*Research Article*

# INCREASED ERROR-RELATED BRAIN ACTIVITY IN YOUTH WITH OBSESSIVE-COMPULSIVE DISORDER AND UNAFFECTED SIBLINGS

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**Background:** *The pathophysiology of obsessive-compulsive disorder (OCD) involves increased activity in cortico-striatal circuits connecting the anterior cingulate cortex (ACC) with other brain regions. The error-related negativity (ERN) is a negative deflection in the event-related potential following an erroneous response and is thought to reflect ACC activity. This study was done to assess the ERN as a biomarker for OCD by comparing ERN amplitudes in pediatric OCD patients, unaffected siblings of pediatric OCD patients, and healthy controls.* **Methods:** *The ERN and correct response negativity (CRN) were measured during an Eriksen flanker task to assess performance monitoring in 40 youth with a lifetime diagnosis of OCD, 19 unaffected siblings of OCD patients, and 40 unrelated healthy comparison subjects ranging in age from 10 to 17 years. ERN and CRN amplitudes were compared between groups using linear regression by the generalized estimating equation method to account for correlated data.* **Results:** *Compared to healthy controls, ERN amplitude was significantly increased in both pediatric OCD patients and unaffected siblings. There were no significant group differences in CRN amplitude. ERN amplitude in patients was unrelated to OCD symptom severity, current diagnostic status, or treatment effects.* **Conclusions:** *Increased error-related brain potentials were observed not only in pediatric OCD patients but also in unaffected siblings. The results provide evidence that enhanced error-related brain activity may serve as a biomarker for OCD in youth that is independent of the presence of clinical symptoms. The ERN may be a useful quantitative phenotype in genetic studies of OCD. Depression and Anxiety 30:39–46, 2013.* 

**Key words:** *anxiety disorder; relatives; error-related negativity; response monitoring; flanker task; medial frontal cortex; biomarker*

## INTRODUCTION

Obsessive-compulsive disorder (OCD) [http://www.omim.org/entry/164230] is a heterogeneous psychiatric disorder with lifetime prevalence estimates ranging from 1 to 3% and a median age at onset of 19 years.[1] Twin and family studies provide evidence that OCD is a complex trait with both genetic and environmental susceptibility factors.[2–11] Estimates of the heritability of obsessive-compulsive (OC) symptoms range from 27 to 47% in adults and from 45 to 65 in children.[2–5] Family studies indicate that the lifetime prevalence of OCD is

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substantially higher in case compared to control first-degree relatives, and that OCD risk is at least doubled in case relatives of pediatric probands compared to case relatives of adult probands.[6–11] Genetic linkage analyses have provided suggestive evidence for susceptibility loci on chromosomes 9p24[12,13] and 15q14;[14,15] however, linkage findings for those and other chromosomal regions have not been consistently replicated.[12–17] Further efforts to identify susceptibility loci for OCD may benefit from use of a quantitative phenotype, which either mediates between genes and the clinical phenotype on the causal pathway or indicates risk by sharing sets of genes with the clinical phenotype.[18,19]

Functional brain imaging studies suggest the pathophysiology of OCD involves increased activity in cortico-striatal circuits connecting the anterior cingulate cortex (ACC) with other brain regions.[20,21] Functional magnetic resonance imaging (fMRI) studies of OCD patients have found increased error-related brain activity localized to the ACC.[22,23] The observation of increased error-related brain activity in OCD patients is consistent with the hypothesis that OCD involves defects in an error-detection system, which may give rise to repeated doubts about actions and excessive worries about potential mistakes.[24] It remains unclear, however, whether increased error-related brain activity may contribute to the expression or suppression of OCD symptoms. Consistent with the latter possibility, improvement in OCD symptoms during intensive cognitive-behavioral therapy was associated in an imaging study with increased dorsal ACC metabolic activity.[21]

The error-related negativity (ERN)[25,26] or error negativity [27] is a frontally maximal negative deflection in the response-locked event-related potential that peaks within 100 ms after an incorrect response, which can be evoked by errors committed outside of conscious awareness.[28] Studies using fMRI,[29] magnetoencephalography,[30] and dipole source localization[31] have suggested the ERN is generated mainly by the dorsal ACC. ERN amplitude generally increases with age, which may reflect ACC maturation.[32] The ERN has been hypothesized to reflect error detection, response conflict, or reward prediction errors in which outcomes are worse than expected.[26] A study of 12-year-old twins found that genetic factors account for 47% of the variance in the ERN, suggesting it may serve as an endophenotype in genetic studies of psychopathology.[33]

