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Increased Error-Related Brain Activity in Adolescents with Obsessive-Compulsive Disorder and Major Depressive Disorder

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Abstract

Background: The error-related negativity (ERN) is a negative deflection in the event-related potential following a mistake that is often increased in patients with obsessive-compulsive disorder (OCD). The relationship of the ERN to comorbid major depressive disorder (MDD) has not been examined in adolescents with OCD. This study compared ERN amplitudes in OCD patients with MDD (OCD+MDD), OCD patients without MDD (OCD-MDD), MDD patients, and healthy controls (HC).

Method: The ERN, correct response negativity, and accuracy were measured during a flanker task to assess performance monitoring in 53 adolescents with a lifetime diagnosis of OCD, 36 adolescents with a lifetime diagnosis of MDD, and 89 matched HC ages 13 to 18 years. Fourteen OCD patients had a history of MDD.

Results: ERN amplitude was significantly increased in OCD patients compared to HC and significantly correlated in OCD patients with age at OCD symptom onset, particularly in the OCD-MDD patients. The ERN was significantly enlarged in OCD+MDD patients compared to HC, but not in MDD patients compared to HC. There was a trend for an increased ERN amplitude in OCD-MDD patients compared to HC. OCD patients were significantly less accurate than either MDD patients or HC.

Conclusions: An enlarged ERN is a neural correlate of adolescent OCD that is associated with age at OCD symptom onset. Adolescents with OCD may have impaired cognitive

control on a flanker task. Follow-up studies with larger samples may determine whether an enlarged ERN in adolescents with OCD is associated with a higher risk for MDD.

Increased Error-Related Brain Activity in Adolescents with Obsessive-Compulsive Disorder and Major Depressive Disorder

1 | INTRODUCTION

Major depressive disorder (MDD) is the mood disorder most frequently associated with obsessive-compulsive disorder (OCD) (Ruscio, Stein, Chiu, & Kessler, 2010). In youth with OCD, adolescents had a six-fold greater likelihood of a comorbid depressive disorder than their younger counterparts (Peris et al., 2017). The findings are consistent with longitudinal studies in which depression onset appears to peak between the ages of 15 and 18, especially among females (Hankin et al., 1998). Twin and family studies indicate the overlap between OCD and MDD in adolescents is primarily due to shared genetic factors (Bolhuis et al., 2014; Hanna et al., 2011). However, a putative biomarker for OCD has not been examined in youth with OCD and MDD.

The error-related negativity (ERN or Ne) is a negative deflection in the response-locked event-related potential that peaks within 80 ms after an erroneous response (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring et al., 1993). The ERN appears to reflect the activity of a system that detects errors, increases cognitive control, and adjusts behaviors (Gehring, Liu, Orr, & Carp, 2012). The ERN has a heritability of 47%,

indicating it may serve as an endophenotype in genetic studies of psychopathology (Anokhin, Golosheykin, & Heath, 2008). The ERN is a unit of measurement in the Research Domain Criteria (RDoC) matrix in three different domains and constructs: cognitive systems (cognitive control), negative valence systems (sustained threat), and positive valence systems (reward learning) (Weinberg, Dieterich, & Riesel, 2015). Its placement in those domains suggests it can reflect interactions between cognitive and motivational factors.

Increased ERN amplitudes have been found in most studies of OCD patients using tasks eliciting response conflict (Endrass, & Ullsperger, 2014). An enlarged ERN has been detected in unaffected first-degree relatives of OCD probands, demonstrating that overactive performance monitoring may occur in relatives at risk for developing OCD (Carrasco et al., 2013; Riesel, Endrass, Kaufmann, & Kathmann, 2011). Most studies reporting an enhanced ERN in OCD patients have detected no association between the ERN and OCD symptom severity (Riesel, Endrass, Auerbach, & Kathmann, 2015). Those observations suggest the ERN is a state-independent measure that may serve as a biomarker or endophenotype for OCD (Weinberg, Dieterich, & Riesel, 2015). In a study finding decreased accuracy but an enlarged ERN in youth with OCD, the ERN was more strongly associated with Child Behavior Checklist/6-18 (CBCL/6-18) Withdrawn/Depressed Scale scores than with a lifetime diagnosis of OCD, suggesting that MDD symptoms may account for a significant portion of the ERN variance in OCD patients (Achenbach, & Rescorla, 2001; Hanna et al., 2016). However, in studies of MDD patients, ERN amplitudes have been increased (Aarts et al., 2013; Chiu & Deldin, 2007; Tang et al., 2013), decreased (Ladouceur et al., 2012;

Schrijvers et al., 2007), or similar to those of healthy controls (HC) (Olvet, Klein, & Hajcak, 2010; Schrijvers et al., 2009).

