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Electrophysiological Changes Related to Childhood Trauma in Patients with Major Depressive Disorder: An Event-related Potential Study

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Objective: Childhood trauma is the most important environmental factor for several psychiatric disorders. Depressed patients with childhood trauma appear to have severe symptoms that frequently recur. This study investigated whether depressed patients with childhood trauma showed attenuated Nogo event-related potentials (ERPs) and source activity during response-inhibition tasks.
Methods: Forty-four patients patients with major depressive disorder (MDD) were instructed to perform a Go/Nogo task during electroencephalography. Sensors and source activities of N2 and P3 of the Nogo ERPs were analyzed. The participants' clinical symptoms were assessed using the Childhood Trauma Questionnaire (CTQ), Beck Depression Inventory, State-Trait Anxiety Inventory, Barratt Impulsivity Scale, and Affective Lability Scale. The participants were divided into two groups (low and high), based on their total CTQ scores.
Results: MDD subjects with high CTQ scores showed significantly decreased Nogo P3 amplitudes at the frontal, frontocentral, central, and parietal electrodes than those with low CTQ scores (all $p < 0.01$). In Nogo P3, the source activities of the right cuneus, right posterior cingulate cortex, right precuneus, left supramarginal gyrus, and left lingual gyrus were significantly lower in the high CTQ group than in the low one (all $p < 0.01$). There were significant negative correlations between the total CTQ scores and the Nogo P3 amplitudes in the frontocentral ($p = 0.03$) and parietal regions ($p = 0.02$), which showed lower source activity in the Nogo P3 condition.
Conclusion: Depressed patients with severe childhood trauma showed different Nogo-ERP characteristics, which might reflect inhibitory failure and dysfunction in related brain regions.

KEY WORDS: Psychological trauma; Depression; Event-related potentials; Biomarker.

INTRODUCTION

According to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5), psychological trauma refers to an exposure to traumatic experiences, such as threatening or substantial physical violence, threatening or actual sexual violence, or circumstances associated with them [1]. The World Health Organization (WHO) estimates that about a quarter of all adults have been physically abused in childhood, with 1 in 13 males and 1 in 5 females reporting sexual abuse in childhood [2]. Childhood trauma is pathological in nature and causes serious psychological and behavioral disorders such as poor emotional control, unstable interpersonal relationships, and lack of self-awareness. Unlike short-term simple anxiety, it usually lasts throughout the patient's life [3].

In fact, childhood trauma has several effects on one's mental state. It makes patients more susceptible to depres-

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sion and anxiety [4,5]. People with a history of sexual abuse in childhood have significantly increased depression, higher suicide rate, and overall stress vulnerability, due to neurobiological factors, including hormonal changes. [4,6,7]. Moreover, trauma in childhood is associated with intellectual dysfunction and cognitive deficits in both childhood and adulthood [8-10], which is particularly relevant to difficulty in inhibitory control [11]. Childhood trauma contributes to impulsivity or deficits in the executive function in patients with psychiatric disorders [12-14]. In addition, some studies show that childhood trauma is related to affective lability or mood dysregulation in patients with borderline personality disorder or bipolar disorder [15-17]. Bulimia nervosa is one of the effects of childhood trauma on affective lability [18].

Among the conditions listed above, negative childhood experiences are a potential risk factor for major depressive disorders (MDD), and a recent meta-analysis showed that childhood abuse worsens the overall course and treatment outcome of MDD [19]. A link between childhood maltreatment and impulsivity and suicidal behavior in patients with MDD has been suggested [1,6]. In addition, childhood trauma affects cognitive functions such as memory, and executive functions in patients with MDD [20].

These trauma effects can cause long-term changes in brain development [21]. In particular, previous brain imaging studies have reported that childhood trauma is associated with structural changes in the frontal lobe and limbic system [22-25]. In a voxel morphometry study, women who experienced stress early in life had less gray matter in the posterior precuneus than healthy controls [26]. Previous research suggests that childhood maltreatment is accompanied by physiological, hormonal, and biochemical changes that eventually lead to changes in brain structure and function [27,28]. These results further suggest that childhood trauma causes a wide range of structural changes in the brain.

The results of these changes can be determined through electroencephalography (EEG). Also, it reflects the prognosis or the severity of symptoms of various psychiatric disorders [29,30]. In particular, event-related potentials (ERPs) are a neurophysiological tool used to indicate neural activity related to cognitive processes [31]. Using the Go/Nogo task, processes such as behavioral or response inhibition can be explored [32]. The Nogo P3 component has been considered to reflect response evaluation, or success of response inhibition, which is included in later inhibitory processes [33]. In addition, it has been suggested that the Nogo effect is more reliable than the Go effect [34,35]. Previous studies have shown that adolescents and adults who have experienced childhood trauma show changes in Nogo ERP and the source activity of the frontal lobe, suggesting that impulsivity occurs due to the dysfunction of this region [36,37]. Meanwhile, a history of childhood trauma and depressive symptoms is associated with wide-regional brain networks and brain connectivity in patients with MDD [38,39]. Although these changes in brain structure and function in depressed patients with childhood trauma might be reflected in the Nogo task in relation to response inhibition, there have been no reports of neurophysiological differences according to the presence of childhood trauma in patients with MDD.

