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Increased error-related brain activity in youth with obsessive-compulsive disorder and other anxiety disorders

Melisa Carrasco[a], Christina Hong[a], Jenna K. Nienhuis[b], Shannon M. Harbin[b], Kate D. Fitzgerald[b], William J. Gehring[a], Gregory L. Hanna[b,*]

[a] Department of Psychology, University of Michigan, 530 Church Street, Ann Arbor, MI, USA
[b] Department of Psychiatry, University of Michigan, 4250 Plymouth Road, Ann Arbor, MI, USA

HIGHLIGHTS

- The error-related negativity (ERN) reflects activity in the medial frontal cortex.
- Compared to controls, the ERN was increased in youth with anxiety disorders.
- Anxiety problems scale scores correlated with ERN amplitude in all subjects.
- Serotonergic antidepressants and cognitive-behavior therapy had no effect on the ERN.
- Pediatric anxiety disorders involve a dysfunction in the medial frontal cortex.

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ABSTRACT

The error-related negativity (ERN) is a negative deflection in the event-related potential after an incorrect response that is thought to reflect activity in the anterior cingulate cortex (ACC) and is often increased in patients with anxiety disorders. This study measured the ERN and correct response negativity (CRN) during an Eriksen flanker task to assess performance monitoring in 26 youth with obsessive-compulsive disorder (OCD), 13 youth with a non-OCD anxiety disorder consisting of either generalized anxiety disorder or separation anxiety disorder, and 27 age-matched healthy controls ranging in age from 8 to 16 years. Compared to healthy controls, ERN amplitude was significantly increased in patients with either OCD or a non-OCD anxiety disorder. There were no significant group differences in CRN amplitude. Treatment with a serotonergic antidepressant or cognitive-behavior therapy had no effect on the ERN in patients. Scores from the Child Behavior Checklist DSM-oriented anxiety problems scale had a significant correlation with ERN amplitude in all subjects. The results provide further evidence that the pathophysiology of OCD and some non-OCD anxiety disorders involves increased ACC activity and that the ERN may serve as a quantitative phenotype in genetic and longitudinal studies of these complex traits.

1. Introduction

Anxiety disorders are the most common form of psychopathology in youth with a lifetime prevalence of about 32% [22]. Neuroimaging and electrophysiological evidence indicates that increased error-related activity in the anterior cingulate cortex (ACC), a region of the medial frontal cortex associated with integration of cognitive and affective information, is important in the pathophysiology of high trait anxiety, obsessive-compulsive disorder (OCD), and generalized anxiety disorder (GAD) [8,26,37]. GAD is characterized by excessive worries about everyday events that are similar to obsessions in that both refer to unpleasant, repetitive thoughts that are difficult to control. The observation of increased error-related brain activity in patients with obsessions, compulsions, or excessive worries is consistent with the hypothesis that these symptoms are associated with defects in an error-detection system, which may give rise to repeated doubts about actions and excessive concern about potential mistakes [27].

The error-related negativity (ERN) or error negativity (Ne) is a negative deflection in the response-locked event-related potential that peaks within 100 ms following an erroneous response [10], which can be evoked by errors committed outside of conscious awareness [25]. It has been hypothesized to reflect error detection, response conflict, or reward prediction errors in which outcomes are worse than expected [10]. Studies using functional

* Corresponding author. Tel.: +1 734 764 0234; fax: +1 7349368907.
E-mail addresses: melcarr@umich.edu (M. Carrasco), chrishng@umich.edu (C. Hong), jennan@med.umich.edu (J.K. Nienhuis), smharbin@umich.edu (S.M. Harbin), krd@umich.edu (K.D. Fitzgerald), wgehring@umich.edu (W.J. Gehring), ghanna@umich.edu (G.L. Hanna).

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magnetic resonance (MR) imaging, magnetoencephalography, and dipole source localization suggest the ERN is generated mainly by the ACC [17,18,34]. ERN amplitude generally increases with age, which may reflect ACC maturation [4].

