

# Altered Relationship Between Electrophysiological Response to Errors and Gray Matter Volumes in an Extended Network for Error-Processing in Pediatric Obsessive-Compulsive Disorder

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**Abstract:** Pediatric patients with obsessive-compulsive disorder (OCD) show an increased electrophysiological response to errors that is thought to be localized to the posterior medial prefrontal cortex (pmMFC). However, the relation of this response, the error-related negativity (ERN), to underlying brain structures remains unknown. In an examination of 20 pediatric OCD patients and 20 healthy youth, we found that more negative ERN amplitude was correlated with lower gray matter (GM) density in pmMFC and orbital frontal cortex. The association of the ERN with pmMFC gray matter volume was driven by the patient group. In addition, a group difference in the association of ERN with gray matter in right insula was observed, showing an association of these measures in healthy youth (more negative ERN amplitude was associated with lower GM density in insula), but not in patients. These findings provide preliminary evidence linking gray matter volumes in an extended network for error processing to the ERN, and suggest that structural alterations in this network may underlie exaggeration of the ERN in pediatric OCD. *Hum Brain Mapp* 35:1143–1153, 2014. © 2013 Wiley Periodicals, Inc.

**Key words:** pediatric obsessive-compulsive disorder; event-related potential (ERP); error processing; voxel-based morphometry (VBM); magnetic resonance imaging (MRI)

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## INTRODUCTION

Obsessive-compulsive disorder (OCD) is a disabling psychiatric disorder characterized by intrusive thoughts (obsessions) and/or repetitive behaviors (compulsions). It is often reported to begin in childhood and is associated

with chronic impairment if left untreated [Kessler et al., 2005; Micali et al., 2010; Stewart et al., 2004]. Theories of OCD have attributed the exaggerated concerns and ritualistic behaviors of patients to an overactive error detection system, as patients often endorse a nagging sense that an error has been (or could be) made in association with

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symptoms [Pitman, 1987; Schwartz, 1997]. Support for this notion comes from electrophysiological work demonstrating an increased brain response to errors in OCD [Endrass et al., 2008; Gehring et al., 2000; Johannes et al., 2001; Stern et al., 2010; but see Nieuwenhuis et al., 2005]. Exaggeration of this electrophysiological response, the error-related negativity (ERN), has been demonstrated in patients as young as 8 years old [Hajcak et al., 2008], implicating alterations of a neural substrate for error-processing early in the disease course.

The error-related negativity is a frontally maximal negative event-related potential (ERP) component that follows within 100 ms of an error commission [Falkenstein et al., 1991; Gehring et al., 1993] and has been attributed to a likely neural generator in the posterior medial frontal cortex (pmMFC), including dorsal anterior cingulate cortex (dACC) [Dehaene et al., 1994; Van Veen and Carter, 2002] and supplementary or pre-supplementary motor areas (SMA, pre-SMA) [Dehaene et al., 1994; Nachev et al., 2008; Ridderinkhof et al., 2004a,b; Vidal et al., 2000; see Gehring et al., 2012 for review]. Yet, despite the consistent localization of the ERN to the pmMFC, converging lines of evidence suggest that it may derive from a broader network of brain regions. For example, lateral frontal lesions are associated with a smaller difference in amplitude between correct and error responses (dERN) suggesting that connectivity between the pmMFC and lateral frontal cortex may be critical for the generation of the ERN [Gehring et al., 2000; Ullsperger and von Cramon, 2006; Ullsperger et al., 2002]. This notion is supported by research showing an attenuated ERN in patients with lesions of frontal white matter tracts between lateral frontal and medial frontal cortices due to sickle cell disease [Hogan et al., 2006]. Moreover, functional brain imaging studies of error-processing implicate lateral prefrontal regions, including the insula [Taylor et al., 2007] and dorsolateral prefrontal cortex [Kerns et al., 2004], as well as the pmMFC. Diminished ERN activity has also been found in patients with orbitofrontal lesions [Stemmer et al., 2004; Swick and Turken, 2002] which, given the role of the orbitofrontal cortex in processing affectively salient stimuli [Haber and Knutson, 2010], bolsters theories that the ERN is not only associated with error detection, but may be modulated by the affective significance of an error [Hajcak et al., 2005].