Because the relationship of the ERN to comorbid MDD has not been examined in youth with OCD, the following study was conducted in 53 adolescents with a lifetime diagnosis of OCD, 36 adolescents with a lifetime diagnosis of MDD, and 89 age-matchedHC. Fourteen OCD patients had a history of MDD. The first aim was to compare accuracy and ERN amplitudes in OCD patients, MDD patients, and HC, followed by similar comparisons in OCD patients with MDD (OCD+MDD), OCD patients without MDD (OCD-MDD), MDD patients, and HC. The second aim was to examine the relationship of the ERN to the CBCL Problem Scales in patients and HC. The CBCL/6-18 *DSM*-Oriented Scales (DOS) were used in this analysis because they may more clearly differentiate affective from anxiety symptoms than the CBCL/6-18 Syndrome Scales (Spatola et al., 2007).

2 | MATERIALS AND METHODS

2.1 | Participants

OCD and MDD patients were recruited from the Department of Psychiatry at the University of Michigan and surrounding community. HC were recruited from the surrounding community and matched to patients by age and sex. Participants or their parents gave written informed consent in accordance with the Declaration of Helsinki. All tasks and procedures were approved by the University of Michigan Medical School Institutional Review Board. Participants were paid for their interviews and psychophysiological recordings. Some participants were excluded based on poor electroencephalographic data ($n = 2$) or

commission of fewer than 10 errors (n = 15), leaving a total of 178 participants. The final sample consisted of 41 males and 137 females ages 13 to 18 years, with an ethnic and racial breakdown that was 91% Caucasian, 2% Black, 4% Latino, 1% Asian, and 2% Native American.

The 89 patients had a lifetime diagnosis of OCD without MDD (OCD-MDD) (n = 39), a lifetime diagnosis of MDD without OCD (MDD) (n = 36), or lifetime diagnoses of both disorders (OCD+MDD) (n = 14). Patients were excluded if they had a lifetime diagnosis of schizophrenia, bipolar disorder, substance-related disorder, or anorexia nervosa. All 89 HC had no history of a specific axis I disorder. Lifetime and current axis I diagnoses were made independently by two clinicians using all sources of information according to *DSM-5* criteria (American Psychiatric Association, 2013). Participants were excluded if they had a history of intellectual disability, head injury with loss of consciousness, chronic neurological disorder, or scores higher than 14 on the Social Communication Questionnaire (SCQ; Berument et al., 1999). Tables 1 and 2 summarize the demographic, clinical, behavioral, and event-related brain potential data for the participants. Because studies have found that treatment with a selective serotonin reuptake inhibitor (SSRI) has no effect on the ERN, 36 patients were enrolled taking a stable dose of an SSRI but no other psychotropic medications (Stern et al., 2010).

2.2 | Measures

All 178 participants were interviewed with the Schedule for Schizophrenia and Affective Disorders for School-Aged Children-Present and Lifetime Version (Kaufman et al., 1997) and Schedule for Obsessive-Compulsive and Other Behavioral Syndromes (Hanna,

2013). The maximum and current severity of OCD symptoms was assessed with the Children's Yale-Brown Obsessive Compulsive Disorder Scale (CY-BOCS; Scahill et al., 1997). Parents completed the CBCL/6-18 (Achenbach, & Rescorla, 2001) and SCQ (Berument et al., 1999) about their children.

2.3 | Stimulus material and task procedures

Participants performed an arrow version of the flanker task in which arrows appeared on a computer display with congruent (e.g., →→→→→) and incongruent (e.g., →→←→→) conditions (Eriksen, & Eriksen, 1974). They were instructed to respond by pressing one of two buttons indicating the direction of the central arrow (i.e., right versus left), while ignoring the adjacent arrows, and to respond as quickly and accurately as possible, placing equal emphasis on speed and accuracy. The stimuli remained on the screen for 250 ms, with an interval of 1,500 ms between consecutive stimuli. Each participant was seated 0.65 meters directly in front of the computer monitor. Following 32 practice trials, each subject completed 8 blocks of 64 trials with the number of completed trials ranging from 256 to 512. Performance feedback was provided after every block to yield an error rate of approximately 10%, with encouragement to focus on speed if there were fewer than four errors or to focus on accuracy if there were more than ten errors (Hanna et al., 2016).

2.4 | Electrophysiological recording and data reduction

The EEG was recorded from DC-104 Hz with 64 Ag/AgCl scalp electrodes, two mastoid electrodes, and two vertical and two horizontal electro-oculogram electrodes, using the BioSemi ActiveTwo system. Data were digitized at 512 Hz, referenced to a ground

formed from a common mode sense active electrode and driven right leg passive electrode (see http://www.biosemi.com/faq/cms&drl.htm), and re-referenced offline to the average of the two mastoid electrodes. Data were band-pass filtered 0.1-30Hz using zero-phase shift filters. EEG data were screened using automated algorithms that rejected epochs in which absolute voltage exceeded 500 μV and epochs containing peak to peak activity greater than 500 μV within 200 ms, with a 100msec moving window, for midline channels (Fz, FCz, Cz, CPz, Pz). Ocular movement artifacts were then corrected using a regression-based algorithm (Gratton, Coles, & Donchin, 1983). After ocular correction, individual trials were rejected if they contained absolute amplitudes greater than 100 μV, a change greater than 50 μV measured from one data point to the next point, or a maximum voltage difference less than 0.5 μV within a trial in any of the midline electrodes.

