

Error-Related Negativity and Tic History in Pediatric Obsessive-Compulsive Disorder

Gregory L. Hanna, M.D., Melisa Carrasco, Ph.D., Shannon M. Harbin, M.S., Jenna K. Nienhuis, M.Div., M.S.W., Christina E. LaRosa, B.S., Poyu Chen, Ph.D., Kate D. Fitzgerald, M.D., William J. Gehring, Ph.D.

Objective: The error-related negativity (ERN) is a negative deflection in the event-related potential after an incorrect response, which is often increased in patients with obsessive-compulsive disorder (OCD). However, the relation of the ERN to comorbid tic disorders has not been examined in patients with OCD. This study compared ERN amplitudes in patients with tic-related OCD, patients with non-tic-related OCD, and healthy controls. **Method:** The ERN, correct response negativity, and error number were measured during an Eriksen flanker task to assess performance monitoring in 44 youth with a lifetime diagnosis of OCD and 44 matched healthy controls ranging in age from 10 to 19 years. Nine youth with OCD had a lifetime history of tics. **Results:** ERN amplitude was significantly increased in patients with OCD compared with healthy controls. ERN amplitude was significantly larger in patients with non-tic-related OCD than in patients with tic-related OCD or controls. ERN amplitude had a significant negative correlation with age in healthy controls but not in patients with OCD. Instead, in patients with non-tic-related OCD, ERN amplitude had a significant positive correlation with age at onset of OCD symptoms. ERN amplitude in patients was unrelated to OCD symptom severity, current diagnostic status, or treatment effects. **Conclusions:** The results provide further evidence of increased error-related brain activity in pediatric OCD. The difference in the ERN between patients with tic-related and those with non-tic-related OCD provides preliminary evidence of a neurobiological difference between these two OCD subtypes. The results indicate the ERN is a trait-like measurement that may serve as a biomarker for non-tic-related OCD. *J. Am. Acad. Child Adolesc. Psychiatry, 2012;51(9):902-910.* **Key Words:** anxiety disorder, tic disorder, brain potential, performance monitoring, biomarker

Obsessive-compulsive disorder (OCD) is a heterogeneous condition, with lifetime prevalence estimates ranging from 1% to 3%.¹ The National Comorbidity Survey Replication found a median age at onset of 19 years in OCD, with 21% of cases starting by age 10.¹ About 10% to 40% of OCD cases diagnosed in childhood or adolescence have a lifetime history of a chronic tic disorder.² It has been proposed that some forms of OCD are etiologically related to chronic tic disorders.²⁻⁵ Tic-related OCD is characterized by a male predominance.^{2,3} The distinction between tic-related and non-tic-related OCD has been supported by studies of familial aggregation,^{4,5} treatment response,⁶⁻⁸ outcome,⁹ prolactin release,¹⁰ and prepulse inhibition.¹¹

Functional brain imaging studies have indicated the pathophysiology of OCD involves increased activity in corticostriatal circuits connecting the

anterior cingulate cortex (ACC) with other brain regions.^{12,13} Functional magnetic resonance imaging studies of patients with OCD have found increased error-related brain activity localized to the ACC.¹⁴ The observation of increased error-related brain activity in patients with OCD 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.¹⁵ It is 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 has been associated in an imaging study with a significant increase in dorsal ACC metabolic activity.¹²

The error-related negativity (ERN)^{16,17} or error negativity¹⁸ is a frontally maximal negative de-

flexion in the response-locked event-related potential that peaks within 100 ms after an incorrect response, which can be evoked by errors committed outside conscious awareness.¹⁹ Studies using functional magnetic resonance imaging,²⁰ magnetoencephalography,²¹ and dipole source localization²² have suggested the ERN is generated mainly by the dorsal ACC. ERN amplitude generally increases with age, which may reflect ACC maturation.²³ The ERN has been hypothesized to reflect error detection, response conflict, or reward prediction errors in which outcomes are worse than expected.¹⁷ The ERN shows substantial heritability, suggesting it may serve as an endophenotype in genetic studies of psychopathology.²⁴