In these patients, childhood trauma is a potential risk factor, and since it leads to severe symptoms and poor prognosis, the presence of a biomarker capable of detecting the symptoms will greatly aid in understanding the patient's future prognosis. Therefore, this study aimed to compare the difference in the ERP amplitude and latency between the two groups divided by the severity of the trauma, and it identified the relationship between them and the current symptoms such as depression, anxiety, impulsivity, and affective lability. Hence, we hypothesized that MDD patients with severe childhood trauma will have more difficulty in response inhibition or have more impulsivity than those with mild trauma; these characteristics will be reflected in Nogo ERP. In addition, the source activity of Nogo ERP could reflect the dysfunction of the brain regions related to childhood trauma.

METHODS

Subjects

Patients who visited the Department of Psychiatry at Soonchunhyang University Cheonan Hospital between July 2020 and December 2020 were enrolled in this study. We included 44 participants (24 males and 20 females, mean age = [26.95 ± 8.93] year) diagnosed with MDD according to the DSM-5 criteria. Participants with psychotic disorders, bipolar disorder, intellectual disability, neurological or severe medical diseases, a history of alcohol or substance abuse/dependence, or head trau-

ma were excluded from the study by the screening interviews. Some of the participants had comorbid psychiatric diseases: panic disorder (n = 3), attention-deficit/hyperactivity disorder (ADHD) (n = 3), somatic symptom disorder (n = 1), and anorexia nervosa (n = 1). All participants were aged between 19 and 60 years. The Korean version of the Childhood Trauma Questionnaire (K-CTQ) was administered to all the participants. They were allocated to either the high or low CTQ group, based on the total CTQ score using the median score (cut-off score = 48) [40]. Each participant had normal hearing ability. The majority of participants were drug-naïve at the time of the EEG recording. All participants provided written informed consent. This study was approved by the Institutional Review Board and Ethics Committee of Soonchunhyang University Cheonan Hospital, and all experimental protocols were approved by the committee (IRB number: 2020-06-019).

Clinical Measures

All participants were assessed for childhood trauma using the K-CTQ. The CTQ is an instrument used to assess childhood emotional and physical abuse, sexual abuse, and physical and emotional neglect [41]. The sum score of each subtype measures the type and extent of trauma that the patient has suffered, with higher scores indicating greater severity. The Korean translation version of the CTQ has shown adequate reliability and validity among psychiatric patients (Cronbach's $\alpha = 0.88$) [42].

To evaluate psychiatric symptoms such as depressive mood, anxiety, impulsivity, and affective lability, we used the Korean versions of the Beck Depression Inventory (BDI), the State−Trait Anxiety Inventory (STAI), the Korean version of the Barratt Impulsiveness Scale-11-Revised (K-BIS-11-R), and the Affective Lability Scale-Short Form (ALS-SF). The BDI is a self-reporting examination developed to measure depression and has a high internal consistency (Cronbach's $\alpha = 0.93$) [43]. The BDI consists of 21 items. Each item's score ranges from 0 to 3, and the total score ranges from 0 to 63. Higher scores were positively correlated with a severe state of depression [44]. The STAI is a self-reporting examination developed to measure two types of anxiety. It consists of 40 items, and each item's score ranges from 1 to 4. Higher scores were positively correlated with higher levels of anxiety and this inventory has adequate reliability and validity (Cronbach's $\alpha = 0.92$) [45,46]. The BIS is a self-report questionnaire for evaluating impulsiveness, and it consists of three factors: attention impulsiveness, motor impulsiveness, and non-planning impulsiveness [47]. The K-BIS-11-R, which translated this scale into Korean, has proved its reliability and validity for impulsive evaluation (Cronbach's $\alpha = 0.78$) [48]. The ALS-SF is an 18-item questionnaire measuring rapid changes from euthymic mood to other emotional states, including mood elation, depression, and anger [49]. It has three subscale scores: anxiety/depression (ranging from 5 to 20), depression/elation (ranging from 8 to 32), and anger (ranging from 5 to 20). It has high internal consistency and appears to be a reasonable and efficient measure of affect lability (Cronbach's $\alpha = 0.90$) [50].

EEG Data Acquisition and Analysis

Subjects were seated approximately 60 cm away from the computer screen in a relaxed sitting position in a silent room. EEG was acquired using a NeuroScan SynAmps amplifier (Compumedics USA, El Paso, TX, USA) with 64 Ag/AgCl electrodes mounted on a Quik Cap. Electrodes were placed as frontal (Fz), central (Cz), and parietal (Pz), and an earth electrode was placed fronto-parietal (FPz), according to the extended 10−20 placement scheme. An electrode was placed infraorbitally to monitor the eye movement. Reference electrodes were placed at the mastoid, and the impedance was < 10 kΩ. The band-pass filter was set at 0.1−100 Hz and sampled at 1,000 Hz.