In studies using tasks eliciting response conflict, ERN amplitude has been increased in adult patients with OCD [5,6,9,10,29,33,37], undergraduates with self-reported obsessive-compulsive (OC) symptoms [14], pediatric patients with OCD [3,12,15], and children with parent-reported OC symptoms [31]. In a study with pediatric OCD patients, the ERN did not change as a function of the reduction in OC symptoms with cognitive-behavioral therapy, indicating that increased ACC activity during performance monitoring does not necessarily maintain OC symptoms and that an increase in this brain potential may serve as a trait marker for OCD [12]. Increased ERN amplitude has been found 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 [3,29]. As in studies of OC symptoms, ERN amplitude has been increased in studies of adult patients with GAD [35,37], undergraduates reporting high levels of worry relative to phobic and non-anxious control subjects [13], and pediatric patients with GAD and other anxiety disorders [20], indicating that an enlarged ERN is not specific to OCD.

Since the ERN has been examined to a limited extent in pediatric patients with either OCD [3,12,15] or GAD [20] and has not been directly compared in youth with those disorders, the following study was done with 26 youth with OCD, 13 youth with either GAD or separation anxiety disorder (SAD), and 27 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 pediatric patients with a history of OC symptoms, generalized worries, or separation worries compared to healthy controls and to determine whether that deflection is associated with dimensional ratings of anxiety symptoms.

2. Materials and methods

Pediatric patients with OCD, GAD, or SAD were recruited from the Department of Psychiatry at the University of Michigan and surrounding community. Healthy pediatric controls 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. Participant groups were matched for age and gender.

Thirteen patients had diagnoses of GAD and/or SAD without OCD, forming a non-OCD anxiety disorder group that consisted specifically of 5 GAD patients without SAD, 4 SAD patients without GAD, and 4 patients with both disorders. Twenty-six patients had a diagnosis of non-tic-related OCD, with 7 having a history of GAD or SAD and 19 having no history of GAD or SAD. Patients were excluded if they had a lifetime diagnosis of autistic disorder, Asperger's disorder, schizophrenia, other psychotic disorder, bipolar I disorder, chronic tic disorder, substance-related disorder, or anorexia nervosa, or a current diagnosis of major depressive disorder. The healthy control subjects 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-IV-TR criteria. Patients and comparison subjects were excluded if they had a history of mental retardation, head injury with a sustained loss of consciousness, chronic neurological disorder, or a score $\geq$15 on the lifetime version of the Social Communication Questionnaire [2]. All participants lived with at least one English-speaking biological parent who was willing to participate in research.

All 66 participants were interviewed with the Schedule for Schizophrenia and Affective Disorders for School-Aged Children-Present and Lifetime Version [16] and Schedule for Obsessive-Compulsive and Other Behavioral Syndromes. The parent report scales completed for all participants consisted of the Child Behavior Checklist (CBCL) [1] and Social Communication Questionnaire [2]. The self-report scales completed by all participants consisted of the Multidimensional Anxiety Scale for Children (MASC) [21] and Children's Depression Inventory (CDI) [19].

Table 1 summarizes the demographic, clinical, behavioral, and event-related brain potential data for the 13 non-OCD anxiety disorder patients, 26 OCD patients, and 27 healthy controls. Participants ranged in age from 8 to 16 years. The non-OCD anxiety disorder group had 3 males, the OCD group 8 males, and the comparison group 14 males ($\chi^2 = 2.96$, df = 2, $p = .23$). Although all OCD patients had a lifetime diagnosis of that disorder, 17 had a current diagnosis and 9 a past diagnosis with minimal current OCD symptoms that no longer met criteria for diagnosis. Consistent with previous studies finding no effect of serotonergic antidepressants on the ERN [6,29,33], patients were included 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 ($n = 8$), sertraline ($n = 2$), and escitalopram ($n = 1$). No patient was taking more than one SSRI.