Accumulating evidence suggests that the exaggerated ERN in OCD may be not only associated with altered structure in the pmMFC, but also with structural abnormalities in a broader network for error processing. For instance, functional neuroimaging research in OCD shows increased error-related brain responses in a network of regions including the pmMFC [Ursu et al., 2003], insula, and orbital frontal cortex [Stern et al., 2011]. No studies to date have evaluated neuroanatomical correlates of ERN abnormalities in OCD; however, meta-analyses of voxel-based morphometry (VBM) studies in OCD have recently shown reduced gray matter in a network of regions consisting of

the pmMFC, insula, and lateral and orbital prefrontal cortex [Radua et al., 2011; Rotge et al., 2009] that are believed to contribute to the ERN [Gehring et al., 2012]. Taken together, these findings raise the possibility that the exaggeration of the ERN in OCD may be linked to structural brain deficits extending from the pmMFC into a more distributed brain network for error-processing.

To investigate whether hyperactive error processing in OCD is related to alteration of gray matter density, we correlated whole brain regional GM density measured by voxel-based morphometry (VBM) [Ashburner and Friston, 2000; Good et al., 2001] with the ERN as an indicator of error processing. VBM is a structural imaging analysis tool which evaluates subtle changes across the whole brain in association with clinical conditions [Kassubek et al., 2005; Peinemann et al., 2005] or other brain and behavioral measures [Araki et al., 2005; Beste et al., 2008]. First, based on previous ERN studies in OCD, we hypothesized that patients with pediatric OCD would exhibit enhanced ERN. Second, based on previous studies showing the ERN has a potential neural generator in the pmMFC and may depend on frontal cortical and insula regions, we hypothesized that ERN amplitude would associate with GM density in a distributed brain network for error-processing, comprised of these regions. Finally, we hypothesized that abnormalities of the ERN in OCD would associate with structural alterations within this network.

## METHODS

### Subjects

Participants consisted of 20 youth (aged 10–19 years) with pediatric OCD and 20 age- and gender-matched healthy controls (HC). All participants except two healthy controls were right-handed. All subjects participated in a structured clinical interview, the Kiddie Schedule for Affective Disorders, Present and Lifetime version [Kaufman et al., 1996], administered by a masters level clinician. The Scale for Obsessive Compulsive and Other Behavioral Syndromes [Hanna et al., 2010] was used to assess OCD, tic disorders and grooming disorders. At both ERP acquisition and MRI scan times, the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) [Scahill et al., 1997] was used to assess the severity of current OCD symptoms in the OCD group, and the Obsessive-Compulsive Scale (OCS) of the Child Behavior Checklist (CBCL) was used to assess the severity of recent obsessive-compulsive symptoms in all subjects [Hudziak et al., 2005; Nelson et al., 2001]. All participants attended both ERP and MRI sessions, and the gap between ERP and MRI sessions averaged about 5 months. Twenty-two participants underwent ERP then MR scanning, while data for the other 18 participants was obtained in the reverse order. For both ERP and MRI sessions, written informed assent and consent were obtained from the participants and their parents, respectively. The study was approved by the Institutional Review Board (IRB) of the University of Michigan.

**TABLE I. Demographic information for the obsessive-compulsive disorder (OCD) and control groups**

	OCD ( <i>n</i> = 20)	Control ( <i>n</i> = 20)	Difference
Age at ERP (years, mean ± SD)	14.0 ± 2.2	14.6 ± 2.4	ns
Age at MRI (years, mean ± SD)	13.9 ± 2.3	13.8 ± 2.5	ns
Age Gap (years, mean ± SD)	0.2 ± 0.9	0.7 ± 0.9	*
Gender (Female: male)	10:10	8:12	ns
CBCL-OCS at ERP (mean ± SD)	6.0 ± 3.9	0.8 ± 0.9	*
CBCL-OCS at MRI (mean ± SD)	6.0 ± 3.8	0.9 ± 1.0	*
Current CY-BOCs at ERP (mean ± SD)	15.2 ± 9.3		
Current CY-BOCs at MRI (mean ± SD)	16.8 ± 8.1		

CBCL\_OC, Obsessive compulsive symptom measured by Child Behavioral Checklist; CY-BOCS, Children’s Yale-Brown Obsessive Compulsive Scale; OCD, obsessive-compulsive disorder; ns, no significant difference ( $P > 0.05$ ).