In studies using tasks eliciting response conflict, ERN amplitude has been increased in adult patients with OCD[34–41] and young adults with self-reported OC symptoms.[42] Several of those studies also found that serotonergic antidepressants had no effect on the ERN in OCD patients.[38–40] Furthermore, ERN amplitude has been increased in studies of pediatric patients with OCD[43] and children with parent-reported OC symptoms.[44] In the study of pediatric OCD patients, the ERN did not change as a function of the reduction in OCD symptoms with cognitive-behavioral therapy, indicating that increased ACC activity during response monitoring does not necessarily maintain OCD symptoms and that an increase in this brain potential may serve as a trait marker or endophenotype for OCD.[43,45] Similarly, increased ERN amplitude was found in the unaffected first-degree relatives of adult OCD probands, providing further evidence that overactive error monitoring may serve as a biomarker for OCD that is independent of the presence of clinical symptoms.[39]

Since the ERN has been examined to a limited extent in pediatric OCD patients[43] and unaffected adult first-degree relatives of OCD probands,[39] the following study was conducted with 40 youth with a lifetime diagnosis of OCD, 19 unaffected siblings of pediatric OCD probands, and 40 age-matched healthy controls using a flanker task that elicits response conflict. The aim of the study was to demonstrate that ERN amplitude is increased in both pediatric OCD patients and unaffected siblings compared to healthy controls.

# METHOD

## PARTICIPANTS

Pediatric OCD patients and unaffected siblings of pediatric OCD probands were recruited from the Department of Psychiatry at the University of Michigan and surrounding community. Pediatric comparison subjects were recruited from the surrounding community. The control parents reported no history of OCD or tic disorders in the first-degree relatives of their children. After complete description of the study, written informed consent was obtained from at least one parent of the participant and written informed assent from the participant. Participants were paid for their interviews and psychophysiological recordings. Participants were matched for age and gender.

All 40 patients had a lifetime diagnosis of OCD. Patients were excluded if they had a lifetime diagnosis of autistic disorder, Asperger's disorder, schizophrenia, other psychotic disorder, bipolar I disorder, substance-related disorder, or anorexia nervosa, or a current diagnosis of major depressive disorder. All 19 unaffected siblings and 40 comparison subjects had no history of a specific axis I disorder. Eleven unaffected siblings were related to participants in the patient group. The other eight unaffected siblings were recruited through pediatric OCD probands who were evaluated using the same diagnostic instruments as the participants in this study. Lifetime and current axis I diagnoses were made independently by two clinicians using all sources of information according to DSM-IV-TR criteria.[46] Patients, unaffected siblings, and comparison subjects were excluded if they had a history of mental retardation, head injury with a sustained loss of consciousness, chronic neurological disorder such as a seizure disorder, or a score $\geq 15$ on the lifetime version of the Social Communication Questionnaire, to further minimize the possibility of participants having a history of autism spectrum disorder.[47] All participants lived with at least one English-speaking biological parent who was willing to participate in research.

All 99 participants were interviewed with the Schedule for Schizophrenia and Affective Disorders for School-Aged Children-Present and Lifetime Version[48] and Schedule for Obsessive-Compulsive and Other Behavioral Syndromes.[49] The lifetime and current severity of OCD was assessed in patients with a modified version of the Children's Yale–Brown Obsessive Compulsive Disorder Scale (CY-BOCS),[50] with patients and their parents providing item scores retrospectively for the most severe episode of OCD

along with item scores for current severity. The parent report scales completed for all participants consisted of the Child Behavior Checklist (CBCL)[51,52] and Social Communication Questionnaire.[47] The self-report scales completed by all participants consisted of the Multidimensional Anxiety Scale for Children (MASC)[53] and Children's Depression Inventory (CDI).[54]