The EEG data were processed using CURRY 8 (Compumedics USA, Charlotte, NC, USA). The gross artifacts were rejected by visual inspection by a trained person. Eye movement artifacts were removed using the mathematical procedure in the preprocessing software. Data were filtered using a 0.1−30 Hz band-pass filter and epoched from 100 ms pre-stimulus to 600 ms post-stimulus. These epochs were subtracted from the average value of the pre-stimulus interval for baseline correction. If any remaining epochs continued to have significant physiological artifacts (amplitude exceeding ± 75 μV) in any of the 62 electrode sites, they were excluded from further analysis. Only artifact-free epochs were averaged across trials and participants for ERP analysis. Based on previous studies showing that Nogo ERP reflected behavioral inhibition, the present study included Nogo trials in ERP analysis.

Behavioral Task Paradigm

As stimuli for the Go/Nogo task, we applied the "oddball paradigm" of auditory stimulation. ERPs were elicited binaurally through headphones. The subjects were instructed to press the spacebar as accurately and quickly as possible when the target tone appeared, and not to respond when the non-target tone appeared. There were 400 trials, which consisted of Go (85% probability) and Nogo (15% probability) conditions. The target tone (Nogo) was 1,500 Hz, and the non-target tone (Go) was 1,000 Hz, with a 1,500 ms interval before the next trial. These stimuli were generated using the E-Prime software (Psychology Software Tools, Pittsburgh, PA, USA). In the Go/Nogo condition, N200 (the most negative peak between 150 and 350 ms after stimulus onset) and the P300 (the most positive peak between 250 and 500 ms after stimulus onset) were investigated at the Fz, FCz, Cz, and Pz electrodes. The time window we assumed during the trials was based on previous studies. To accumulate behavioral data, Go accuracy, Nogo accuracy, and reaction time were calculated based on the data from the E-prime software. Nogo accuracy was calculated to determine the false alarm rate of responses to non-target stimuli.

Source Activity Analysis

Standardized low-resolution brain electromagnetic tomography (sLORETA) was used to compute the cortical distribution of the standardized source current density of the Nogo activity. sLORETA is a representative source imaging method for solving the EEG inverse problem [51]. sLORETA assumes that the source activation of a voxel is similar to that of the surrounding voxels for calculating a particular solution, and it applies an appropriate standardization of the current density. The lead field matrix was computed using a realistic head model segment based on the Montreal Neurological Institute (MNI) 152 standard template, in which the three-dimensional solution space was restricted only to the cortical gray matter and hippocampus [52]. The solution space was composed of 6,239 voxels with a 5 mm resolution. Anatomical labels such as Brodmann areas (BAs) were provided by using an appropriate transformation from MNI to Talairach space [53]. The source images of N2 and P3 were analyzed in the Nogo condition, and the time frames used to calculate the N2 and P3 source images were defined between 150 and 350 ms and 300 and 550 ms after stimulus onset, respectively.

Statistical Analysis

To compare the differences in demographic data, clinical measurements, and behavioral task data, both groups were compared using the chi-square test for categorical variables. In the case of continuous variables, after verifying whether the normality assumption was satisfied by the Shapiro–Wilk test, the Mann–Whitney U test or independent t test was used. N2 and P3 amplitudes and latencies of patients were initially evaluated using repeated measures analysis of variance (ANOVA) with electrodes (Fz, FCz, Cz, and Pz) as the within-subject factor, groups (high CTQ vs. low CTQ) as the between-subjects factor, and age as covariates. Multivariate analysis of variance (MANOVA) with age as a covariate was used to compare the Go/Nogo ERP amplitude and latency between the groups. In addition, Spearman's correlation analysis was conducted between Go/Nogo sensors, source activities, and psychological measures. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS (version 23.0; IBM Co., Armonk, NY, USA).

RESULTS

Subjects

Table 1 presents the demographic data and clinical measurements of patients with MDD in the high and low CTQ groups. We classified 22 subjects as having MDD with high CTQ, and 22 as MDD with low CTQ. Patients in

Table 1. Demographic and clinical symptoms characteristics for all participants

Variable	High CTQ group (n = 22)	Low CTQ group (n = 22)	p value
Age (yr)	29.55 ± 10.29	24.36 ± 6.60	0.04
Sex (n)			1.00
Male	12	12	
Female	10	10	
Education (yr)	13.18 ± 1.99	13.09 ± 1.57	0.94
Total CTQ score	64.41 ± 14.43	37.36 ± 5.84	< 0.01
BDI	31.00 ± 9.81	26.09 ± 7.44	0.07
STAI state	57.36 ± 11.55	55.86 ± 13.74	0.58
STAI traits	60.23 ± 9.22	58.14 ± 13.74	0.88
ALS-SF	43.64 ± 9.40	36.23 ± 10.65	0.02
BIS	79.05 ± 9.21	77.41 ± 10.60	0.59

Values are presented as mean ± standard deviation.
CTQ, childhood trauma questionnaire; BDI, beck depression inventory; STAI, state-trait anxiety inventory; ALS-SF, affective lability scale-short form; BIS, barratt impulsiveness scale.

the high CTQ group were significantly older than those in the low CTQ group. The two groups did not differ significantly in terms of sex (p = 1.000) and education (p = 0.867). In addition, the ALS-SF score was significantly higher in the high CTQ group (p = 0.019). There were no significant differences in BDI, STAI state, STAT trait, or BIS between the groups.