In studies using tasks eliciting response conflict, ERN amplitude has been increased in adult patients with OCD²⁵⁻³² and young adults with self-reported OC symptoms.^{33,34} Some of those studies also found that serotonergic antidepressants had no effect on the ERN in patients with OCD.^{29,31} ERN amplitude has also been increased in studies of pediatric patients with OCD³⁴ and children with parent-reported OC symptoms.³⁵ In a study of pediatric OCD with 18 patients and 18 controls, the ERN did not change as a function of the decrease 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 for OCD.^{34,36} Similarly, increased ERN amplitude has been found not only in patients with OCD but also in unaffected first-degree relatives of OCD probands, providing further evidence that overactive error monitoring may provide a biomarker for OCD that is independent of the presence of clinical symptoms.³⁰

Increased ERN amplitude has been described in patients with Tourette's disorder, although most patients in that study had significant OC symptoms.³⁷ A magnetic resonance imaging study of siblings concordant for Tourette's disorder found thinning in the cingulate cortex that was associated with greater OC symptom severity.³⁸ Furthermore, a functional brain imaging study of patients with Tourette's disorder found *decreased* metabolic activity in the ACC and dorsolateral prefrontal cortical regions that was associated with greater OC symptom severity.³⁹ Hence, there may be a substantial difference between patients with OCD and pa-

tients with Tourette's disorder in ACC activity,^{12-14,38,39} suggesting the ERN may be larger in patients with non-tic-related OCD than in patients with tic-related OCD.

Because the ERN has been examined to a limited extent in pediatric OCD³⁴ and tic disorders,³⁷ the present study was conducted in 44 youth with a lifetime diagnosis of OCD and 44 age-matched healthy controls using a flanker task that elicits response conflict. The primary aim was to determine that the ERN is larger in patients with OCD than in controls and, more specifically, larger in patients with non-tic-related OCD than in patients with tic-related OCD or controls. The secondary aim was to examine the correlations of the ERN with age in all subjects and age at onset of OCD symptoms in patients.²³

METHOD

Participants

Pediatric patients were recruited in the Department of Psychiatry at the University of Michigan and the surrounding community. Pediatric comparison subjects were recruited from the surrounding community. 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.

All 44 patients had a lifetime diagnosis of OCD. Patients were excluded if they had a lifetime diagnosis of autistic disorder, Asperger disorder, schizophrenia, other psychotic disorder, bipolar I disorder, substance-related disorder, or anorexia nervosa, or a current diagnosis of major depressive disorder. All 44 comparison subjects had no history of an Axis I disorder. Lifetime and current Axis I diagnoses were made independently by two clinicians using all sources of information according to *DSM-IV* criteria. Patients and comparison subjects were excluded if they had a history of mental retardation, head injury with a sustained loss of consciousness, a chronic neurologic disorder such as a seizure disorder, or a score higher than 15 on the lifetime version of the Social Communication Questionnaire.⁴⁰ All participants lived with at least one English-speaking biological parent who was willing to participate in the research.

Consistent with prior 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 but no other psychotropic medications. Medications being taken (number of patients taking the medication) were fluoxetine (11), sertraline (2), escitalopram (2), and citalopram (1). Prior studies have found sero-

tonergic antidepressants have no effect on ERN amplitude.^{29,31}

All 88 participants were interviewed with the Schedule for Schizophrenia and Affective Disorders for School-Aged Children—Present and Lifetime Versions⁴¹ and the Schedule for Obsessive-Compulsive and Other Behavioral Syndromes.⁴² The lifetime (maximum) and current severities of OCD were assessed in the patients with a modified version of the Children's Yale-Brown Obsessive Compulsive Disorder Scale.⁴³ The parent-report scales completed for all participants consisted of the Child Behavior Checklist⁴⁴ and Social Communication Questionnaire.⁴⁰ The self-report scales completed by all participants consisted of the Multidimensional Anxiety Scale for Children⁴⁵ and the Children's Depression Inventory.⁴⁶