\*Significant difference at  $P < 0.05$ .

All patients had a diagnosis of OCD but given high rates of comorbid anxiety and depression in pediatric OCD [Geller et al., 1998], current or prior diagnoses of generalized anxiety disorder ( $n = 2$ ), depressive disorder not otherwise specified ( $n = 4$ ), specific phobia ( $n = 1$ ), and panic disorder ( $n = 1$ ) were also included. 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, attention-deficit hyperactivity disorder, tic disorder, or anorexia nervosa, or a current diagnosis of major depressive disorder. All patients had a lifetime history of moderate to severe OCD severity ( $27.6 \pm 5.6$ ), but more moderate severity at the time of the study (Table I). Seven patients were medicated (fluoxetine,  $n = 5$ ; sertraline,  $n = 2$ ), and 13 were medication-free at the time of study.

### ERP Task, Recording, and Analysis

Participants performed a modified Eriksen flanker task in which arrows appeared on a personal computer display with congruent (e.g.,  $\rightarrow\rightarrow\rightarrow\rightarrow\rightarrow$ ) and incongruent (e.g.,  $\rightarrow\rightarrow\leftarrow\rightarrow\rightarrow$ ) conditions. They were instructed to respond as quickly and accurately as possible to the central arrow target, while ignoring the adjacent arrows. When the central arrow pointed left, they were asked to press left button; when the central arrow pointed right, they were asked to press right button. The stimuli remained on the screen for 250 msec, with the interval between consecutive stimuli lasting 1,500 msec.

Each participant was seated 0.65 meters directly in front of the computer monitor and told to place equal emphasis on speed and accuracy in responding. Following a practice block of 32 trials, each subject completed 8 blocks of 64 tri-

als (32 congruent and 32 incongruent trials randomly presented in each block) 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 with reference 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 digitized at 512 Hz. Following recording, 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 data point 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). Data were also screened by visual inspection. Ocular movement artifacts were then corrected using the algorithm described by Gratton et al. [1983]. 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. Average reaction times on error and correct trials were calculated separately. Reaction times were analyzed with group as a between-subject factor and response type (error, correct) as a within-subject factor.

The ERN was quantified at the electrode Cz using mean amplitude measures relative to a prereponse baseline of -200 to -50 msec. The mean amplitude of the ERN was computed in a window from 0 to 80 msec following the incorrect response. The mean amplitude of the dERN was computed as the difference of ERN from correct response negativity (CRN), which consisted of the mean amplitude from 0 to 80 ms following the correct response at the Cz electrode.

Given the influence of number of errors and age on ERN amplitude [Gehring et al., 2012], planned analyses tested for Pearson correlations of ERN/dERN amplitudes with age and behavioral measures across and within each group. Group differences in ERN/dERN were evaluated using a repeated-measure analysis of covariance (ANCOVA) with total error number and age included as covariates. Meanwhile, Pearson correlations were computed to test for the associations between ERN/dERN amplitude and clinical measures within groups. All statistical tests were two-tailed with the alpha level set at 0.05.

### MRI Acquisition and Data Analysis

High resolution T1-weighted MRI images (whole-brain coverage, resolution  $1.02 \times 1.02 \times 1.2$ , TE = 1.84 ms, TR = 9.04 ms, flip angle 15 degree, matrix  $256 \times 256$ , FOV 26.1 cm) were acquired on a 3.0T GE Signa scanner.