Table 1 summarizes the demographic, clinical, behavioral, and event-related brain potential data for the OCD patients, unaffected siblings of OCD probands, and healthy controls. Participants ranged in age from 10 to 17 years. The OCD group had 18 males, the unaffected sibling group 13 males, and the comparison group 20 males ($\chi^2 = 2.89$, $df = 2$, $P = .24$). The current and lifetime CY-BOCS scores in the OCD patients ranged from 0 to 34 and 12 to 36, respectively. Although all patients had a lifetime diagnosis of OCD, 25 had a current diagnosis and 15 a past diagnosis with minimal current OCD symptoms that no longer met criteria for diagnosis. Of the 40 OCD patients, 24 had a history of at least one other axis I diagnosis. The disorders (and number of patients with the diagnosis) were the following: tic disorder ($N = 8$), trichotillomania ($N = 2$), attention-deficit hyperactivity disorder ($N = 2$), separation anxiety disorder ($N = 6$), panic disorder ($N = 1$), specific phobia ($N = 6$), social phobia ($N = 7$), agoraphobia ($N = 1$), generalized anxiety disorder ($N = 7$), and past major depressive disorder ($N = 4$). Consistent with previous studies of the ERN in OCD, patients were included in the study if they were taking a stable dose of a selective serotonin reuptake inhibitor (SSRI) but no other psychotropic medications. Medications being taken (and number of patients taking the medication) were the following: fluoxetine ($N = 11$), sertraline ($N = 2$), escitalopram ($N = 2$), and citalopram ($N = 1$). No patient was taking more than one SSRI. Prior studies have found no effect of serotonergic antidepressants on the ERN.[38–40]

### TASK AND PROCEDURE

Participants performed a modified Eriksen flanker task in which arrows appeared on a computer display with congruent (e.g. →→→→→) and incongruent (e.g. →→←→→) conditions.[55] 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, while placing equal emphasis on speed and accuracy. The stimuli remained on the screen for 250 ms, with an interval 1,500 ms between consecutive stimuli.

Each participant was seated 0.65 m directly in front of the computer monitor. Following a practice block of 32 trials, each subject completed 8 blocks of 64 trials for 512 trials. Performance feedback was provided after every block to yield error rates of approximately 10%, ensuring an adequate number of trials for stable error-related waveforms.

### ELECTROPHYSIOLOGICAL RECORDING, DATA REDUCTION, AND ANALYSIS

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 (Amsterdam, the Netherlands). Data were recorded 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 were re-referenced offline to the average of the two mastoid electrodes. Data were digitized at 512 Hz. Following recording, the data were resampled at 256 Hz. Prior to eye movement correction, EEG data were screened using automated algorithms that rejected individual sweeps in which (a) the absolute voltage range for any individual electrode exceeded 500 $\mu$V, (b) a change greater than 50 $\mu$V was measured from one datapoint to the next, or (c) the data deviated by more than +25 or –100 dB in the 20–40 Hz frequency window (for detecting muscle artifacts). The amplitude range used for rejection was fairly large so that trials with correctable eye movements were not eliminated. Data were also screened by visual inspection. Ocular movement artifacts were then corrected using the algorithm described by Gratton, Coles, and Donchin.[56] Waveforms shown in figures were filtered with a nine-point Chebyshev II low-pass, zero-phase-shift digital filter (Matlab R2010a; Mathworks, Natick, MA), with a half-amplitude cutoff at approximately 12 Hz.

Behavioral measures included the number of erroneous and correct trials for each subject, as well as accuracy expressed as a percentage of valid trials. Average reaction times on error and correct trials were calculated separately, after excluding trials with reaction times greater than 1,500 ms. Reaction time and accuracy after errors were evaluated to determine if there were group differences in post-error behavioral adjustments.[57] 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 57.4 (SD = 23.4; range = 16–121).

The ERN was quantified using mean amplitude measures relative to a preresponse baseline –200 to –50 ms. 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. Amplitudes were calculated for electrodes FCz and Cz. However, recent studies with children suggest their ERN is slightly more posterior but temporally similar to the adult ERN,[58] so the focus of the data presented herein is the ERN at Cz.

ERN amplitude was compared between groups using linear regression by the generalized estimating equation (GEE) method to account for correlated data, including error number as a covariate, with the GENMOD procedure in SAS Version 9.2 software (SAS Institute Inc., Cary, NC).[59] Other variables were compared between groups using linear regression by the GEE method without including error number as a covariate. ERN amplitude was compared between subgroups of pediatric OCD patients using analysis of variance. In the comparison of patients with a past or current diagnosis of OCD, tic history was included as a variable because the ERN and the course and treatment response of OCD may be influenced by comorbid tics.[60,61] Pearson correlation coefficients or Spearman rank-order correlation coefficients were used to examine associations of response-related amplitudes with age, behavioral measures, and clinical measures. All statistical tests were two-tailed with the alpha level set at 0.05.