Behavioral Outcomes

Table 2 presents the Nogo N2 and P3 behavioral

Table 2. Comparison of behavioral outcomes

Variable	High CTQ group (n = 22)	Low CTQ group (n = 22)	p value
Go accuracy (%)	93.18 ± 12.65	98.95 ± 2.17	0.05
Nogo accuracy (%)	92.77 ± 11.74	95.68 ± 6.95	0.32
False alarm rate (%)	7.23 ± 11.74	4.32 ± 11.74	0.32
Reaction time (ms)	501.00 ± 113.03	460.90 ± 63.45	0.16

Values are presented as mean ± standard deviation.
CTQ, childhood trauma questionnaire.

Table 3. Comparison of the amplitudes and latencies in Nogo condition

Variable	High CTQ group (n = 22)	Low CTQ group (n = 22)	p value
Amplitude (μV)			
N2 Fz	−8.23 ± 4.55	−8.55 ± 6.15	0.98
N2 FCz	−8.51 ± 5.22	−8.69 ± 6.25	0.94
N2 Cz	−7.51 ± 4.95	−6.40 ± 6.61	0.63
N2 Pz	−4.06 ± 3.29	−3.83 ± 5.75	0.95
P3 Fz	5.43 ± 3.68	10.90 ± 7.14	< 0.01
P3 FCz	6.77 ± 3.94	12.75 ± 7.74	< 0.01
P3 Cz	7.30 ± 4.34	13.34 ± 7.71	< 0.01
P3 Pz	8.02 ± 4.22	13.42 ± 6.18	< 0.01
Latency (ms)			
N2 Fz	257.14 ± 20.54	250.36 ± 18.26	0.54
N2 FCz	255.05 ± 20.06	245.41 ± 13.42	0.28
N2 Cz	253.27 ± 16.12	248.86 ± 13.09	0.75
N2 Pz	253.14 ± 23.90	246.55 ± 20.24	0.38
P3 Fz	371.27 ± 31.24	366.36 ± 28.54	0.74
P3 FCz	366.55 ± 29.86	365.23 ± 28.85	0.85
P3 Cz	368.59 ± 31.25	369.41 ± 26.80	0.71
P3 Pz	377.18 ± 27.82	372.23 ± 33.70	0.96

Values are presented as mean ± standard deviation.
CTQ, childhood trauma questionnaire; Fz, frontal; Cz, central; Pz, parietal; FCz, fronto-central.