The average age of the patients with OCD was 13.8 years (range, 10–19 years), and the average age of the healthy controls was 13.9 years (range, 10–18 years; $t_{86} = 0.09, p = .93$). The group with OCD had 20 male subjects and the comparison group had 22 male subjects ($\chi^2_1 = 0.18, p = .67$). The current and lifetime Children's Yale-Brown Obsessive Compulsive Disorder Scale scores in the patients with OCD ranged from 0 to 34 and from 12 to 36, respectively. Although all patients had a lifetime diagnosis of OCD, 29 had a current diagnosis and 15 had a past diagnosis with minimal current OCD symptoms that no longer met the criteria for the diagnosis.

Nine patients with OCD had a lifetime history of tics, consisting of six with Tourette's disorder, one with chronic motor tic disorder, one with transient tic disorder, and one with tic disorder not otherwise specified. All patients with tic-related OCD had a current OCD diagnosis. The tic-related group had six male subjects and the non-tic-related group had 14 male subjects ($\chi^2_1 = 2.05, p = .15$). One patient with tic-related OCD had a history of attention-deficit/hyperactivity disorder. There were no significant differences between the patients with tic-related and the patients with non-tic-related OCD in their history of depressive disorders ($\chi^2_1 = 0.15, p = .70$) or non-OCD anxiety disorders ($\chi^2_1 = 2.46, p = .12$). Table 1 presents other demographic and clinical data for the patients and controls.

Task and Procedure

Participants performed a modified Eriksen flanker task in which arrows appeared on a personal computer display with congruent (e.g., $\rightarrow\rightarrow\rightarrow\rightarrow$) and incongruent (e.g., $\rightarrow\leftarrow\rightarrow\rightarrow$) conditions.⁴⁷ They were instructed to respond to the central arrow target by pressing one of two buttons indicating the direction of the middle 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 the interval between consecutive stimuli lasting 1,500 ms.

Each participant was seated 0.65 m directly in front of the computer monitor. After a practice block of 32 trials, each subject completed 8 blocks of 64 trials for a total of 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.

Electrophysiologic Recording, Data Reduction, and Analysis

The EEG was recorded at direct current using 104 Hz with 64 Ag/AgCl scalp electrodes, two mastoid electrodes, and two vertical and two horizontal electro-oculographic 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 (<http://www.biosemi.com/faq/cms&drl.htm>). Data were digitized at 512 Hz; after recording, the data were resampled at 256 Hz. Before eye movement correction, EEG data were screened using automated algorithms that rejected individual sweeps in which the absolute voltage range for any individual electrode exceeded 500 μV , a change greater than 50 μV was measured from one data point to the next, or the data deviated by more than +25 or -100 dB in the 20- to 40-Hz frequency window (for detecting muscle artifacts). Data were also screened by visual inspection. Ocular movement artifacts were then corrected using the algorithm described by Gratton *et al.*⁴⁸ Waveforms shown in the 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 measurements included the number of correct and incorrect trials for each subject and accuracy expressed as a percentage of valid trials. Average reaction times on error and correct trials were calculated separately. Reaction time and accuracy after errors were evaluated to determine if there were group differences in post-error behavioral adjustments. 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 57.7 (SD = 24.5; range, 8–121).

The ERN was quantified using mean amplitude measurements relative to a prereshponse baseline -200 to -50 ms. The mean amplitude of the ERN was computed on incorrect response trials in a window 0 to 80 ms after the incorrect response. The correct response negativity consisted of the same measurement computed on correct response trials. Amplitudes were calculated for the central frontal (FCz) and central (Cz) electrodes. Results are presented for the

TABLE 1 Demographic and Clinical Data in Youth With Non-Tic-Related Obsessive-Compulsive Disorder (OCD), Youth With Tic-Related OCD, and Healthy Comparison Subjects