## RESULTS

### BEHAVIORAL DATA IN OCD PATIENTS, UNAFFECTED SIBLINGS, AND HEALTHY CONTROLS

There were no significant group differences in the number of error trials, reaction time during correct or error trials, or posterror slowing (Table 1). Correct responses were significantly slower than incorrect responses (paired $t = 9.91$, $df = 98$, $P < .0001$). No main effect of group on response type for reaction time and no interaction between group and response type for reaction time reached significance ($P = .52$ and $P = .68$, respectively). In all subjects, age had significant negative correlations with reaction time on correct trials ($r = –.39$, $P < .0001$), reaction time on error trials ($r =$

**TABLE 1. Demographic, clinical, behavioral, and brain potential data in OCD Patients, unaffected siblings of OCD Patients, and healthy comparison subjects**

| Variable | OCD patients ($n = 40$) Mean | SD | Unaffected siblings ($n = 19$) Mean | SD | Healthy control control subjects ($n = 40$) Mean | SD | Comparisons of OCD patients, unaffected siblings, and healthy control subjects: Test statistic[a] | *P* |
|---|---|---|---|---|---|---|---|---|
| **Demographic and clinical data** | | | | | | | | |
| Age (years) | 13.9 | 2.4 | 13.9 | 2.4 | 13.8 | 2.3 | $\chi^2_2 = 0.04$ | .98 |
| Child Behavior Checklist | | | | | | | | |
| Total score | 35.1 | 22.5 | 7.4 | 4.7 | 7.5 | 5.3 | $\chi^2_2 = 33.27$ | <.0001[b] |
| Internalizing score | 14.2 | 9.1 | 2.5 | 2.4 | 2.5 | 2.1 | $\chi^2_2 = 35.04$ | <.0001[b] |
| Externalizing score | 6.4 | 6.9 | 2.2 | 2.6 | 1.9 | 2.0 | $\chi^2_2 = 13.18$ | <.0014[c,d] |
| Obsessive-Compulsive Scale score | 6.6 | 3.9 | 0.9 | 1.4 | 0.6 | 0.8 | $\chi^2_2 = 42.14$ | <.0001[b] |
| Multidimensional Anxiety Scale For Children (total score) | 47.4 | 20.8 | 28.6 | 12.0 | 27.6 | 13.1 | $\chi^2_2 = 20.09$ | <.0001[b] |
| Children's Depression Inventory | 9.8 | 7.3 | 3.4 | 3.8 | 2.8 | 2.7 | $\chi^2_2 = 23.33$ | <.0001[b] |
| Age at onset of Obsessive-Compulsive Symptoms (years) | 8.1 | 3.2 | | | | | | |
| Duration of Obsessive-Compulsive Symptoms (years) | 5.6 | 3.6 | | | | | | |
| Children's Yale–Brown Obsessive Compulsive Scale—lifetime score | 28.2 | 6.1 | | | | | | |
| Children's Yale–Brown Obsessive Compulsive Scale—current score | 16.0 | 8.9 | | | | | | |
| **Behavioral data** | | | | | | | | |
| Total number of error trials | 61.6 | 24.0 | 56.6 | 20.8 | 53.5 | 23.8 | $\chi^2_2 = 2.48$ | .29 |
| Total number of correct trials | 432.0 | 48.7 | 438.7 | 30.6 | 449.1 | 46.8 | $\chi^2_2 = 2.00$ | .37 |
| Correct reaction time (ms) | 455.5 | 94.5 | 464.5 | 131.0 | 479.4 | 115.8 | $\chi^2_2 = 1.04$ | .60 |
| Error reaction time (ms) | 393.7 | 100.6 | 405.5 | 128.4 | 428.7 | 146.8 | $\chi^2_2 = 1.56$ | .46 |
| Post-error reaction time (ms) | 470.7 | 145.8 | 453.0 | 250.5 | 511.4 | 234.7 | $\chi^2_2 = 1.10$ | .58 |
| **Event-related brain potential data** | | | | | | | | |
| Error-related negativity, FCz ($\mu$V) | –4.04 | 5.36 | –4.71 | 3.92 | –2.31 | 3.65 | $\chi^2_2 = 5.74$ | .057[e,f] |
| Error-related negativity, Cz ($\mu$V) | –1.46 | 5.75 | –1.39 | 5.20 | 1.51 | 4.90 | $\chi^2_2 = 8.32$ | .016[g,h] |
| Correct response negativity, FCz ($\mu$V) | 2.10 | 5.52 | 1.44 | 4.61 | 1.94 | 4.04 | $\chi^2_2 = 0.28$ | .87 |
| Correct response negativity, Cz ($\mu$V) | 3.36 | 5.92 | 2.31 | 4.92 | 3.68 | 4.88 | $\chi^2_2 = 1.05$ | .59 |