Behavioral measures included the number of erroneous and correct trials for each subject, as well as accuracy expressed as a percentage of valid trials. Mean reaction times on error and correct trials were calculated separately, and trials were excluded if their reaction times were more than 3 standard deviations from the mean. Reaction time and accuracy after errors were evaluated to determine if there were group differences in post-error behavioral adjustments (Gehring, Liu, Orr, & Carp, 2012). Reaction times were analyzed with group as a between-subject factor and response type as a within-subject factor. The mean number of errors per subject contributing to the analysis was 41.9 (SD = 22.6; range = 10 to 133).

The ERN was quantified using mean amplitude measures relative to a pre-response baseline -200 to -50 msec. The mean amplitude of the ERN was computed on incorrect response trials in a window from 0 to 80 ms following the incorrect response. The correct

response negativity (CRN) consisted of the same measure computed on correct response trials. The ΔERN was calculated by subtracting the CRN from the ERN because it may isolate activity unique to error processing from activity more broadly related to response monitoring (Gehring, Liu, Orr, & Carp, 2012). Amplitudes were calculated for electrodes FCz, Cz, and CPz; however, the focus of the data presented herein is the ERN at Cz because prior studies have found larger group differences at that electrode (Hanna et al., 2016).

2.5 | Statistical analyses

Student *t*-tests or χ^2 tests were used to evaluate group differences in demographic data. Pearson correlation coefficients were used to examine associations of response-related amplitudes with age, behavioral measures, and clinical measures. Clinical and behavioral data were analyzed using an analysis of covariance (ANCOVA) with group (OCD patients, MDD patients, HC) as a between-subject factor and age as a covariate. Electrocortical indicators (ERN, CRN) of performance monitoring were analyzed separately using a repeated-measure ANCOVA with group (OCD patients, MDD patients, HC) as a between-subject factor and response type (correct, error) as a within-subject factor and with age and accuracy as covariates (Gehring, Liu, Orr, & Carp, 2012). These analyses were repeated to examine performance monitoring in OCD patients with and without MDD. Analyses were performed with JMP Version 12 software. All tests were two-tailed with $\alpha = 0.05$.

3 | RESULTS

3.1 | Behavioral data in OCD patients, MDD patients, and healthy controls

Participants were significantly more accurate on congruent than incongruent trials (paired t (117) = 26.64, $P < .0001$). HC and MDD patients were significantly more accurate than OCD patients on all trials (Table 1). There were no significant group differences in reaction time during correct or incorrect trials or in post-error slowing. Correct responses were significantly slower than incorrect responses, paired t (117) = 9.72, $P < .0001$. No main effect of group and no interaction between group and response type for reaction time reached significance ($P = .20$ and $P = .24$, respectively). Age in all subjects had significant negative correlations with reaction time on correct ($r = -.22$, $P = .003$) and incorrect trials ($r = -.15$, $P = .04$), but had no significant correlation with post-error slowing ($P = .76$). Age in all subjects had no significant correlations with accuracy, post-correct accuracy, post-error accuracy, or post-error slowing (all P values > .2). There were no significant sex differences in accuracy, post-correct accuracy, post-error accuracy, or post-error slowing (all P values > .2). Medication status was not significantly associated with accuracy in patients (all P values > .4).

3.2 | Event-related potential data in OCD patients, MDD patients, and healthy controls

Age in all participants had a significant correlation with CRN amplitudes ($r = .21$, $P = .005$), but not with ERN amplitudes ($P = .43$), indicating that smaller (less negative) CRN amplitudes were associated with increasing age. Accuracy in all participants had a significant correlation with the ERN ($r = -.24$, $P = .002$), but not with the CRN ($P = .15$). ERN amplitudes in all participants had no significant correlations with reaction times on either correct or incorrect trials or with post-error slowing (all P values > .4). CRN amplitudes had significant correlations in all subjects with reaction times on correct ($r = -.33$, $p < .0001$) and

incorrect trials (r = -.38, P < .0001), but not with post-error slowing (P = .11). There were no significant sex differences in any brain potentials (all P values > .19).

In a comparison of ERN amplitudes in the three groups, there was a significant group effect, F (2, 173) = 3.69, P = .027, with a significant effect for accuracy, F (1, 173) = 14.54, P = .0002, but not for age, P = .46 (Table 1; Figure 1). The ERN was significantly enlarged in OCD patients compared to HC, F (1, 138) = 7.82, P = .006, Cohen's d = 0.27. ERN amplitudes were not significantly different either between OCD patients and MDD patients (P = .17) or MDD patients and HC (P = .49). In a comparison of CRN amplitudes in the three groups, there was no significant group effect (P = .73).

