earlier research.[2,15] This agreement suggests that performance monitoring is altered not only during error processing, but also during correct response processing, regardless of emotional interference. The "conflicting theory" of ERN[80] suggests that ERN amplitude increases in both incorrect and high-conflict correct response trials, indicating an overactive conflict monitoring system in OCD patients. According to this theory, patients can frequently overevaluate possible conflict responses during motor and/or cognitive activities. Their overactive conflict monitoring system causes them to adopt a very cautious approach to test performance to avoid mistakes. This approach potentially explains patients' constant doubting and need for repetitive action, despite correct performance.[81] One possibility is that OCD patients may show overactive response monitoring or evaluation that contributes to both ERP components.[15] Alternatively, CRN may reflect an independent monitoring process that signals a response strategy conflict and the need to optimize performance.[82] According to this account the larger CRN in OCD can be interpreted independent of ERN alterations and may reflect an error-independent monitoring process that represents an increased signal to further optimize performance even during correct behavior.

In present study, there was no significant correlation between the clinical symptom scales and the ERN amplitude in both conditions across the two

subject groups or in subgroup analysis. My results provided further evidence that ERN is a trait-like measure that is independent of obsessive–compulsive symptom severity measured by OCI-R or Y-BOCS. Correlation analysis indicate that individuals with higher OC-TCDQ incompleteness sub-scores who have greater feeling of incompleteness showed greater increase in negative response-related amplitudes in fearful condition than neutral condition. This can implicate the notion suggested by several authors[83,84] that incompleteness may play a role in symptoms that have been traditionally considered to be harm avoidance behaviors, such as checking and washing, to prevent 'feared' consequences. To the best of our knowledge, no study has used the OC-TCDQ assessing two hypothesized core dimensions of OCD, harm avoidance and incompleteness for ERN investigation. Research on the heterogeneity and idiosyncratic nature of obsessive–compulsive symptoms support the dimensional approach in OCD studies. Further ERN studies with distinguishing motivations underlying compulsions are needed for replication.

Some limitations of the current work are worth noting. Certain patients involved in the study were medicated, bringing forth concerns over the effect of medication on ERN. Although previous studies[85,86] clarified that increased ERN in OCD is unrelated to medication, I cannot exclude this possibility under exposure to face stimuli. The healthy control sample was small. The failure to detect possible differences at a behavioral level may be explained by a lack of statistical power. Another important issue is that this study focused exclusively on fearful faces and anxiety as representations of negative emotions, but I cannot exclude a different outcome under other negative or positive emotions.

Researchers should address the effects of other negative and positive emotions on cognitive processing.

V. CONCLUSION

This research examined the psychophysiological indicators of performance monitoring in OCD patients and compared them with those of healthy comparison subjects under exposure to emotional interference. The patients with OCD showed higher ERN amplitude during trials with fearful face stimuli than did the control. The OCD patients also exhibited significantly increased ERN for errors following fearful face stimuli than for errors following neutral emotional face stimuli. This finding implies that emotional interference via emotionally valent facial pictures alters performance monitoring processes in OCD. On the basis of ERN as a state affect-independent property, changes in performance monitoring associated with emotional interference suggest that affective function in the fronto-striatal network be considered in understanding the neural bases of OCD.

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ABSTRACT (IN KOREAN)

강박장애환자에서 에러 관련 뇌활동의 신경매개체

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반복되는 강박 사고와 행동을 특징으로 하는 강박장애환자는 실수를 확인하고 행위를 모니터링 하려는 인지적 기제를 과도하게 사용한다. 이는 뇌파의 사건 관련 전위 중에서 앞쪽 대상회 피질에서 기인하는 에러 관련 음전위의 과활성화로 나타난다. 에러 관련 음전위는 다양한 증상 유형의 강박장애 병태생리에서 공통적인 역할을 하는 유력한 내적 형질의 하나로 알려져 있다. 한편, 특성(trait) 의존적이라고 여겨지는 오류 관련 음전위와 정서 상태 또는 감정의 관련성에 대한 기존의 연구들은 그 결과가 일관되지 않았다. 강박장애 환자는 불안이 높고 정서조절에 이상이 있는 것으로 알려져 있으나, 감정 상태가 에러 관련 음전위에 미치는 영향에 대해서는 아직까지 연구된 바가 없다. 이에 본 연구에서는 강박장애 환자의 에러 관련 음전위의 신경매개체를 밝히고, 정서 간섭과의 관련성을 알아보고자 하였다. 또한 에러 관련 음전위와 다양한 임상 증상과의 상관 관계도 조사하였다. 22명의 강박장애 환자와 22명의 대조군 피험자가 사건 유발 반응 전위 뇌파 검사에 참여하여 정서간섭이 부가된 수정된 반응 간섭 과제 (Flanker task)를 수행하였다. 피험자는 두려움 얼굴 자극 또는 중성 얼굴 자극이 제시된 이후 가능한 한 빠르게 과제를 수행하도록 하였으며, 오반응과 정반응 시 나타난 뇌파의 전위가 측정되었다. 이에 따라 나타난 뇌파의 사건 관련 전위를

반복측정 분산분석 결과, 전체 대상자에서 오반응 시 나타나는 에러 관련 음전위가 정반응 시 나타나는 전위보다 유의하게 높게 나타났다. 또한 강박장애 환자에서 두려움 얼굴 자극 조건 시 중성 얼굴자극보다 에러 관련 음전위가 증가하였으나, 대조군에서는 유의한 차이가 없었다. 강박장애 환자에서 두려움 얼굴 자극 선행 시 에러 관련 음전위가 대조군에 비해 더 높게 나타났다. 또한 정반응 시 나타나는 음전위는 얼굴자극의 종류와 상관없이 환자군에서 항상 높았다. 모든 피험자에 대한 임상적 변수의 상관 분석 결과, 자극에 따른 음전위의 차이는 강박 특질 핵심 차원의 불완전감 차원과 유의한 연관이 있었다. 본 연구에서 확인된 강박장애 환자의 정서 간섭에 의한 에러 관련 음전위의 증가는 강박장애의 과도한 에러 탐지 및 행동 모니터링의 인지적 기제가 정서 조절의 어려움과 관련되어 있을 가능성을 의미한다. 본 연구는 강박장애의 주요 병리 기전의 이해를 위해서 대뇌의 피질-선조체-시상-피질회로의 이상뿐 아니라 정서 조절 회로와의 통합적인 접근이 필요함을 시사한다.

핵심되는 말 : 강박장애, 에러 관련 음전위, 사건유발전위, 대상회 피질, 정서 간섭