OCD, obsessive-compulsive disorder.
[a]Determined using linear regression by the generalized estimating equation method. Degrees of freedom are presented as subscript figures.
[b]OCD patients significantly different from unaffected siblings, and OCD patients significantly different from healthy controls, $P < .0001$.
[c]OCD patients significantly different from unaffected siblings, $P = .0009$.
[d]OCD patients significantly different from healthy controls, $P < .0001$.
[e]Trend for a difference between OCD patients and healthy controls, $P = .052$.
[f]Unaffected siblings significantly different from healthy controls, $P = .039$.
[g]OCD patients significantly different from healthy controls, $P = .006$.
[h]Unaffected siblings significantly different from healthy controls, $P = .037$.

–.24, $P = .014$), and posterror slowing ($r = –.23$, $P = .020$). However, there was no significant correlation between age and error number ($P = .40$). There were no significant sex differences for error number, reaction time on correct trials, reaction time on error trials, or posterror slowing (all $P$ values > .10).

### EVENT-RELATED POTENTIAL DATA IN OCD PATIENTS, UNAFFECTED SIBLINGS, AND HEALTHY CONTROLS

ERN amplitude at Cz was correlated with age in all subjects, becoming larger (or more negative) with increasing age ($r = –.25$, $P = .011$). ERN amplitude at Cz had no significant correlations with error number, reaction time on correct trials, reaction time on error trials, or posterror slowing (all $P$ values > .30).

In a comparison of ERN amplitudes at Cz in OCD patients, unaffected siblings, and healthy controls, there was a significant group effect ($\chi^2 = 8.32$, $df = 2$, $P = .016$) without a significant error number effect ($\chi^2 = 1.15$, $df = 1$, $P = .28$; Table 1 and Fig. 1). Compared to controls, ERN amplitude at Cz was significantly increased in both patients ($P = .006$, Cohen's $d = .56$) and unaffected siblings ($P = .037$, Cohen's $d = .57$). In an analysis using both error number and CDI scores as covariates, the group effect remained significant ($\chi^2 = 8.11$, $df = 2$, $P = .017$) without a significant effect for error number ($\chi^2 = 1.15$, $df = 1$, $P = .28$) or depression severity ($\chi^2 = 0.00$, $df = 1$, $P = .97$). In an analysis using only the 11 sibling pairs and healthy controls, there was a significant group effect ($\chi^2 = 6.77$, $df = 2$, $P = .034$) without a significant error number effect ($\chi^2 = .01$, $df = 1$, $P = .90$). Compared to controls, ERN amplitude at Cz was significantly increased in the 11 OCD patients ($P = .002$, Cohen's $d = .97$), but not in the 11 unaffected siblings ($P = .33$, Cohen's $d = .35$). There was no significant difference in ERN amplitude at Cz between the 11 unaffected siblings with an affected sibling and the eight unaffected siblings without an affected sibling in the study ($F = 1.03$, $df = 2,16$, $P = .38$).

There were no significant differences between the three groups in CRN amplitudes at Cz ($P$ value > .50; Table 1). There were no significant sex differences in any brain potentials (all $P$ values > .10).

### CLINICAL CORRELATIONS AND COMPARISONS IN OCD PATIENTS, UNAFFECTED SIBLINGS, AND HEALTHY CONTROLS

As expected, the groups differed significantly in symptom severity scores from the CBCL, MASC, and CDI, with OCD patients having significantly higher scores than unaffected siblings and healthy controls (Table 1). Moreover, there were no significant differences between the unaffected siblings and healthy controls on any of these measures. In the healthy controls, there was a significant negative correlation between the CBCL obsessive-compulsive scale (CBCL-OCS) scores[52] and ERN amplitude at Cz (Spearman $\rho = –.35$, $P = .025$). There were no significant correlations between the CBCL-OCS scores and any brain potentials in either the OCD patients (all $P$ values > .30) or unaffected siblings (all $P$ values > .40).