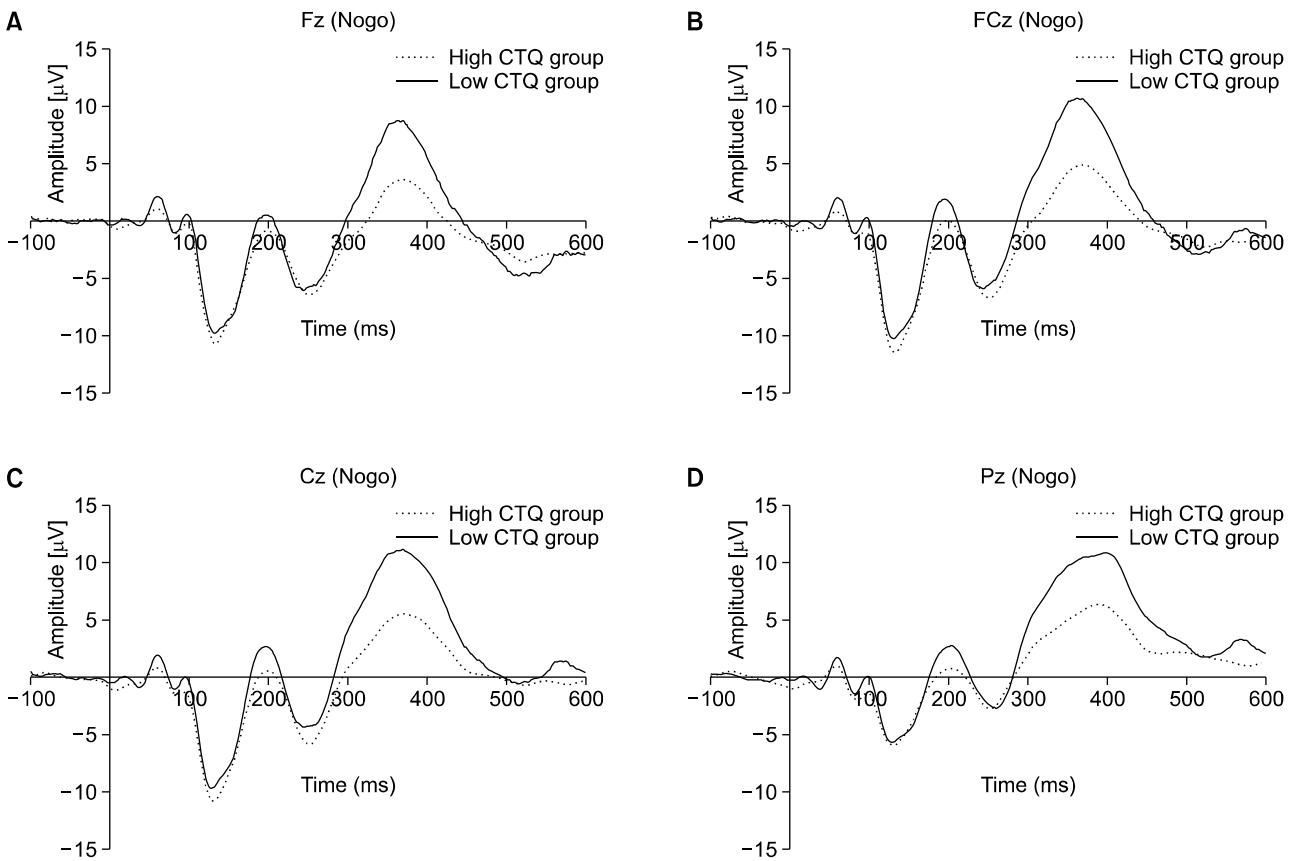

Fig. 1. Comparison of the amplitudes and latencies in Nogo condition. Grand average of P3 at the Fz (A), FCz (B), Cz (C), and Pz (D) electrodes for the low and high CTQ groups.
CTQ, childhood trauma questionnaire; Fz, frontal; Cz, central; Pz, parietal; FCz, fronto-central.

outcomes. Go accuracy was significantly low in the high CTQ group. There were no significant differences in other behavioral outcomes between the two groups.

Event-related Potentials

Amplitude and latency

As there were no group differences in the latencies of the N2 and P3 components in the Nogo condition, the following analysis focused on the amplitude of each component. In the N2 amplitude, there was no significant difference between the two groups (F = 0.016, df = 1, p = 0.901). In the P3 amplitude, there was a significant main effect of group (F = 10.967, df = 1, p = 0.002). The main effects of the electrode site were significant (F = 9.958, df = 3, $p < 0.001$). Table 3 presents the amplitude and latency data for Nogo N2 and P3. The high CTQ group showed significantly low amplitudes in Nogo P3 at all electrodes (Fz, p = 0.003; FCz, p = 0.002; Cz, p = 0.003; Pz, p = 0.002) (Table 3, Fig. 1).

Correlations

In the correlation analysis between the clinical measurements and ERP data for all participants, Nogo P3 amplitudes at the FCz and Pz were negatively correlated with the total CTQ score (r = −0.321, p = 0.034; r = −0.349, p = 0.020, respectively). There was also a negative tendency between other Nogo P3 amplitudes and the total CTQ score (Fz, r = −0.296, p = 0.051; Cz, r = −0.287, p = 0.059) (Fig. 2).

Source P300 of Nogo condition

Source analysis of the Nogo P3 revealed decreased source densities of the cuneus (BA 18), posterior cingulate (BA 31), precuneus (BA 31), supramarginal gyrus (BA 40), and lingual gyrus (BA 18) in the high CTQ group ($p < 0.01$; Fig. 3) compared to the low CTQ group. Detailed information on the statistical values and voxel coordinates is provided in Table 4.

DISCUSSION

This study investigated Nogo ERP amplitudes and latencies during tasks in patients with MDD with or without a history of severe trauma. As hypothesized, the high CTQ group showed significantly attenuated Nogo ERP amplitudes in the present study. First, the high CTQ groups showed significantly decreased Nogo P3 amplitudes at all electrodes. Second, Nogo P3 amplitudes in the frontocentral and parietal electrodes were negatively correlated with the severity of childhood trauma. Third, the source activity of the significantly different Nogo P3 amplitudes was shown to be reduced in the region associated with these electrodes.

As expected, depressed patients with higher childhood trauma had decreased Nogo P3 amplitudes in all electrodes. Additionally, the higher the severity of childhood trauma, the lower the Nogo P3 amplitudes at the