3.3 | Even-related potential data in OCD+MDD patients, OCD-MDD patients, MDD patients, and healthy controls

In a comparison of ERN amplitudes in the four groups, there was a significant group effect, F (3, 172) = 2.98, P = .033, with a significant effect for accuracy, F (1, 172) = 13.51, P = .0003, but not for age, P = .61 (Table 2; Figure 2). The ERN was significantly enlarged in OCD+MDD patients compared to HC, F (1, 99) = 6.71, P = .011, Cohen's d = 0.60. There were trends for an enhanced ERN in both OCD+MDD patients compared to MDD patients, F (1, 46) = 3.70, P = .06, and OCD-MDD patients compared to HC, F (1, 124) = 3.40, P = .07, Cohen's d = 0.14. The ERN was not significantly enlarged in either OCD+MDD patients compared to OCD-MDD patients (P = .18) or OCD-MDD patients compared to MDD patients (P = .84). In a comparison of CRN amplitudes in the four groups, there was no significant group effect (P = .69).

3.4 | Clinical and event-related potential data in OCD patients, MDD patients, and healthy controls

There were no significant differences in any brain potentials between patients with a current diagnosis of OCD and those with a past diagnosis of OCD (all *P* values > .2). There were no significant correlations in OCD patients between any brain potentials and either current or maximum CY-BOCS scores (all *P* values > .3). The ERN had a significant correlation with age at onset of OCD symptoms in OCD patients ($r = .29$, $P = .04$), indicating that larger (more negative) ERN amplitudes were associated with an earlier onset. The age at onset correlation was significant in OCD-MDD patients ($r = .43$, $P = .007$), but not in OCD+MDD patients ($r = -.22$, $P = .46$). The ERN had a significant correlation with CBCL/6-18 Anxiety Problems scores in the total sample ($r = -.27$, $P = .0003$) (Table 3). The correlation was significant in OCD patients ($r = -.46$, $P = .006$), but not in MDD patients ($P = .12$) or HC ($P = .98$), indicating that larger (more negative) ERN amplitudes were associated with more severe anxiety symptoms in OCD patients but not in MDD patients or HC. The ERN had a significant correlation with CBCL/6-18 Affective Problems scores in the total sample ($r = -.15$, $P = .04$), but not in the three groups considered separately (all *P* values > .1). Accuracy had a significant correlation with CBCL/6-18 Anxiety Problems scores in OCD patients ($r = .35$, $P = .013$), but not in MDD patients ($P = .29$) or HC ($P = .19$).

4 | DISCUSSION

Consistent with previous studies of performance monitoring, we found an enlarged ERN in adolescents with OCD compared to HC during a task eliciting response conflict (Endrass, & Ullsperger, 2014). The enlarged ERN was demonstrated at electrodes Cz and

CPz but not at FCz, suggesting that error-related brain activity is localized more posteriorly in adolescents with OCD than in HC. Consistent with a previous study of youth ages 10 to 19 (Hanna et al., 2012), a larger (more negative) ERN in adolescents with OCD was associated with an earlier age at OCD symptom onset; however, that correlation remained significant in OCD-MDD patients but not in OCD+MDD patients. As in most studies of the ERN in OCD, there was no association between the ERN and OCD symptom severity as measured by either the CY-BOCS or current diagnostic status (Weinberg, Dieterich, & Riesel, 2015). However, the ERN had a significant correlation with CBCL/6-18 Anxious Problems scores in OCD patients but not in MDD patients or HC, indicating that non-OCD anxiety symptoms may account for a significant portion of the ERN variance in OCD patients and perhaps parallel the anxious arousal noted in the RDoC sustained threat construct (Weinberg, Dieterich, & Riesel, 2015).

The ERN was significantly enlarged in OCD+MDD patients compared to HC, whereas there was a trend for a larger ERN in OCD-MDD patients compared to HC. The ERN increase in OCD+MDD patients is consistent with the hypothesis that the ERN is associated with the anhedonic and avoidant behaviors described in the RDoC sustained threat construct (Hanna et al., 2016). It is possible that the enlarged ERN in OCD+MDD patients is at least partially due to genetic factors shared by both disorders (Bolhuis et al., 2014). Follow-up studies with larger samples may determine whether an enlarged ERN in adolescents with OCD is associated with a higher risk for MDD (Peris et al., 2017).

ERN amplitudes were not significantly different either between MDD patients and HC or OCD and MDD patients. The lack of a significant difference in the ERN between

MDD patients and HC is consistent with some studies of the ERN in adults with MDD (Olvet, Klein, & Hajcak, 2010; Schrijvers et al., 2009). However, a previous study requiring at least 20 error trials for each participant found significantly decreased ERN amplitudes in youth with MDD compared to HC (Ladouceur et al., 2012). We repeated our analyses using 32 MDD patients and 75 HC each with at least 20 errors trials, but found no significant group difference in the ERN (data not shown).