Structural MRI data were preprocessed and analyzed by VBM toolbox [Good et al., 2001; <http://dbm.neuro.uni-jena.de/vbm.html>] using the SPM8 software package (Wellcome Department of Imaging Neuroscience Group, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>). The procedure has been described by Good et al. [2001]. Images were bias-corrected, tissue classified, and registered using linear (12-parameter affine) and nonlinear transformations (warping), within a unified model [Ashburner and Friston, 2005]. The nonlinear transformation parameters are calculated via the high dimension DARTEL algorithm; for the spatial normalization, we used our own age-appropriate tissue probability maps (TPMs) created with Template-O-Matic (TOM 8) software. The modulated GM volumes were smoothed with a Gaussian kernel of 8 mm full width at half maximum (FWHM).

Whole brain voxelwise analyses were conducted to test the effect of ERN and dERN amplitude on GM density across all subjects, and to test for between-group differences in this association, using SPM8. Given the known influence of age on both ERN and gray matter measures [Davies et al., 2004; Shaw et al., 2006], and the group difference in age gap between ERP acquisition and MRI scan, these measures were regressed out in these analyses. To avoid possible edge effects between different tissue types, we excluded all voxels with less than 0.2 probability of containing GM. Our threshold for statistical significance was set at  $P < 0.001$  uncorrected for multiple comparisons with an extent of at least 100 contiguous voxels within a frontal brain search volume (MNI coordinate  $y > -10$ ) as suggested by Beste et al. [2008], since the ERN has been linked to frontal networks [Gehring et al., 2012].

Gray matter densities were extracted from areas demonstrating significant associations with ERN across groups, or significant differences in associations with ERN between groups, so that we could more closely examine the gray matter- ERN relationship among OCD and healthy subjects in scatter plots, and to test the relationship of extracted values to clinical measures. All these correlations were Pearson correlations for two-tailed tests with the alpha level set at 0.05.

## RESULTS

### Behavioral Data

There was no group difference in reaction times for error or correct trials (RT,  $P > 0.10$ , see Table II), or number of errors. There was no correlation of OC symptom severity with error number or reaction times ( $P > 0.10$ ).

### ERP Data

In the group comparisons controlling for total error number and age at ERP acquisition, children with OCD showed enhanced ERN ( $P = 0.04$ ) and dERN ( $P = 0.03$ ) amplitudes compared to healthy children (see Fig. 1).

**TABLE II. Behavioral and ERP measures for the obsessive-compulsive disorder (OCD) and control groups**

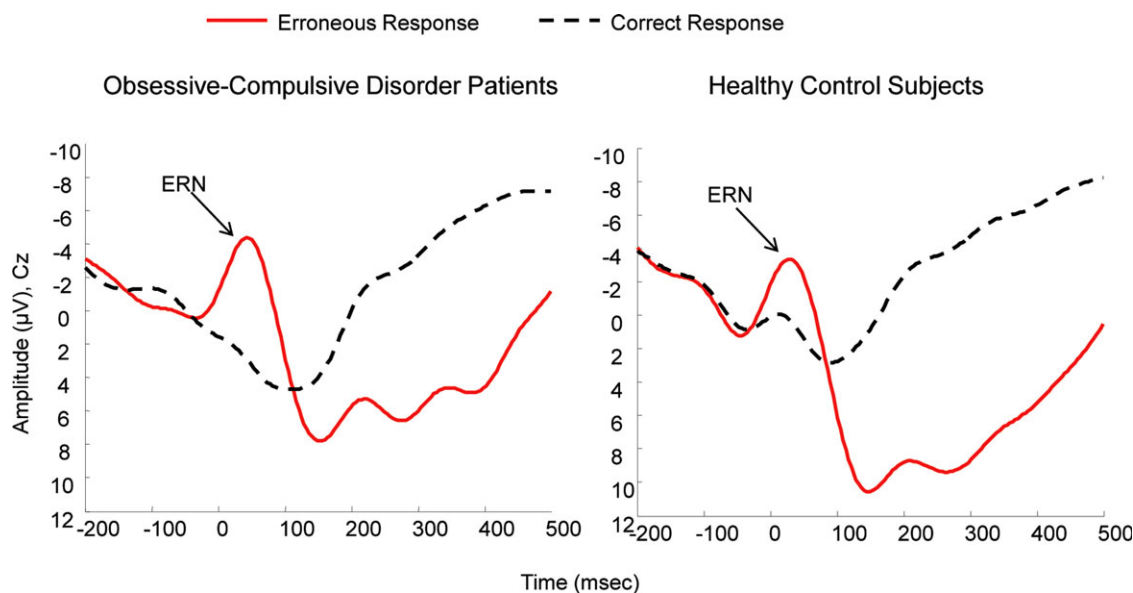
	OCD ( $n = 20$ ) (mean $\pm$ SD)	Control ( $n = 20$ ) (mean $\pm$ SD)	Group effect controlled for error rate and age ( $P$ value)
Total number of errors	64.6 $\pm$ 23.3	53.8 $\pm$ 20.7	
Correct reaction times (ms)	453.5 $\pm$ 111.2	494.2 $\pm$ 108.0	0.14
Error reaction times (ms)	481.0 $\pm$ 239.3	465.0 $\pm$ 203.2	0.814
ERN at Cz (uV)	-1.9 $\pm$ 5.1	0.0 $\pm$ 3.9	0.04
dERN at Cz (uV)	-6.2 $\pm$ 6.8	-3.1 $\pm$ 4.6	0.03