Variable	Youth with Non-Tic-Related OCD (n = 35)		Youth with Tic-Related OCD (n = 9)		Healthy Control Subjects (n = 44)		Comparisons of Non-Tic-Related OCD, Tic-Related OCD, and Healthy Control Subjects	
	Mean	SD	Mean	SD	Mean	SD	Test Statistic	p
Age (y)	13.9	2.3	13.6	3.5	13.9	2.3	$F_{2,85} = 0.04$.96
Child Behavior Checklist								
Total score	31.1	20.5	44.6	23.4	6.9	5.4	$F_{2,85} = 36.9$	<.0001 ^{a,b}
Internalizing score	12.8	8.7	16.6	9.5	2.3	2.1	$F_{2,85} = 35.5$	<.0001 ^c
Externalizing score	5.7	6.5	7.6	7.8	1.7	1.9	$F_{2,85} = 9.0$	<.0003 ^{d,e}
Obsessive-Compulsive Scale score	5.7	3.8	8.8	3.6	0.6	0.8	$F_{2,85} = 53.0$	<.0001 ^{f,g}
Multidimensional Anxiety Scale for Children	47.0	19.9	43.2	21.8	26.9	13.5	$F_{2,85} = 15.1$	<.0001 ^{h,i}
Children's Depression Inventory	10.0	7.2	9.3	5.7	2.6	2.7	$F_{2,85} = 6.19$	<.0001 ^{i,k}
Age at onset of OC symptoms (y)	8.4	3.0	5.8	3.4			$F_{1,42} = 5.40$.025
Duration of OC symptoms (y)	7.8	4.1	5.3	3.5			$F_{1,42} = 3.32$.08
CY-BOCS								
Lifetime score	27.4	6.3	29.9	4.7			$F_{1,42} = 1.17$.29
Current score	15.2	8.9	21.1	5.8			$F_{1,42} = 3.60$.06

Note: CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale; y = years.

^aPatients with non-tic-related OCD significantly different from patients with tic-related OCD, $p = .02$.

^bPatients with non-tic-related OCD significantly different from healthy controls and patients with tic-related OCD significantly different from healthy controls, $p < .0001$.

^cPatients with non-tic-related OCD significantly different from healthy controls and patients with tic-related OCD significantly different from healthy controls, $p < .0001$.

^dPatients with non-tic-related OCD significantly different from healthy controls, $p = .002$.

^ePatients with tic-related OCD significantly different from healthy controls, $p = .0006$.

^fPatients with non-tic-related OCD significantly different from healthy controls and patients with tic-related OCD significantly different from healthy controls, $p < .0001$.

^gPatients with non-tic-related OCD significantly different from patients with tic-related OCD, $p = .004$.

^hPatients with non-tic-related OCD significantly different from healthy controls, $p < .0001$.

ⁱPatients with tic-related OCD significantly different from healthy controls, $p = .01$.

^jPatients with non-tic-related OCD significantly different from healthy controls, $p < .0001$.

^kPatients with tic-related OCD significantly different from healthy controls, $p = .0007$.

FCz and Cz electrodes, with findings generally stronger at the Cz electrode.

ERN amplitude was compared between groups using a repeated-measure analysis of covariance with error number included as a covariate. Analyses of clinical variables were conducted with analysis of variance and the Student *t* tests. Pearson correlation coefficients were used to examine associations of response-related amplitudes with age, behavioral measurements, and clinical measurements. All statistical tests were two-tailed with the α level set at 0.05.

RESULTS

Behavioral Data in Patients With OCD and Healthy Controls

Behavioral and event-related brain potential data for participants are presented in Table 2. Com-

pared with the control group, there was a trend for the OCD group to make more errors ($F_{1,86} = 3.74$, $p = .056$), using the number of error trials that remained after data cleaning, with patients with non-tic-related OCD making more errors than healthy controls ($F_{1,77} = 5.34$, $p = .024$). No main effect of the OCD and control groups and no interaction between those groups and response type for reaction time reached significance. There was no significant difference between the OCD and control groups in post-error reaction time. In a comparison of patients with tic-related OCD, patients with non-tic-related OCD, and control subjects, there was no significant main effect for groups or significant interaction between those groups and response type for reaction time. There were no significant sex dif-