In contrast to studies observing fewer errors in adults with OCD (Riesel, Endrass, Auerbach, & Kathmann, 2015; Riesel, Endrass, Kaufmann, & Kathmann, 2011), we found that adolescents with OCD were less accurate than either HC or MDD patients. Our previous study also found that OCD patients ages 8 to 18 were less accurate than HC (Hanna et al., 2016), indicating that youth with OCD have impaired cognitive control on a flanker task. However, accuracy in OCD patients still had a significant negative correlation with the ERN in the present study, becoming larger (more negative) as accuracy improved. Accuracy had a significant positive correlation with CBCL/6-18 Anxiety Problems scores in OCD patients, but not in MDD patients or HC, indicating that more severe anxiety symptoms did not interfere necessarily with task performance in OCD patients. A meta-analysis found no noteworthy neuropsychological deficits in youth with OCD, although a flanker task was not included in those tests (Abramovitch et al., 2015). Given our findings in OCD+MDD patients, it is possible that cognitive control deficits coupled with increased sensitivity to sustained endogenous threat may be associated with more severe depressive symptoms in adolescents with OCD (Weinberg et al., 2016).

Our study has limitations requiring further consideration. The MDD group was significantly older than the OCD-MDD group. Moreover, the number of OCD and MDD patients was low, so the findings regarding accuracy and the ERN require replication in studies with larger samples and broader age ranges. Treatment was not controlled; nonetheless, there is no evidence that either cognitive-behavior therapy or SSRI treatment alter ERN amplitudes (Kujawa et al., 2016). The MDD group was necessary to assess the specificity of an enlarged ERN in the OCD+MDD group and is a notable strength of the study.

5 | CONCLUSION

Our study provides evidence that an enlarged ERN is a neural correlate of adolescent OCD that is related to age at OCD symptom onset. Despite having an enlarged ERN, OCD patients were less accurate than either MDD patients or HC indicating that adolescents with OCD may have impaired cognitive control on a flanker task (Hanna et al., 2016). The relationship between the ERN and risk for MDD warrants further research in youth with OCD, as it may provide a better understanding of the pathogenesis of both disorders and lead to new prevention and treatment strategies (Peris et al., 2017).

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TABLE 1. Demographic, clinical, behavioral, and brain potential data in OCD patients, MDD patients, and healthy controls

Variable	Comparisons of OCD, MDD, and HC groups		OCD group *n* = 53 Mean (SD)	MDD group *n* = 36 Mean (SD)	HC group *n* =89 Mean (SD)
	Test Statistic	*P*			
Demographic and Clinical Data					
Age (years)			15.9 (1.8)†	16.8 (1.4)	16.2 (1.8)
	F (2, 175) = 2.92	.056			
Sex (M/F)			14 / 39	7 / 29	20 / 69
	χ^2 (2) = 0.62	.73			
SSRI (treatment/no treatment)			25 / 28	11 / 25	
	χ^2 (1) = 2.46	.12			
Child Behavior Checklist					
Obsessive-Compulsive Problems			5.5 (3.7)***††††	3.0 (2.4)***	0.9 (1.0)
	F (2, 174) = 60.7	<.0001			
Total score			33.3 (23.7)***	41.0 (27.8)***	8.6 (9.3)
	F (2, 174) = 49.0	<.0001			

Internalizing score	13.3 (9.6)***†	17.1 (10.5)***	3.2	(3.2)	F (2, 174) = 57.5 <.0001
Externalizing score	6.5 (6.7)***	8.4 (9.4)***	2.1	(3.4)	F (2, 174) = 17.2 <.0001
Affective Problems	4.7 (4.2)***††	7.8 (4.9)***	0.6	(1.0)	F (2, 174) = 68.2 <.0001
Anxiety Problems	3.8 (3.0)***	3.8 (2.9)***	0.6	(1.0)	F (2, 174) = 48.8 <.0001
Somatic Problems	1.9 (2.6)**	3.1 (2.9)***	0.7	(1.4)	F (2, 174) = 17.3 <.0001
Attention Deficit/Hyperactivity Problems	2.8 (3.1)***	2.9 (2.7)***	0.9	(1.7)	F (2, 174) = 14.9 <.0001
Oppositional Defiant Problems	2.3 (2.1)***	2.9 (2.5)***	0.9	(1.4)	F (2, 174) = 17.9 <.0001
Conduct Problems	1.3 (2.4)*	2.4 (4.4)***	0.5	(1.3)	F (2, 174) = 6.4 .002
Social Communication Questionnaire	3.5 (2.9)***	2.9 (2.4)*	1.7	(2.1)	F (2, 174) = 9.6 <.0001
Behavioral Data					
Total number of trials	484.2 (54.2)	501.3 (34.0)	490.6	(53.1)	F (2, 174) = 1.05 .35
Total number of error trials	50.4 (27.9)**†	38.4 (16.9)	38.2 (19.7)	F (2, 174) = 5.28	.006
Accuracy on all trials	0.89 (.05)*** ††	0.92 (.03)	0.92 (.04)	F (2, 174) = 8.01	.0005