As expected, ERN amplitude was correlated with number of commission errors in all subjects, becoming smaller (or less negative) with increasing errors ( $r = 0.35$ ,  $P = 0.03$ ). dERN amplitude was correlated with age at ERP acquisition in all subjects, becoming larger (or more negative) with increasing age ( $r = -0.40$ ,  $P = 0.01$ ), consistent with prior work in a similar age range [see Gehring et al., 2012 for a review]. ERN and dERN amplitude had no other significant correlations with age or total error number. The correlation between ERN and performance was not different between groups ( $P > 0.05$ ).

ERN amplitude correlated with OC symptoms measured by CBCL in healthy children, becoming larger (or more negative) with increasing symptom severity ( $r = -0.46$ ,  $P = 0.04$ ). No significant associations between the ERN and OC symptom severity measured with either the CBCL or the CY-BOCS were observed in the patient group ( $r = -0.22$ ,  $P = 0.35$ ). Correlation of dERN with OC symptom severity was not significant in either OCD ( $r = -0.33$ ,  $P = 0.12$ ) or HC groups ( $r = -0.38$ ,  $P = 0.09$ ). No other clinical measures were correlated with ERN or dERN for either group.

### Relationship of ERN with VBM Across All Subjects

Across all subjects, the whole brain analysis revealed that ERN amplitude correlated with gray matter volume at the left orbitofrontal cortex (OFC,  $-28, 39, -20$ ; 159; BA 11; Fig. 2A), becoming larger (or more negative) with smaller OFC, while dERN amplitude correlated with gray matter volume at the pmFC (3, 2, 52; 122; BA 24; Fig. 3A), becoming larger (or more negative) with smaller pmFC. Post-hoc testing on extracted OFC gray matter estimates revealed an inverse relation with ERN in both OCD and healthy groups ( $P$ -values  $< 0.05$ ; Fig. 2B). In contrast, the relation of dERN with pmFC gray matter was only significant in OCD patients, but not in healthy youth (all subjects,  $r = 0.48$ ,



**Figure 1.**

Grand Averages of ERP recordings at Cz for patients with OCD and healthy controls. Responses occurred at 0 msec. The mean amplitude of the error-related negativity (ERN) was computed in a time window of 0 to 80 ms following incorrect response trials. OCD, obsessive-compulsive disorder. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

$P < 0.01$ ; patient only,  $r = 0.62$ ,  $P < 0.01$ ; healthy youth only,  $r = 0.19$ ,  $P > 0.05$ ; Fig. 3B). However, the group difference in this correlation was not significant ( $P > 0.10$ ). Extracted gray matter estimates from the OFC were negatively correlated with OC symptoms measured by CBCL in healthy youth ( $r = -0.56$ ,  $P = 0.013$ ), but not OCD patients ( $r = 0.20$ ,  $P = 0.40$ ; Fig. 2C). Extracted gray matter estimates from the pMFC were negatively correlated with OC symptoms measured by CBCL across all subjects ( $r = -0.37$ ,  $P = 0.02$ ) and within the OCD group ( $r = -0.45$ ,  $P = 0.05$ ; Fig. 3C). No other correlations with clinical measures were found ( $P > 0.10$ ).