In the pediatric OCD patients, there were no significant correlations between any brain potentials and either current or lifetime measures of OCD symptom severity (all $P$ values > .20). There were no significant differences in any brain potentials between patients with a current or past diagnosis of OCD (all $P$ values > .20). Furthermore, in a comparison of ERN amplitudes at Cz in patients with a past diagnosis of OCD and healthy controls, there was a significant group effect ($P = .0013$) without a significant error number effect ($P = .24$). Similarly, in a comparison of ERN amplitudes at Cz in patients with a current diagnosis of OCD and healthy controls, there was a significant group effect ($P = .018$) without a significant error number effect ($P = .14$). There were no significant differences in any behavioral measures or brain potentials between OCD patients receiving and not receiving a serotonin reuptake inhibitor (all $P$ values > .10), or between patients receiving and not receiving cognitive-behavioral therapy with exposure/response prevention (all $P$ values > .30).

## DISCUSSION

Our finding of an increased ERN in pediatric OCD patients during a task-eliciting response conflict is consistent with previous reports of increased error-related brain activity in adults[20–23,34–41] and children[43] with OCD. ERN results have been more variable, however, in studies of adult OCD patients using probabilistic learning tasks or other tasks, indicating the increase is specific to particular conditions.[62–65] Our results also provide further evidence that an enlarged ERN in OCD patients is a more trait-like measure that appears independent of OCD symptom severity, current diagnostic status, or treatment effects.[37–39,43] Nonetheless, it is important to note this finding is not specific to OCD, as an enhanced ERN has also been found in generalized anxiety disorder.[41,45,66,67] The negative correlation between the ERN and CBCL-OCS scores observed in our healthy controls is similar to the correlation found in a previous study of OC behaviors in a nonclinical sample of children.[44] The ERN may have a stronger correlation with OC behavior severity in individuals without a clinical diagnosis than in patients with OCD, if the correlation in patients is confounded by tics, depression, or treatment effects.[45,60]

The ERN in our study was as large in the pediatric unaffected siblings of OCD probands as the pediatric OCD patients themselves. Our data parallel those described in a study of unaffected adult first-degree relatives of OCD probands that consisted mainly of parents of those probands.[39] However, the effect sizes in our study for pediatric OCD patients and unaffected siblings at Cz (Cohen's $d = .56$ and .57, respectively) are smaller than those in the previous adult study for patients and