Accuracy on congruent trials	0.97 (.03)*	0.98 (.02)	0.98 (.02)	F (2, 174) = 2.97	.054
Accuracy on incongruent trials	0.81 (.09)*** ††	0.86 (.06)	0.86 (.06)	F (2, 174) = 8.11	.0004
Accuracy after correct trials	0.89 (.05)***†	0.92 (.04)	0.92 (.04)	F (2, 174) = 6.85	.0014
Accuracy after incorrect trials	0.89 (.09)**†††	0.96 (.04)	0.93 (.06)	F (2, 174) = 8.66	.0003
Error reaction time (ms)	390.0 (102.3)	365.6 (34.6)	409.5 (147.8)	F (2, 174) = 1.50	.23
Correct reaction time (ms)	440.1 (79.6)	423.4 (35.1)	447.7 (90.1)	F (2, 174) = 0.84	.43
Reaction time on congruent trials (ms)	411.9 (69.8)	395.8 (32.0)	418.6 (78.3)	F (2, 174) = 0.93	.40
Reaction time on incongruent trials (ms)	474.4 (96.0)	455.2 (41.1)	481.2 (105.1)	F (2, 174) = 0.68	.51
Post-error slowing (ms)	55.1 (33.1)†	67.8 (40.7)*	41.1 (66.8)	F (2, 174) = 3.34	.038
Event-Related Brain Potential Data					
Error-related negativity, FCz (μV)	-4.88 (6.16)	-5.14 (5.24)	-4.18 (5.46)	F (2, 173) = 1.27	.28
Correct response negativity, FCz (μV)	3.16 (4.93)	3.55 (5.08)	3.24 (4.34)	F (2, 173) = 0.04	.96
Error-related negativity, Cz (μV)	-2.76 (5.76)*	-2.11 (5.14)	-1.17 (5.93)	F (2, 173) = 3.69	.03

Correct response negativity, Cz (μV)	4.18 (5.32)	4.97 (5.94)	4.60 (4.86)	F (2, 173) = 0.32 .72
Error-related negativity, CPz (μV)	1.18 (4.73)**	2.07 (4.36)	2.74 (5.28)	F (2, 173) = 4.60 .01
Correct response negativity, CPz (μV)	5.53 (5.31)	6.19 (4.86)	5.41 (4.73)	F (2, 173) = 0.23 .80
ΔERN, FCz (μV)	-8.04 (6.90)	-8.69 (6.53)	-7.42 (6.52)	F (2, 173) = 0.70 .50
ΔERN, Cz (μV)	-6.94 (6.66)	-7.08 (7.76)	-5.77 (6.56)	F (2, 173) = 1.39 .25
ΔERN, CPz (μV)	-4.35 (6.11)	-4.11 (6.50)	-2.67 (5.56)	F (2, 173) = 2.40 .09

OCD, obsessive-compulsive disorder;

MDD, major depressive disorder;

SSRI, selective serotonin reuptake inhibitor;

ΔERN, error-related negativity amplitude minus correct response negativity amplitude.

*P < .05 compared to HC, ** P < .01 compared to HC, ***P < .001 compared to HC.

†P < .05 compared to MDD, ††P < .01 compared to MDD, †††P<.001 compared to MDD.

TABLE 2. Demographic, clinical, behavioral, and brain potential data in OCD patients with MDD, OCD patients without MDD, MDD patients, and healthy controls

Variable	OCD+MDD Mean (SD)	OCD-MDD Mean (SD)	MDD Mean (SD)	HC Mean (SD)	Group comparisons Test Statistic	*P*
	n = 14	*n = 39*	*n =36*	*n = 89*		
Demographic and Clinical Data						
Age (years)	16.6 (1.6)	15.6 (1.4)†	16.8 (1.4)	16.2 (1.7)	F (3, 174) = 3.76	.012
Sex (M/F)	1 / 13	13 / 26	7 / 29	20 / 69	χ^2 (3) = 4.61	.20
SSRI (treatment/no treatment)	7 / 7	18 / 21	11 / 25		χ^2 (2) = 2.52	.12
CY-BOCS, lifetime score	27.3 (6.7)	27.1 (6.2)			t(51) = 0.08	.94
CY-BOCS, current score	22.4 (6.6)	14.2 (8.6)			t(51) = 3.21	.002
Age at onset of OCD symptoms (years)	7.0 (3.0)	8.9 (3.6)			t(51) = 2.94	.09