#### Difference in Relationship of ERN with VBM Between Pediatric OCD and Healthy Groups

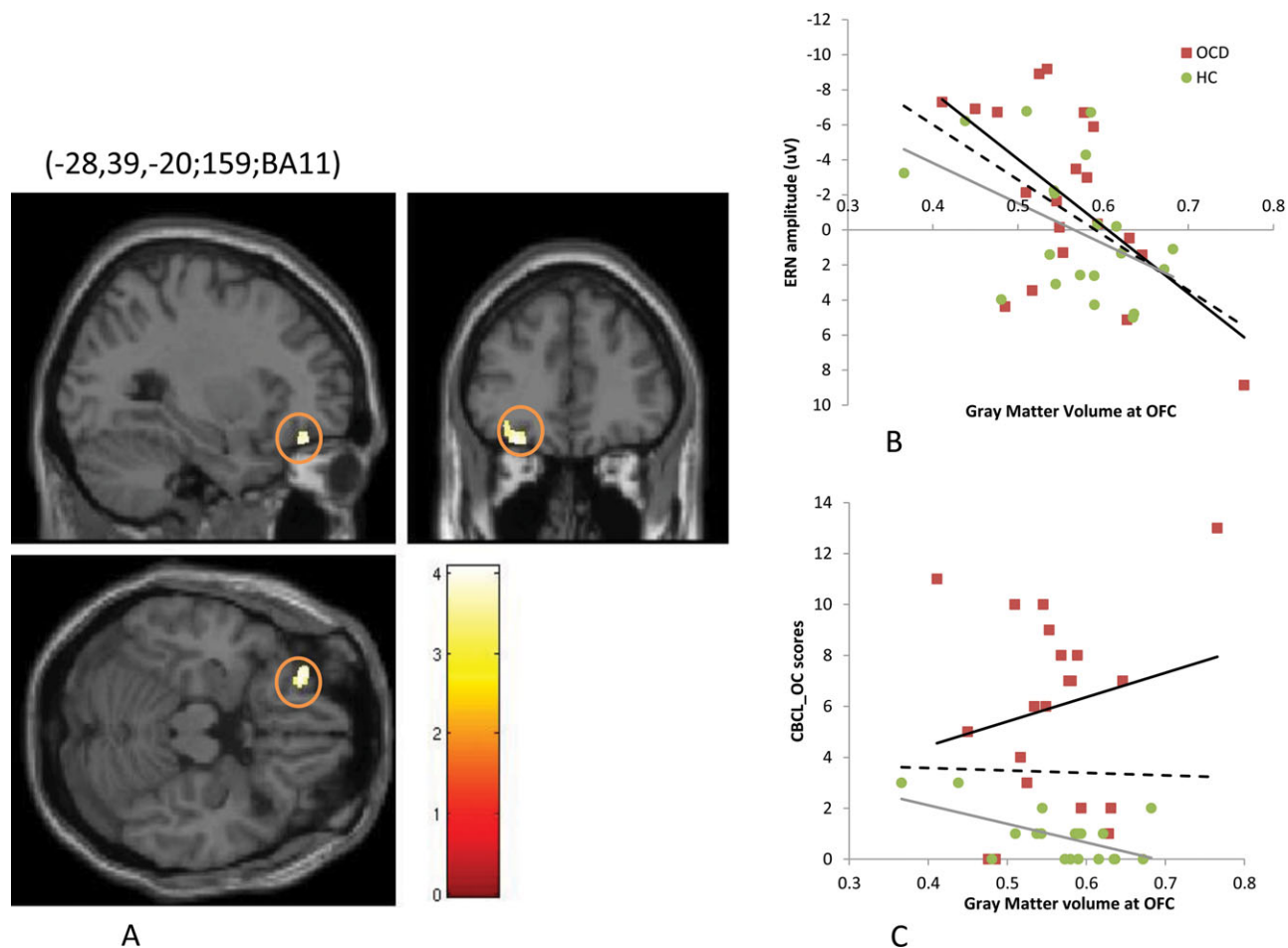
The whole brain analysis testing for group differences in correlation of ERN amplitude with gray matter volume revealed a significant cluster in the right insula (54, 18, -5; 354; Fig. 4). This group difference derived from a correlation in healthy youth (ERN becoming larger or more negative with smaller insula,  $r = 0.72$ ,  $P = 0.001$ ) and a lack of correlation ( $r = -0.25$ ,  $P = 0.32$ ) in pediatric patients with OCD. Gray matter values from the right insula region were negatively correlated with OC symptoms, as measured by CBCL in healthy ( $r = -0.45$ ,  $P = 0.05$ ), but not OCD ( $r = -0.07$ ,  $P = 0.77$ ) groups, after covarying age at the time of scanning. However, right insula gray matter volume showed a trend-level negative correlation with the CY-BOCS obsessional score in the OCD group ( $r = -0.41$ ,  $P = 0.08$ ).