Participants performed a modified Eriksen flanker task in which arrows appeared on a computer display with congruent (e.g., →→→→→) and incongruent (e.g., →→←→→) conditions [7]. They were instructed to respond 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 an interval of 1500 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 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.

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 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. Prior to eye movement correction, EEG data were screened using automated algorithms [3,15] and by visual inspection. Ocular movement artifacts were then corrected using a standard algorithm [11].

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 1500 ms. 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 57.2 (SD = 25.3; range = 5–121).

The ERN was quantified using mean amplitude measures relative to a pre-response baseline of −200 to −50 ms. The mean amplitude of the ERN was computed on incorrect response trials

Table 1
Demographic, Clinical, Behavioral, and Event-Related Brain Potential Data in Anxiety Disorder Patients without Obsessive-Compulsive Disorder, Obsessive-Compulsive Disorder Patients, and Healthy Comparison Subjects.

Variable	Non-OCD anxiety disorder patients ($n = 13$)		OCD patients ($n = 26$)		Healthy control subjects ($n = 27$)		Comparisons of non-OCD anxiety disorder patients, OCD patients, and healthy controls	
	Mean	SD	Mean	SD	Mean	SD	Test statistic	p
Demographic and Clinical Data								
Age (years)	11.8	2.3	12.7	2.2	12.4	2.2	$F_{2,63} = 0.64$	0.53
Child Behavior Checklist								
Total score	41.0	18.6	31.0	15.5	6.9	5.4	$F_{2,63} = 37.01$	<0.0001[a,b,c]
Internalizing score	17.7	7.0	13.8	7.8	2.1	2.0	$F_{2,63} = 39.84$	<0.0001[b,c]
Externalizing score	8.4	7.8	4.2	3.9	2.2	2.5	$F_{2,63} = 8.31$	0.0006[b,d]
Anxiety Problems score	6.8	3.2	4.1	2.4	0.2	0.5	$F_{2,63} = 48.41$	<0.0001[b,c,e]
Obsessive-Compulsive Scale score	4.2	2.0	5.7	3.7	0.6	0.8	$F_{2,63} = 28.20$	<0.0001[b,c]
Multidimensional Anxiety Scale For Children (total score)	47.6	17.6	51.9	20.9	27.6	13.2	$F_{2,63} = 13.93$	<0.0001[f,c]
Children's Depression Inventory	7.0	4.2	9.4	7.4	2.5	2.9	$F_{2,63} = 11.40$	< 0.0001[f,c]
Age at onset of anxiety symptoms (years)	6.6	2.4	8.5	2.7			$F_{1,37} = 4.26$	0.046
Behavioral Data								
Total number of correct trials	434.4	48.9	440.6	43.9	442.6	53.1	$F_{2,63} = 0.12$	0.88
Total number of error trials	54.5	19.3	62.5	24.9	53.4	28.1	$F_{2,63} = 0.95$	0.39
Correct trial reaction time (msec)	494.7	99.6	494.1	129.7	566.9	145.6	$F_{2,63} = 2.43$	0.10
Error trial reaction time (msec)	421.2	101.6	495.4	212.9	566.7	294.5	$F_{2,63} = 1.75$	0.18
Post-error reaction time (msec)	519.9	214.0	509.3	259.3	578.4	267.2	$F_{2,63} = 0.54$	0.59
Event-Related Brain Potential Data								
Error-related negativity, FCz (μV)	−5.24	5.15	−4.30	4.64	−1.41	4.05	$F_{2,62} = 4.68$	0.013[g,h]
Error-related negativity, Cz (μV)	−1.45	6.10	−1.94	5.14	2.78	4.82	$F_{2,62} = 7.25$	0.002[g,i]
Correct response negativity, FCz (μV)	0.86	4.55	1.75	4.00	1.15	3.86	$F_{2,63} = 0.25$	0.78
Correct response negativity, Cz (μV)	2.27	5.75	2.99	4.84	2.70	4.42	$F_{2,63} = 0.10$	0.91

OCD, obsessive-compulsive disorder; age at onset of anxiety symptoms refers specifically to the onset age of symptoms of obsessive-compulsive disorder, generalized anxiety disorder, or separation anxiety disorder.