Age at onset of MDD symptoms (years)	13.0 (1.9)		13.6 (2.0)		
	$t(51) = 0.92$	.36			
Child Behavior Checklist					
Obsessive-Compulsive Problems	6.9 (4.2)***†††‡	5.1 (3.4)***†††‡	3.0 (2.4)***	0.9 (1.0)	$F(3, 173) = 43.6$ <.0001
Total score	50.1 (28.9)***	27.3 (18.5)***†	41.0 (27.8)***	8.6 (9.3)	$F(3, 173) = 41.7$ <.0001
Internalizing score	21.4 (9.8)***	10.3 (7.8)***†††‡	17.1 (10.5)***	3.2 (3.2)	$F(3, 173) = 53.2$ <.0001
Externalizing score	10.3 (9.0)***	5.1 (5.1)***	8.4 (9.4)***	2.1 (3.4)	$F(3, 173) = 14.7$ <.0001
Affective Problems	8.6 (4.6)***	3.4 (3.1)***†††‡	7.8 (4.9)***	0.6 (1.0)	$F(3, 173) = 64.2$ <.0001
Anxiety Problems	5.1 (3.5)***	3.4 (2.7)***	3.8 (2.9)***	0.6 (1.0)	$F(3, 173) = 36.3$ <.0001
Somatic Problems	4.1 (3.4)***	1.2 (1.6)**†††‡	3.1 (2.9)***	0.7 (1.4)	$F(3, 173) = 20.6$ <.0001
Attention Deficit/Hyperactivity Problems	3.7 (3.7)***	2.5 (2.8)***	2.9 (2.7)***	0.9 (1.7)	$F(3, 173) = 11.1$ <.0001
Oppositional Defiant Problems	3.3 (2.3)***	2.0 (2.0)**	2.9 (2.5)***	0.9 (1.4)	$F(3, 173) = 14.4$ <.0001
Conduct Problems	2.8 (3.9)*	0.8 (1.4)	2.4 (4.4)**	0.5 (1.3)	$F(3, 173) = 6.3$ .0004

Behavioral Data

Total number of trials 503.0 (52.3) 477.5 (53.9) 501.3 (34.0) 490.6 (53.1) F (3, 173) = 1.52 .21 Total number of error trials 46.7 (36.8) 51.7 (24.5)**† 38.4 (16.9) 38.2 (19.7) F (3, 173) = 3.64 .014 Accuracy on all trials 0.90 (.07) 0.89 (.05)***††† 0.92 (.03) 0.92 (.04) F (3, 173) = 5.94 .0007

Accuracy on congruent trials 0.98 (.03) 0.96 (.03)**† 0.98 (.02) 0.98 (.02) F (3, 173) = 2.65 .051 Accuracy on incongruent trials 0.83 (.12) 0.81 (.08)******††† 0.86 (.06) 0.86 (.06) F (3, 173) = 5.84 .0008

Accuracy after correct trials 0.91 (.05) 0.88 (.05)***†† 0.92 (.04) 0.92 (.04) F (3, 173) = 6.02 .0006

Accuracy after incorrect trials 0.88 (.13)*†† 0.90 (.04)*††† 0.96 (.01) 0.93 (.06) F (3, 173) = 6.12 .0006 Error reaction time (ms) 432.7 (156.8) 374.6 (70.7) 365.6 (34.6) 409.5 (147.8) F (3, 173) = 2.26 .08

Correct reaction time (ms) 474.1 (116.0) 427.8 (59.2) 423.4 (35.1) 447.7 (90.1) F (3, 173) = 2.62 .052

Reaction time on congruent trials (ms) 444.2 (69.8) 400.3 (53.5) 395.8 (32.0) 418.6 (78.3) F (3, 173) = 3.21 .02

Reaction time on incongruent trials (ms) 512.2 (147.6) 460.9 (66.6) 455.2 (41.1) 481.2 (105.1) F (3, 173) = 2.13 .10

Post-error slowing (ms) 48.6 (34.8) 57.4 (32.6) 67.8 (40.7) 41.1 (66.8) F (3, 173) = 2.32 .08

Event-Related Brain Potential Data

Error-related negativity, FCz (μV)	-7.75 (8.26)*	-3.85 (4.94)	-5.14 (5.24)	-4.18 (5.46)	F (3, 172) = 2.29 .08
Correct response negativity, FCz (μV)	3.13 (5.05)	3.17 (4.95)	3.55 (5.08)	3.24 (4.34)	F (3, 172) = 1.69 .14
Error-related negativity, Cz (μV)	-4.97 (6.76)*	-1.96 (5.23)	-2.11 (5.14)	-1.17 (5.93)	F (3, 172) = 2.98 .03
Correct response negativity, Cz (μV)	3.47 (4.74)	4.43 (5.54)	4.97 (5.95)	4.60 (4.86)	F (3, 172) = 0.50 .69
Error-related negativity, CPz (μV)	-0.78 (4.70)**†	1.88 (4.60)*	2.07 (4.36)	2.74 (5.28)	F (3, 172) = 3.51 .02
Correct response negativity, CPz (μV)	4.21 (5.10)	6.00 (5.37)	6.18 (5.67)	5.41 (4.73)	F (3, 172) = 0.81 .49
ΔERN, FCz (μV)	-10.88 (9.63)	-7.02 (5.42)	-8.69 (6.53)	-7.42 (6.52)	F (3, 172) = 1.21 .31
ΔERN, Cz (μV)	-8.44 (8.08)	-6.40 (6.10)	-7.08 (7.76)	-5.77 (6.65)	F (3, 172) = 0.96 .41
ΔERN, CPz (μV)	-4.99 (7.58)	-4.12 (5.59)	-4.11 (6.50)	-2.67 (5.56)	F (3, 172) = 1.61 .19

OCD, obsessive-compulsive disorder;

MDD, major depressive disorder;

CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale;

SSRI, selective serotonin reuptake inhibitor;

ΔERN, error-related negativity amplitude minus correct response negativity amplitude.