## DISCUSSION

We examined hyperactivity of error processing (indicated by the ERN) in pediatric OCD and its association with underlying gray matter volume. Consistent with previous studies, patients with pediatric OCD exhibited enhanced ERNs (more negative in amplitude) relative to healthy youth. In line with prior work on the neural generator of the ERN [Dehaene et al., 1994; Nachev et al., 2008; Ridderinkhof et al., 2004a; Vidal et al., 2000; Gehring et al., 2012], dERN amplitude was correlated with GM density in the pMFC, specifically in an area spanning dACC into pre-SMA. In addition, ERN amplitude was associated with GM density in orbitofrontal and insula regions, implicating an extended network for error processing in the generation of the ERN. A group difference in the association of the ERN with gray matter localized to the insula—a region that has been previously implicated in normal error processing [Debener et al., 2005; Mathalon et al., 2003; Matthews et al., 2005; Menon et al., 2001; Polli et al., 2005; Taylor et al., 2007; Ullsperger and von Cramon, 2001; see Taylor et al., 2007 for review] and abnormal response to errors in OCD [Stern et al., 2011].

#### Error-Related Brain Activity

The findings of increased ERN and dERN amplitude in patients with pediatric OCD compared to healthy controls, is consistent with previous reports of hyperactive error processing in both adults and children with OCD [Endrass et al., 2008; Gehring et al., 2000; Hajcak et al., 2008; Hajcak



**Figure 2.**

**A:** The gray matter volume in the left orbital frontal cortex (OFC, BA 11) revealed a significant correlation with the ERN measured at Cz for **(B)** all the subjects (indicated by the black dashed line), as well as in individual group (OCD, indicated by the black solid line; HC, indicated by the gray solid line). **C:** Extracted gray matter estimates from the OFC were negatively

correlated with OC symptoms measured by CBCL in healthy youth, but not in OCD patients. ERN, error-related negativity in error trials; OCD, obsessive-compulsive disorder; HC, healthy controls. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