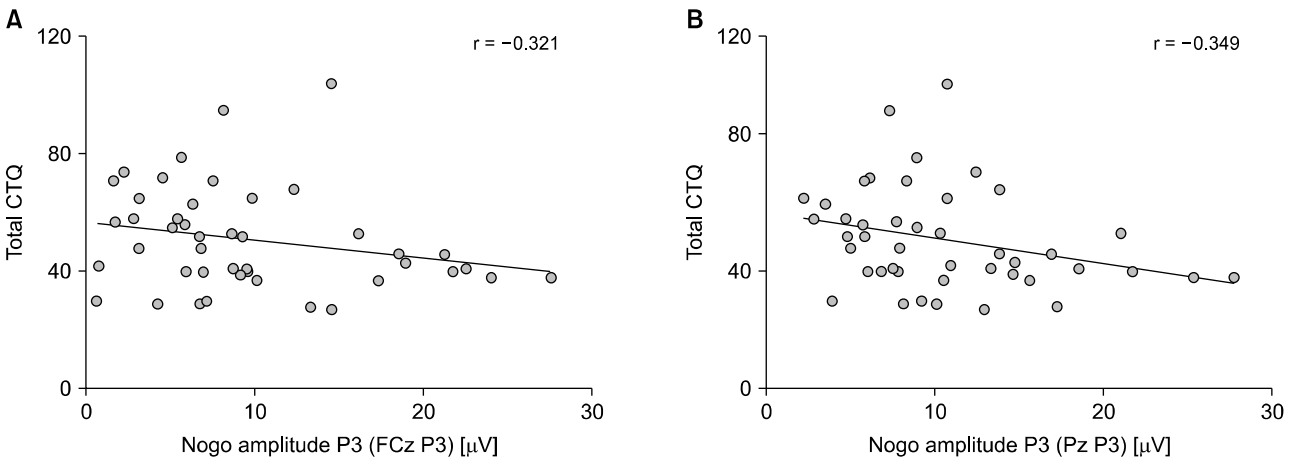

Fig. 2. The correlation between electrodes with total CTQ scores in all paticipants. Nogo P3 amplitudes at the FCz (A) and Pz (B) electrodes were negatively correlated with the total CTQ score.
CTQ, childhood trauma questionnaire; Pz, parietal; FCz, fronto-central.

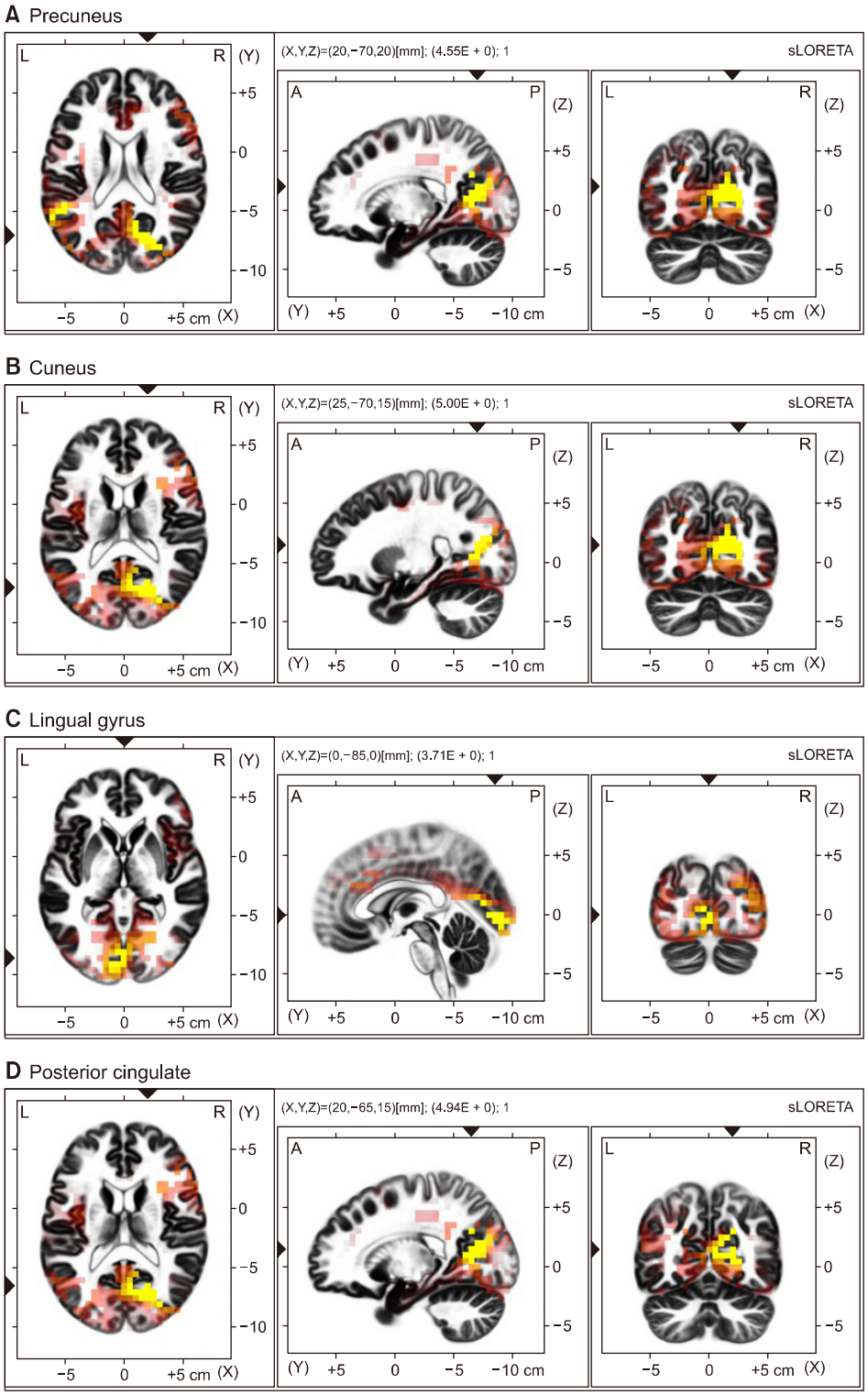

Fig. 3. Differences in the source activity of the Nogo P3 activity between high and low CTQ group in the precuneus (A), cuneus (B), lingual gyrus (C), posterior cingulate (D) and supramarginal gyrus (E). The yellow color highlights the significant difference of the source activity of the Nogo P3 in the high CTQ group.
CTQ, childhood trauma questionnaire.