*P < .05 compared to HC, ** P < .01 compared to HC, ***P < .001 compared to HC.

†P < .05 compared to MDD, ††P < .01 compared to MDD, †††P<.001 compared to MDD.

TABLE 3. Correlation matrix for Child Behavior Checklist *DSM*-Oriented Scales, error-related negativity (ERN), correct response negativity (CRN), and ERN minus CRN (ΔERN) at electrode Cz in 178 adolescent participants

	Affective Problems	Anxiety Problems	Somatic Problems	Attention Deficit/ Hyperactivity Problems	Oppositional Defiant Problems	Conduct Problems
Affective Problems	1	0.72****	0.64****	0.58****	0.68****	0.57****
Anxiety Problems	0.72****	1	0.43****	0.48****	0.44****	0.36****
Somatic Problems	0.64****	0.43****	1	0.38****	0.48****	0.47****
Attention Deficit/Hyperactivity	0.58****	0.48****	0.38****	1	0.62****	0.61****

Problems						
Oppositional Defiant Problems	0.68****	0.44****	0.48****			
0.62****	1		0.69****			
Conduct Problems	0.57****	0.36****	0.47****			
0.61****	0.69****	1				
ERN, Cz	-0.15*	-0.27***	-0.15*	-0.06		
-0.07	-0.08					
CRN, Cz	-0.04	-0.003	-0.04	-0.13		-(
ΔERN, Cz	-0.16*	-0.23**	-0.10	-0.04		-(

ΔERN, error-related negativity amplitude minus correct response negativity amplitude.

* $P < .05$, ** $P < .01$, *** $P < .001$, **** $P < .0001$.

Figure 1. Grand averages of electroencephalogram (EEG) recordings in patients with obsessive-compulsive disorder (OCD), major depressive disorder (MDD), and healthy controls (HC). Note: The images depict response-locked grand average waveforms recorded at the central (Cz) electrode for correct and incorrect responses. Responses occurred at 0 ms. The mean amplitude of the error-related negativity (ERN) was computed in a window 0 to 80 ms after incorrect response trials.

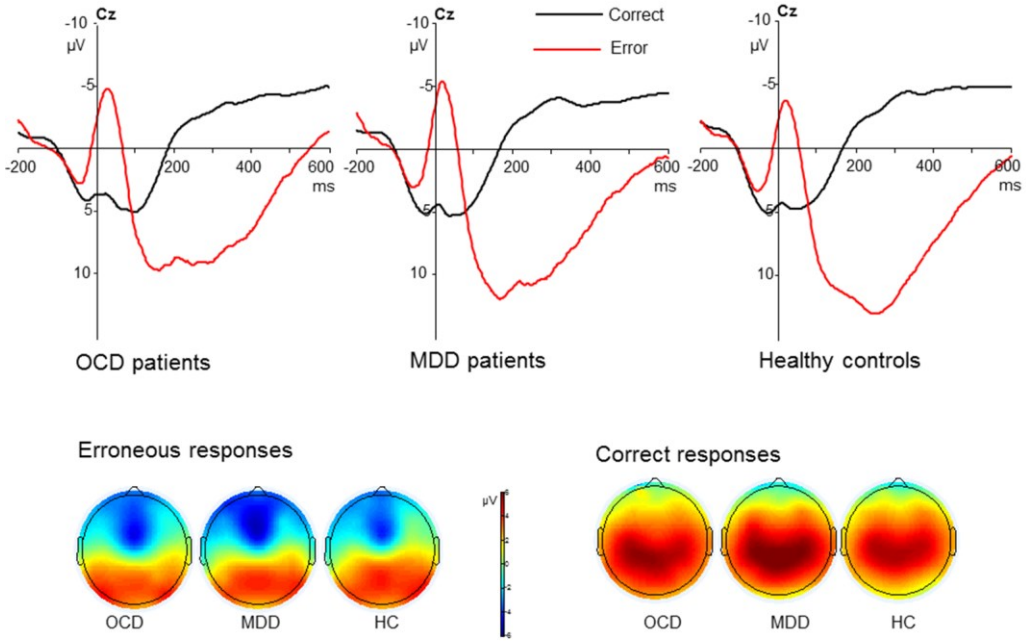

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Figure 2. Grand averages of electroencephalogram (EEG) recordings in patients with both obsessive-compulsive disorder (OCD) and major depressive disorder (MDD) (OCD+MDD), OCD without MDD (OCD-MDD), MDD, and healthy controls (HC). Note: The images depict response-locked grand average waveforms recorded at the central (Cz) electrode for correct and incorrect responses. Responses occurred at 0 ms. The mean amplitude of the error-related negativity (ERN) was computed in a window 0 to 80 ms after incorrect response trials.