[a] Non-OCD anxiety disorder patients significantly different from OCD patients, $p < 0.05$.
[b] Non-OCD anxiety disorder patients significantly different from healthy controls, $p < 0.0001$.
[c] OCD patients significantly different from healthy controls, $p < 0.0001$.
[d] Non-OCD patients significantly different from OCD patients, $p < 0.01$.
[e] Non-OCD patients significantly different from OCD patients, $p < 0.0005$.
[f] Non-OCD anxiety disorder patients significantly different from healthy controls, $p < 0.005$.
[g] Non-OCD anxiety disorder patients significantly different from healthy controls, $p < 0.05$
[h] OCD patients significantly different from healthy controls, $p < 0.05$.
[i] OCD patients significantly different from healthy controls, $p < 0.0005$.

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, since recent studies with children suggest their ERN is slightly more posterior but temporally similar to the adult ERN [23], the focus of the data presented herein is the ERN at Cz.

ERN amplitude was compared between the three groups using a repeated-measure analysis of covariance (ANCOVA) with error trial number [3,15] and age [24] included as covariates. Analyses of clinical variables were conducted with analysis of variance and Student's t-tests. 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.

3. Results

There were no significant group differences in the number of error trials, reaction time during correct or error trials, or post-error slowing (Table 1). There was no significant difference in reaction times between correct and incorrect responses (paired $t_{65} = 0.66$, $p = 0.52$). No main effect of group on response type for reaction time and no interaction between group and response type for reaction time reached significance ($p = 0.12$ and $p = 0.39$, respectively). In all subjects, age had significant negative correlations with reaction time on correct trials ($r = -0.32$, $p = 0.009$) and with post-error slowing ($r = -0.30$, $p = .014$). However, age had no significant correlations with error trial number ($r = 0.04$, $p = 0.76$) or with reaction time on error trials ($r = -0.08$, $p = 0.51$). There were no significant sex differences for error number, reaction time on correct trials or error trials, or post-error slowing (all p values > 0.3). ERN amplitude at Cz had significant negative correlations with reaction time on incorrect trials ($r = -0.026$, $p = 0.038$) and post-error slowing ($r = -0.26$, $p = 0.034$), but no significant correlations with age, error number, or reaction time on correct trials (all p values > 0.1).

In a comparison of non-OCD anxiety disorder patients, OCD patients, and healthy controls, there was a significant effect on ERN amplitude at Cz for diagnosis ($F_{2,62} = 7.16$, $p = 0.0016$), with a trend for an error trial number effect ($F_{2,61} = 3.62$, $p = 0.06$) but no significant effect for age ($F_{2,61} = 0.11$, $p = 0.74$) (Table 1 and Fig. 1). Compared to controls, the ERN was significantly larger in non-OCD anxiety disorder patients ($F_{1,37} = 5.65$, $p = 0.023$, Cohen's $d = 0.77$), without a significant effect for error trial number ($F_{1,37} = 0.48$, $p = 0.50$). Similarly, compared to controls, the ERN was significantly larger in OCD patients ($F_{1,50} = 14.47$, $p = 0.0004$, Cohen's $d = 0.95$), with a trend for an error trial number effect ($F_{1,50} = 3.50$, $p = 0.07$). There was no significant difference in ERN amplitude between patients receiving and not receiving an SSRI ($F_{1,36} = 1.28$, $p = 0.27$). There was also no significant difference in the ERN between patients receiving and not receiving cognitive behavior therapy ($F_{1,36} = 2.02$, $p = 0.16$). There was no significant difference between the three groups in CRN amplitude at ($p > 0.9$) (Table 1). There were no significant sex differences in any brain potentials (all p values > 0.3).