TABLE 2 Behavioral and Event-Related Brain Potential Data in Youth With Non-Tic-Related Obsessive-Compulsive Disorder (OCD), Youth With Tic-Related OCD, and Healthy Comparison Subjects

Variable	Youth with Non-Tic-Related OCD (n = 35)		Youth with Tic-Related OCD (n = 9)		Healthy Control Subjects (n = 44)		Comparisons of Non-Tic-Related OCD, Tic-Related OCD, and Healthy Control Subjects	
	Mean	SD	Mean	SD	Mean	SD	Test Statistic	p
Behavioral data								
Total number of errors	65.3	24.1	52.2	22.3	52.7	24.1	$F_{2,85} = 2.96$.06 ^a
Correct reaction time (ms)	464.0	103.5	524.8	112.6	504.0	136.8	$F_{2,85} = 1.44$.24
Error reaction time (ms)	456.2	203.8	520.9	167.6	484.1	252.9	$F_{2,85} = 0.32$.73
Post-error reaction time (ms)	452.8	137.7	566.1	142.0	506.4	224.8	$F_{2,85} = 1.60$.21
Error-related potential data								
Error-related negativity, FCz (μV)	-4.52	5.39	-2.34	3.92	-2.61	4.17	$F_{2,84} = 3.71$.03 ^{b,c}
Error-related negativity, Cz (μV)	-2.25	5.61	0.88	4.46	1.04	5.43	$F_{2,84} = 6.93$.002 ^{d,e}
Correct response negativity, FCz (μV)	1.91	5.61	2.56	3.13	1.85	4.03	$F_{2,85} = 0.09$.92
Correct response negativity, Cz (μV)	3.16	6.05	4.23	3.62	3.51	4.87	$F_{2,85} = 0.15$.86

Note: Cz = central electrode; FCz = frontal central electrode.
^aPatients with non-tic-related OCD significantly different from healthy controls, $p = .02$.
^bPatients with non-tic-related OCD significantly different from patients with tic-related OCD, $p = .04$.
^cPatients with non-tic-related OCD significantly different from healthy controls, $p = .02$.
^dPatients with non-tic-related OCD significantly different from patients with tic-related OCD, $p = .01$.
^ePatients with tic-related OCD significantly different from healthy controls, $p = .001$.

ferences for error total, reaction time on correct or error trials, or post-error slowing.

Event-Related Brain Potential Data in Patients With OCD and Healthy Controls

ERN amplitudes at the FCz and Cz electrodes were significantly correlated with error number in all subjects, becoming smaller (or less negative) with increasing errors ($r = 0.24$, $p = .024$ and $r = 0.25$, $p = .021$, respectively). ERN amplitudes at the FCz and Cz electrodes were significantly correlated with error number in the OCD group ($r = 0.44$, $p = .003$ and $r = 0.47$, $p = .001$, respectively) but not in the control group ($r = 0.09$, $p = .57$ and $r = 0.15$, $p = .34$, respectively). In particular, the ERN at the FCz and Cz electrodes was highly correlated with error number in the patients with non-tic-related OCD ($r = 0.46$, $p = .006$ and $r = 0.49$, $p = .003$). ERN amplitudes at the FCz and Cz electrodes had no significant correlations with reaction time on correct or error trials or with post-error slowing.