frontocentral and parietal electrodes in the present study. The attenuation of Nogo P3 amplitudes is known to be related to behavioral disinhibition or impulsivity in many psychiatric diseases [34,37,54,55]. Our results are consistent with those of previous studies that included various populations of depression patients with a reduced Nogo P3 amplitude, which impairs inhibitory control [54,56]. Considering that the participants with childhood trauma

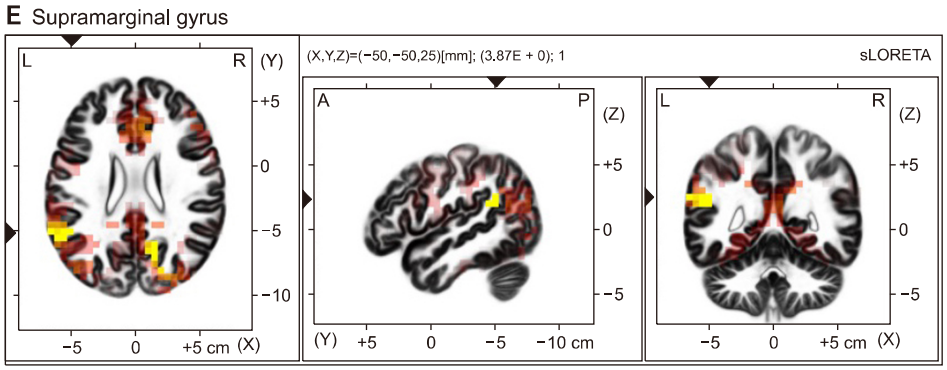

Fig. 3. Continued.

Table 4. Brain regions showing significant differences of Nogo P3 source activity between low and high CTQ groups

ROI (structure)	Brodmann area	MNI coordinates			Talairach coordinates			t
		X	Y	Z	X	Y	Z	
Cuneus	18	25	−70	15	25	−67	17	−5.05[a]
Posterior cingulate	31	20	−65	15	20	−62	17	−4.88[a]
Precuneus	31	20	−70	20	20	−67	22	−4.62[a]
Supramarginal gyrus	40	−50	−50	25	−50	−47	25	−4.11[a]
Lingual gyrus	18	0	−85	0	0	−82	4	−3.92[a]

CTQ, childhood trauma questionnaire; ROI, region of interest; MNI, montreal neurological institute.
[a]$p < 0.01$.

seem to have difficulties in impulse control and behavioral inhibition compared to those without trauma [11], our results that the high CTQ group had attenuated Nogo P3 amplitudes might be plausible.

Surprisingly, there was no significant difference in BIS between the high and low CTQ groups. This might be due to the bias of self-report scales, or it might not have fully reflected our patients' impulsivity. Unexpectedly, there was no difference in the performances of Go/Nogo tasks between the two groups, excluding Go accuracy. No difference in the performances of Go/Nogo tasks might be caused by task difficulties [57]. Our Nogo tasks were too easy to differentiate performance, reflecting behavioral disinhibition between the high and low CTQ groups. ERP also reflects the high-order cognitive function of the behavioral control such as neural representation or task demands [58], so it may reflect more fundamental deficit of the behavioral control than the behavioral data itself. Although the difference was not statistically significant, the false alarm rate of the high CTQ group was higher than that of the low CTQ group.

Interestingly, the high CTQ group had significantly higher ALS scores in this study. These results imply that depressed patients with high CTQ experience more affective dysregulation. The results were consistent with previous studies showing that higher childhood trauma can contribute to the development of emotional dysregulation [59-61]. It can be inferred that such affective dysregulation is associated with interpersonal trauma and post-traumatic stress [59]. Brain systems related to emotional regulation are shaped by early experience and reflect developmental history. Therefore, it is possible that early life adversity changes perceptual and cognitive appraisals related to threat [62]. As behavioral inhibition could be one of the phenotypes of emotional dysregulation, Nogo P3 might also reflect the affective lability or emotional regulation related to poor impulse control, although the ALS score was not correlated with Nogo P3 ERP in the present study. In addition, when children with ADHD are exposed to negative emotional situations, there is an increased need for top-down inhibitory control, which is reflected by the change in Nogo P3 amplitude [63]. Patients with affective lability similarly showed attenuation of the Nogo P3 amplitude [34,55]. In this regard, the reduction in the Nogo P3 amplitudes in the present study might reflect the inhibitory process of emotions in patients with depression who had suffered childhood trauma. Moreover, patients with affective lability similarly showed attenu-

ation of the Nogo P3 amplitude [34,55]. It may be inferred that the high CTQ groups had more affective lability due to impairment of this process. Because there was no significant correlation between ALS and Nogo ERP in the study, the above speculation should be supported by further studies.