ERN amplitude at Cz was significantly larger in patients with past OCD than in controls ($F_{1,32} = 11.81$, $p = 0.002$, Cohen's $d = 1.41$),

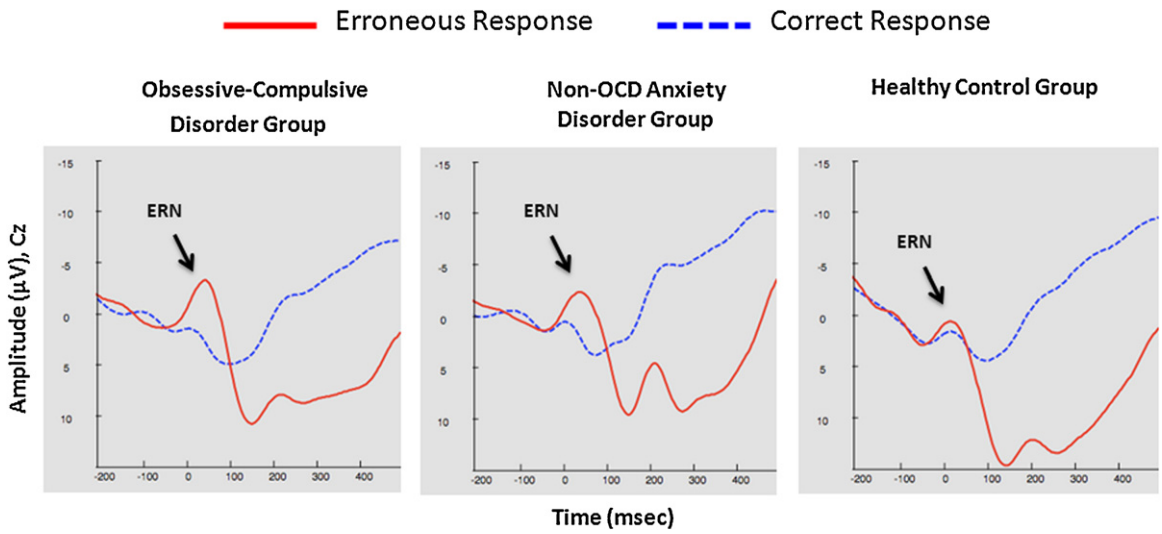

Fig. 1. Grand averages of EEG recordings in non-OCD anxiety disorder patients, OCD patients, and healthy comparison subjects[a].
[a]The images depict response-locked grand average waveforms recorded at electrode Cz for correct and incorrect responses. Responses occurred at 0 ms. The mean amplitude of the error-related negativity (ERN) was computed in a window from 0 to 80 ms following the incorrect response. OCD = obsessive-compulsive disorder. Non-OCD anxiety disorder = generalized anxiety disorder or separation anxiety disorder.

without a significant effect for error trial number ($F_{1,32} = 0.11$, $p = 0.75$), and in patients with current OCD than in controls ($F_{1,32} = 8.39$, $p = 0.006$, Cohen's $d = 0.75$), with a trend for an error trial number effect ($F_{1,32} = 3.39$, $p = 0.073$). There was no significant difference in ERN amplitude between current and past OCD patients ($F_{1,23} = 0.40$, $p = 0.53$). Finally, there was no significant difference in the ERN between OCD patients with and without a history of GAD or SAD ($F_{1,23} = 1.79$, $p = 0.19$).

The groups differed significantly in symptom severity scores from the CBCL, MASC, and CDI, with both OCD and non-OCD anxiety disorder patients having higher scores than healthy controls (Table 1). Of the internalizing measures, scores from the CBCL DSM-oriented anxiety problems scale had the strongest correlation with ERN amplitude at Cz in all subjects (Pearson $r = -0.30$, $p = 0.013$; Spearman $\rho = -0.33$, $p = 0.007$). The effect of the CBCL anxiety problems scale on ERN amplitude remained significant ($F_{1,63} = 6.53$, $p = 0.013$) when error trial number was included in the analysis ($F_{1,63} = 1.79$, $p = 0.18$). The correlation between the ERN and the CBCL anxiety problems scale scores increased slightly when patients with past OCD were excluded from the analysis (Pearson $r = -0.34$, $p = 0.009$; Spearman $\rho = -0.37$, $p = 0.005$), perhaps because they tended to have lower scores on the CBCL anxiety problems scale than patients with current OCD. None of the other correlations between the ERN and scores from the CBCL, MASC, or CDI reached significance (all p values > 0.05).