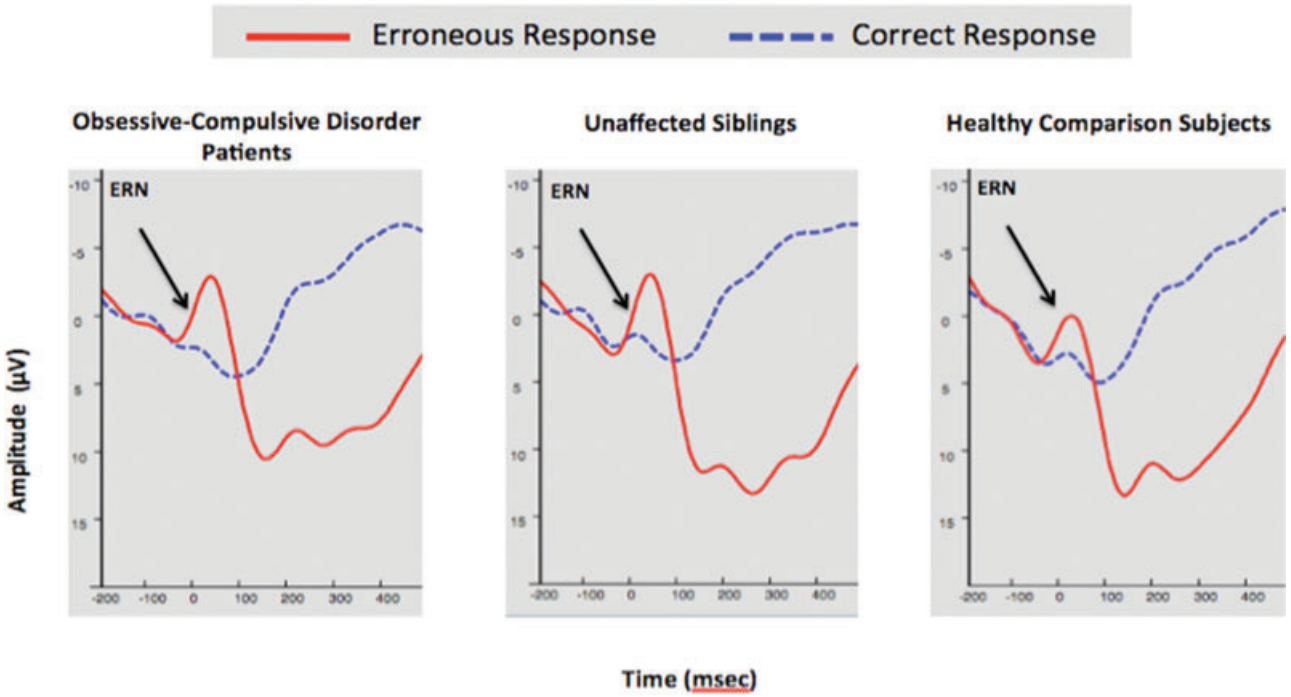


**Figure 1. Grand averages of EEG recordings in OCD patients, unaffected siblings, and healthy comparison subjects.[a] Note: [a]The images depict response-locked grand average waveforms recorded at electrode Cz for correct and incorrect responses. Responses occurred at 0 ms. The mean amplitude of the ERN was computed in a window from 0 to 80 ms following the incorrect response. OCD, obsessive-compulsive disorder.**

unaffected first-degree relatives at FCz (Cohen's $d = .82$ and .79, respectively), suggesting the ERN differences may be more robust in adults. Our preliminary results require replication with a larger sample of unaffected siblings of pediatric OCD probands with a wider age range.

The ERN has been proposed as an endophenotype for OCD because it is heritable, reliable, continuously variable in the general population, associated with at least a form of the illness, primarily state-independent, and increased more often in unaffected case relatives than in the general population.[18,19,37–39,43,45] However, it is unknown whether an enlarged ERN tends to cosegregate with OCD in multiply affected families or lies on the causal pathway between genes and disorder and is, thereby, more reflective of the causes than the consequences of the disorder. There are no studies, in particular, showing association or linkage between the ERN and a consistently replicated candidate gene for OCD. Further research is necessary to determine whether variation in the ERN mediates the genetic risk for the clinical phenotype rather than indicating risk through pleiotropic effects by sharing a set of genes with the clinical phenotype. Even if the ERN is a liability index rather than an intermediate phenotype, it may still be useful in identifying susceptibility alleles depending on whether it defines a more genetically homogeneous disease subgroup or identifies carriers of the risk genotype among unaffected relatives.[18] An alternative term such a "biomarker" may be more appropriate in this instance, as well as better describing the current status of the ERN as a possible genetic correlate of OCD.[19]

Our study has several limitations requiring further consideration. The sample size for the unaffected sibling group, in particular, was small. Examination of all first-degree relatives may have provided a more rigorous examination of the hypothesis that ERN amplitude is elevated in unaffected as well as affected relatives of OCD probands. No corrections were made for multiple testing, although one-tailed tests may have been justified for the main comparisons. The treatment of patients in this study was uncontrolled, with the exception that patients on medications other than the SSRIs were excluded. Although unaffected siblings and healthy controls had no history of an axis I disorder or significant differences with CBCL, MASC, or CDI measures, it is possible the two groups had psychological differences that were not assessed. For example, the unaffected siblings and healthy controls may have differed on measures of perfectionism, excessive concern about errors, negative affect, intolerance of uncertainty, inflated responsibility, or overestimation of threat.[68,69] Assessment of these psychological factors may be useful in future family and longitudinal studies of the ERN in OCD.

Our study provides further evidence of increased error-related brain activity in pediatric OCD patients

that appears independent of symptom severity, current diagnostic status, and treatment effects.[43] Moreover, our results demonstrate a similar increase in error-related brain activity in unaffected pediatric siblings of OCD probands in analyses accounting for correlated data, which extend the findings from a previous study with unaffected adult relatives of OCD probands.[39] Thus, the ERN is a promising biomarker for OCD that may be a useful quantitative phenotype in genetic studies of this complex trait.[18,19,70] and predictor of outcome in longitudinal studies.

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