In this study, depressed patients with high CTQ showed significantly decreased Nogo P3 source activities compared to those with low CTQ in the cuneus, posterior cingulate, precuneus, supramarginal gyrus, and lingual gyrus. The results also support our suggestion that depressed patients with severe trauma might have difficulty in inhibitory deficits. The lingual gyrus is one of the activated regions in error processing, inhibition function, and divergent thinking in healthy control studies [64,65]. The gray matter volume of the cuneus is positively correlated with the inhibitory control [66] and the reduced volume of the precuneus is associated with higher impulsive sensitivity [67]. The posterior cingulate is also associated with response inhibition [65,68], and the decreased volume or functional connectivity of this region is related to higher impulsivity [69,70]. It is noteworthy that the posterior cingulate and precuneus are part of the hub region of the default mode network (DMN) [71]. Many previous studies have pointed out that childhood trauma history might be linked to altered network connectivity, including the DMN [39,72,73]. Although our study has not been conducted in the resting state, some studies conducted with tasks associated with executive function and working memory also found altered DMN activation in groups with higher early life stress [73]. Decreased activity in these regions is associated with inferior performance during cognitive tasks [74,75]. This suggests that the severity of childhood trauma might affect the activation of default mode networks such as the posterior cingulate and precuneus in the present study. Moreover, considering that the posterior cingulate is engaged in various cognitive functions such as learning, memory, and reward [76], childhood trauma might affect efficient network connectivity, leading to impaired cognitive functions. The supramarginal gyrus is widely known to contribute to phonological word processing and auditory working memory [77-81]. Considering that our Go/Nogo paradigm has a task with auditory stimuli, deactivation of the supramarginal gyrus might affect impaired response inhibition by the dysfunctional auditory working memory process. This suggests that the attenuated Nogo P3 amplitude and the neural activity of the relevant region might reflect a reduced cognitive efficiency for impulse control in depression with childhood trauma. That is, early childhood trauma leads to chronic stress, which might affect brain function and efficiency to regulate emotional response [82-84]. Considering the functions of the supramarginal gyrus and the precuneus, our study noted the role of parietal lobe related to the difficulty in behavioral inhibition shown frequently in patients with childhood trauma. The finding in present study that there was significantly negative correlation between the total CTQ and Nogo P3 amplitude at Pz also supports our point. In previous studies, childhood trauma was highly associated with decreased frontal lobe activity measured by Nogo P3, which might reflect poor cognitive control in the group with severe trauma [36,37]. Unexpectedly, there was no difference in frontal lobe activity between MDD patients with high and low CTQ in the present study. This might be due to the fact that both the groups were suffering from depression at the time of the study. Many studies have reported that patients with depression show frontal lobe dysfunction and alterations in frontal lobe activity [85-88]. Therefore, it could be assumed that the difference in frontal lobe activity affected by childhood trauma might not be very statistically significant in this study.

This study had several limitations. First, the results were obtained with relatively few participants compared to other studies. Future studies should include more participants to verify the present results. Second, both groups were not matched for age, although we controlled this mismatch by the variable as a covariate in MANOVA. Third, comorbidities such as anxiety disorder and ADHD in each patient were not sufficiently considered. These diseases have a high coexistence rate with MDD in clinical practice, and therefore, it is difficult to completely exclude them. However, other major psychiatric disorders were part of the exclusion criteria. Further studies to consider comorbidities are necessary. Finally, since our study mainly used self-reporting scales in psychological assessment, it is possible that the measurements of the present study did not fully reflect the objective clinical data of the participants.

Despite these limitations, this study might be worthwhile, as this is the first attempt, to the best of our knowledge, to explore whether Nogo ERPs differ between pa-

tients with MDD who experience very severe trauma and those who experience less severe trauma. Furthermore, the attenuated Nogo P3 amplitudes in depressed patients with high childhood trauma might reflect inhibitory dysfunction and emotional dysregulation in patients with higher early life stress. In particular, our source activity analysis also showed deactivated regions related to childhood trauma and poor inhibitory function. This suggests the possibility of using Nogo ERP as a biomarker to determine whether a patient with depression has suffered severe trauma. It is necessary to examine whether our findings will be applicable to a large sample size in future studies.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: In Soo Heo, Se-Hoon Shim, Ji Sun Kim. Data acquisition: In Soo Heo. Formal analysis: In Soo Heo, Hee-Jung Yoon. Funding: Young Joon Kwon, Hwa-Young Lee, Se-Hoon Shim, Ji Sun Kim. Supervision: Young Joon Kwon, Hwa-Young Lee, Ho Sung Lee, Se-Hoon Shim, Ji Sun Kim. Writing－original draft: In Soo Heo. Writing－review & editing: In Soo Heo, Se-Hoon Shim, Ji Sun Kim.

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