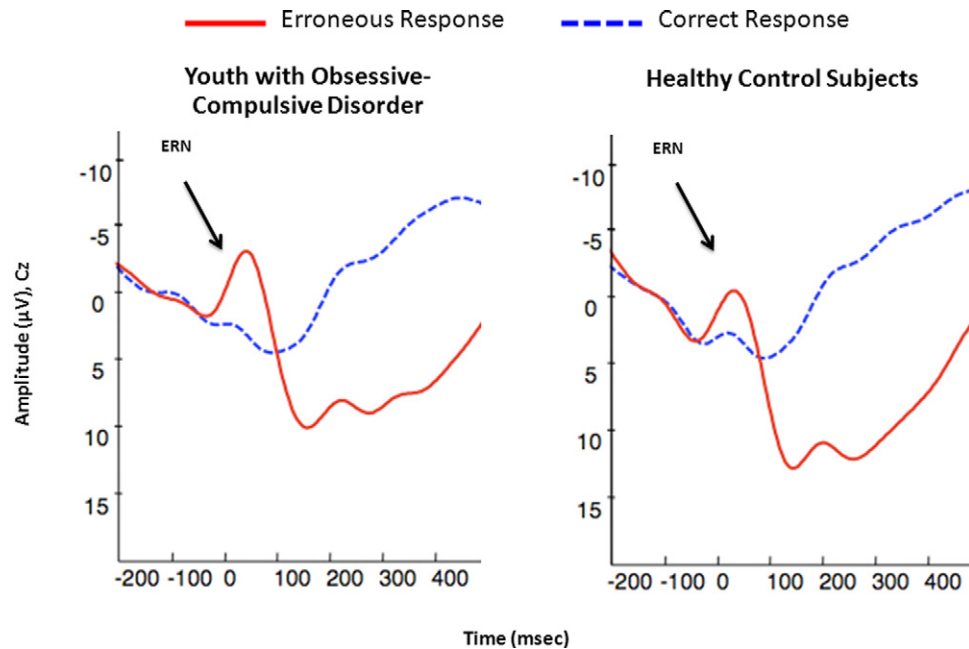
Although there was no significant correlation between ERN amplitude at the FCz electrode and age, ERN amplitude at the Cz elec-

trode had a significant correlation with age in all subjects, becoming larger (or more negative) with increasing age ($r = -0.21$, $p = .049$). The correlation of ERN amplitude at the Cz electrode with age was significant in the control group ($r = -0.36$, $p = .017$) but not in the OCD group ($r = -0.09$, $p = .55$).

ERN amplitudes at the FCz and Cz electrodes were significantly increased in patients with OCD compared with healthy controls ($F_{1,85} = 4.21$, $p = .043$ and $F_{1,85} = 8.70$, $p = .004$, respectively) with significant effects for error number ($F_{1,85} = 7.33$, $p = .008$ and $F_{1,85} = 9.06$, $p = .003$, respectively; Figure 1). There were no significant interactions between the two groups and error number at either electrode. There were no significant differences between the OCD and control groups in correct response negativity amplitudes at either electrode. There were no significant sex differences in any brain potentials.

In a comparison of patients with tic-related OCD, patients with non-tic-related OCD, and healthy controls, there were significant effects on ERN amplitude at the FCz and Cz electrodes for diagnosis ($F_{2,84} = 3.71$, $p = .028$ and $F_{2,84} = 6.83$, $p = .002$, respectively) and error number ($F_{1,84} =$

FIGURE 1 Grand averages of electroencephalogram (EEG) recordings in youth with obsessive-compulsive disorder (OCD) and healthy control subjects. 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.



8.90, $p = .004$ and $F_{1,84} = 11.36$, $p = .001$, respectively; Figure 2). There were no significant interactions between the three diagnostic groups and error number at either electrode.