4. Discussion

Our finding of an enlarged ERN in youth with OCD, GAD, or SAD during a task eliciting response conflict is consistent with previous reports of increased error-related brain activity in adults with high trait anxiety [13,26], OCD [5,6,8–10,29,33,37], or GAD [35,37] and in youth with OCD [3,12,15] or other anxiety disorders [20]. The ERN in our study was almost as large in youth with non-OCD anxiety disorders as in those with OCD, which is consistent with the only study to compare ERN amplitudes in adults with either OCD or GAD [37]. The correlation between the ERN and scores from the CBCL DSM-oriented anxiety problems scale also indicates the ERN may be increased in youth with symptoms other than obsessions or compulsions – including worry, anxiety, nervousness, tension, fearfulness, and clinging or being too dependent on adults – which suggests that OCD and some non-OCD anxiety disorders are associated with similar abnormalities in ACC activity. The enlarged ERN observed in these anxiety disorders may reflect other features common to them, including perfectionism, excessive concern over errors, increased intolerance of uncertainty, and negative affect [35,36]. Assessment of these psychological factors may be useful in future studies of the ERN in patients with OCD, GAD, and SAD.

Our results also provide added evidence that an enlarged ERN in OCD patients is a more trait-like measure that appears independent of OC symptom severity, current diagnostic status, or treatment effects [3,6,12,15,29,33]. Compared to controls, the ERN was enlarged in youth with either a past or current diagnosis of OCD. The ERN in patients with OCD, GAD, or SAD also appeared to be unaffected by ongoing treatment with either an SSRI or cognitive-behavior therapy, suggesting that the ERN is a more trait-like measure in GAD and SAD as well as OCD. Studies of the ERN in unaffected relatives of GAD and SAD patients are necessary to determine whether it is a plausible biomarker for these disorders [3,29].

Studies have suggested that oxidative stress is associated with anxiety-related behavior in animals [28,30]. However, it is unknown whether oxidative stress is associated with either pediatric anxiety disorders or increased ACC activity. MR spectroscopic imaging studies of glutathione in youth with chronic anxiety disorders may be provide information about the possible relationship of oxidative stress to these conditions [32].

Our study has several limitations requiring further consideration. The sample size for the non-OCD anxiety disorder group was small, so that it was not possible to determine that GAD without comorbid SAD and SAD without comorbid GAD are each associated with an enlarged ERN. The estimated statistical power for the difference in ERN amplitudes between the non-OCD anxiety disorder and control groups was only 63%. The correlation between the ERN and scores from the CBCL DSM-oriented anxiety problems scale requires replication in a larger sample of untreated patients and controls. A study with a larger sample of participants with non-OCD anxiety disorders will be necessary to determine whether an enhanced ERN is specific to anxiety disorders characterized more by worry, distress, and trait defensive reactivity than by fear, phobic arousal, and cue-specific defensive reactivity [36]. 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, although patients on medications other than an SSRI were excluded.

Our study provides further evidence of an enlarged ERN in pediatric OCD patients that appears independent of current diagnostic status, comorbid anxiety disorders, and treatment effects [3,12,15]. Our results also demonstrate a comparable increase in the ERN in youth with either GAD or SAD, which extend the findings from previous studies of adults with GAD [35,37] and youth with non-OCD anxiety disorders [20], and indicate that increased error-related brain activity is crucial in the pathophysiology of some forms of OCD and non-OCD anxiety disorders.. The ERN is a promising biomarker for several anxiety disorders that may serve as a quantitative phenotype in genetic and longitudinal studies of these complex traits [3,12,15,29].

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