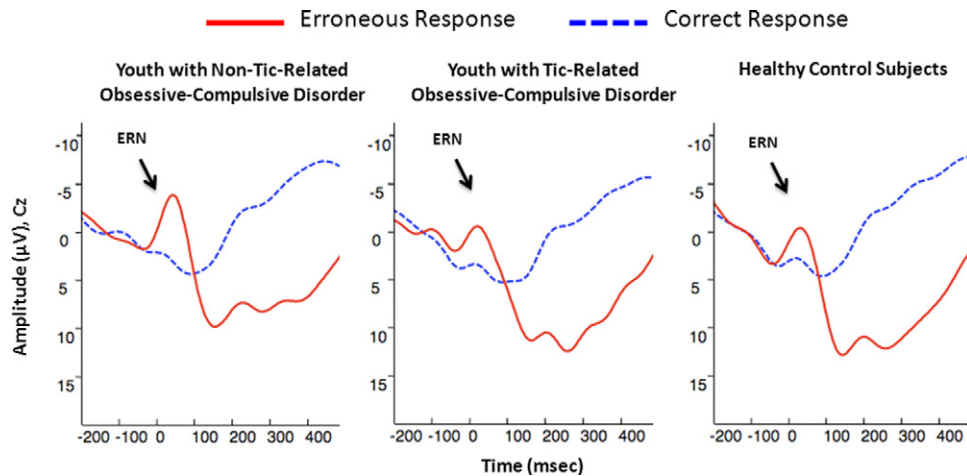
In comparisons of patients with non-tic-related OCD with healthy controls and patients with tic-related OCD, ERN amplitude at the FCz electrode was significantly larger in patients with non-tic-related OCD than in healthy controls ($F_{1,76} = 5.86$, $p = .018$), with a significant effect for error number ($F_{1,76} = 6.12$, $p = .016$), and significantly larger in patients with non-tic-related OCD than patients with tic-related OCD ($F_{1,41} = 4.38$, $p = .043$), with a significant effect for total error number ($F_{1,41} = 13.65$, $p = .0006$; Table 2). Moreover, ERN amplitude at the Cz electrode was significantly larger in patients with non-tic-related OCD than in healthy controls ($F_{1,76} = 11.32$, $p = .001$), with a significant effect for error number ($F_{1,76} = 7.62$, $p = .007$), and significantly larger in patients with non-tic-related OCD than in patients with tic-related OCD ($F_{1,41} = 7.41$, $p = .010$), with a significant effect for error number ($F_{1,41} = 17.62$, $p = .0001$). There were no significant differences between the patients with tic-related OCD and healthy controls in ERN amplitude at either electrode.

Clinical Correlations and Comparisons in Patients With OCD

In all patients with OCD, ERN amplitude at the FCz and Cz electrodes had no significant correlations with age at onset or duration of OCD symptoms. However, in patients with non-tic-related OCD, ERN amplitude had a significant positive correlation with age at onset of OCD symptoms at the Cz electrode ($r = 0.37$, $p = .029$) but not the FCz electrode ($r = 0.31$, $p = .07$). Conversely, in patients with non-tic-related OCD, ERN amplitude had significant negative correlations with duration of OCD symptoms at the Cz ($r = -0.41$, $p = .015$) and FCz ($r = -0.34$, $p = .043$) electrodes, becoming larger (or more negative) with increasing duration.

In all patients with OCD and in the tic-related and non-tic-related groups, there were no significant correlations between any event-related brain potentials and current or lifetime measurements of OCD symptom severity. There were no significant differences in any brain potentials between patients with a current diagnosis and those with a past diagnosis of OCD. There were no significant differences in any brain potentials between patients with OCD receiving and those not receiving a serotonin reuptake inhibitor or

FIGURE 2 Grand averages of electroencephalogram (EEG) recordings in youth with non-tic-related obsessive-compulsive disorder (OCD), youth with tic-related OCD, and healthy control subjects. 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.



between patients receiving and not receiving cognitive-behavioral therapy with exposure/response prevention.

DISCUSSION

The finding of a larger ERN in youth with a lifetime diagnosis of OCD is consistent with previous reports of increased error-related brain activity in adults and children with OCD.^{14,25-32,34} However, the ERN increase appeared to be specific to patients with non-tic-related OCD, who made more mistakes than controls and had a strong positive correlation between the ERN and error number, suggesting that increased error-related brain activity in this OCD subtype may arise to compensate for cognitive deficits. The ERN had a negative correlation with age in healthy controls, as described in previous studies,^{23,34} but not in patients with OCD. Instead, the ERN had a positive correlation with age at onset of OCD symptoms in patients with non-tic-related OCD, suggesting that development of error-related brain activity may be accelerated in this OCD subtype. Although patients with tic-related OCD had a younger age at onset of OCD symptoms than patients with non-tic-related OCD,³ the patients with tic-related OCD had no evidence of increased error-related brain activity.

The observation of a larger ERN in patients with non-tic-related OCD compared with pa-

tients with tic-related OCD provides preliminary evidence of another neurobiological difference between these two OCD subtypes.^{10,11} The ERN difference between the two OCD subtypes is consistent with functional brain imaging studies showing increased metabolic activity in the ACC in OCD¹² and decreased metabolic activity in the same region in Tourette's disorder.³⁹ Nonetheless, the results require replication with a larger sample of patients with OCD with and without chronic tics before concluding the ERN increase is specific to non-tic-related OCD.

The results provide further evidence that the ERN with tasks eliciting response conflict is a trait-like measurement in OCD that appears independent of OCD symptom severity, current diagnostic status, or treatment effects.^{29-31,34} ERN results have been more variable, however, in studies of adults with OCD using probabilistic learning tasks or other tasks.⁴⁹⁻⁵² The study showing enlarged ERN amplitudes in the unaffected first-degree relatives of OCD probands excluded probands with motor tics,³⁰ so that the effect of proband tic history on ERN amplitude in unaffected relatives remains unknown. Although the ERN has been proposed as an endophenotype for OCD,^{30,34,36} it is often difficult to determine whether a putative endophenotype is associated with the causes rather than the effects of a disorder.^{53,54} Further research is necessary to show that increased error-related brain activity

mediates the genetic risk for non-tic-related OCD rather than merely indicating risk through a pleiotropic effect.^{53,54} An alternative term such as *biomarker* may better describe the current status of an enlarged ERN as a possible genetic correlate of non-tic-related OCD.

The present study has several limitations requiring further consideration. The sample size for the group with tic-related OCD, in particular, was small. No corrections were made for multiple testing, although one-tailed tests may have been justified for the main comparisons. The assessment of lifetime OC symptom severity and age at onset of OCD symptoms was done retrospectively rather than prospectively. The treatment of patients in this study was not controlled, albeit patients on medications other than the selective serotonin reuptake inhibitors were excluded.

In summary, the present results provide further evidence of increased error-related brain activity in pediatric OCD.³⁴ Greater error-related brain activity was found in the non-tic-related than in the tic-related OCD subtype, with a significant correlation between the ERN and age at OCD symptom onset in non-tic-related OCD. If the results are replicated, they will provide another validation of the distinction between

tic-related and non-tic-related OCD.²⁻¹¹ A larger ERN was found in patients with non-tic-related OCD who varied considerably in their current and lifetime symptom severity, indicating the ERN is a trait-like measurement that may serve as a biomarker for this OCD subtype.^{30,34,36} Hence, the ERN may be a useful quantitative phenotype in genetic studies of tic-related and non-tic-related OCD. &

Accepted June 26, 2012.

Drs. Hanna, Carrasco, Fitzgerald, and Gehring, Ms. Harbin, and Ms. Nienhuis are with the University of Michigan. Ms. LaRosa is with the Wayne State University School of Medicine. Dr. Chen is with the National Chung Cheng University.

This research was supported by National Institute of Mental Health grants R01 MH086321 (G.L.H.), F31 MH086273 (M.C.), and K23 MH 082176 (K.D.F.); the International Obsessive-Compulsive Disorder Foundation (G.L.H.); the Dana Foundation (K.D.F.); the National Alliance for Research on Schizophrenia and Depression Young Investigator Award (K.D.F.); the Undergraduate Research Opportunity Program (C.E.L.); and the Studying Abroad Scholarship from the Ministry of Education, Taiwan (P.C.).

Disclosure: Drs. Hanna, Carrasco, Chen, Fitzgerald, and Gehring, Ms. Harbin, Ms. Nienhuis, and Ms. LaRosa report no biomedical financial interests or potential conflicts of interest.

Correspondence to Gregory L. Hanna, M.D., 4250 Plymouth Road, Ann Arbor, MI 48109-5766; e-mail: ghanna@umich.edu

0890-8567/\$36.00/©2012 American Academy of Child and Adolescent Psychiatry

<http://dx.doi.org/10.1016/j.jaac.2012.06.019>

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