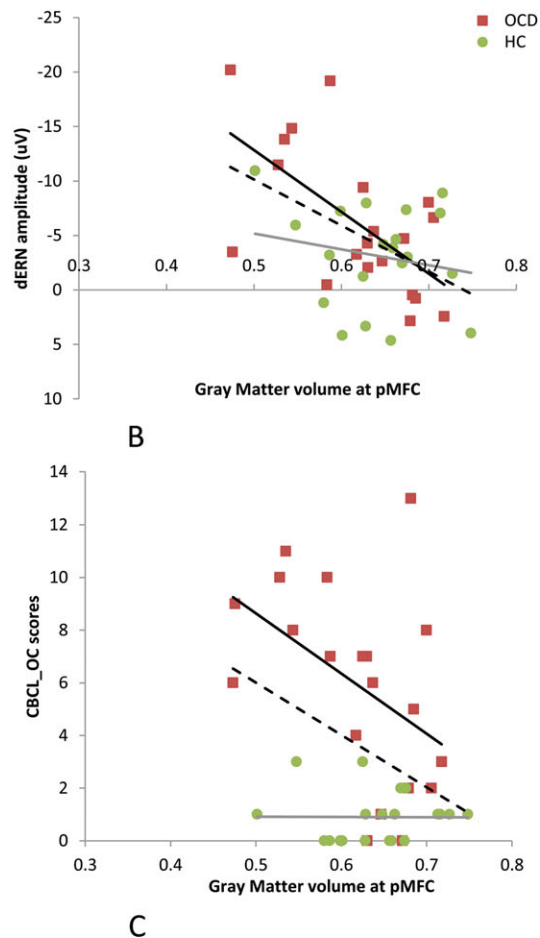
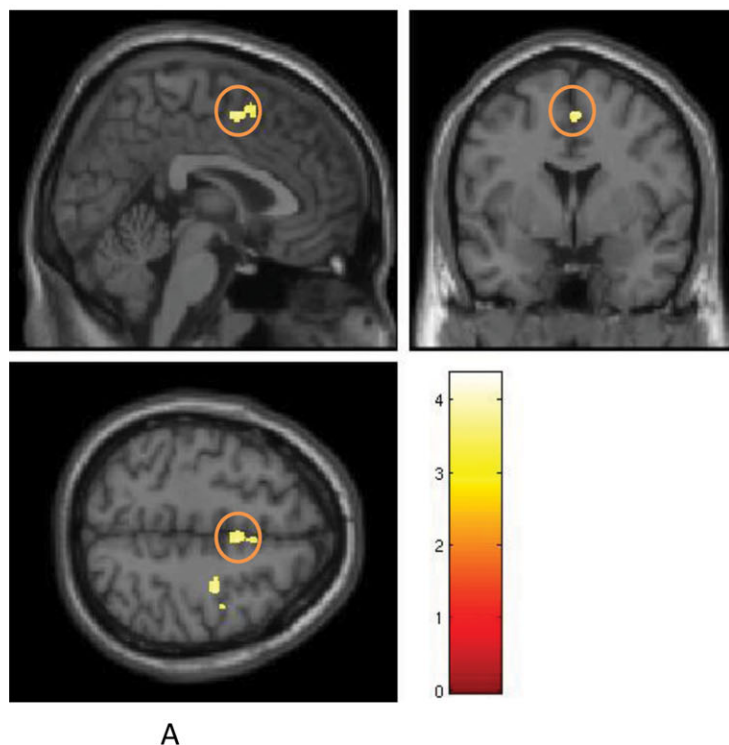
and Simons, 2002; Johannes et al., 2001; Stern et al., 2010]. Increased ERN amplitude has also been associated with increased subclinical OC symptom severity in healthy youth, as assessed by parent report on a CBCL subscale for OC symptomatology [Santesso et al., 2006], suggesting that abnormalities in error monitoring may establish vulnerability for OCD in children who are not affected by the full-blown disorder [Hajcak and Simons, 2002; Taylor et al., 2007]. This possibility was supported by our observation of an association between subclinical OC symptomatology, as measured on the CBCL, and larger ERN amplitude in the healthy youth in our sample. We also observed increased ERN with decreased rates of error commission—a consistent finding across prior studies of the ERN, which has been previously suggested to reflect a

sensitivity of the ERN to the motivational significance of an error [Gehring et al., 1993; Hajcak et al., 2005].

### Association Between ERN and VBM

To characterize the relationship of ERN to underlying brain structure, we collapsed across all subjects, reasoning that increased variance for the combined sample would increase our power to detect associations between the ERN and VBM-based measures of gray matter density. This analysis revealed association of the dERN with pMFC gray matter, consistent with prior source localization of the ERN to neural generators in this region [see Gehring et al., 2012 for review]. Additionally, we tested for differences in the relation of the ERN to gray matter between

(3,2,52;122;BA24)



**Figure 3.**

**A:** The gray matter volume in the posterior medial frontal cortex (pMFC, BA 24), revealed a significant correlation with the dERN measure at Cz for **(B)** all the subjects (indicated by the black dashed line); for the individual groups, the correlation was significant in OCD (indicated by the black solid line), but not in HC (indicated by the gray solid line). **C:** The gray matter extraction was negatively correlated with OC symptoms measured by

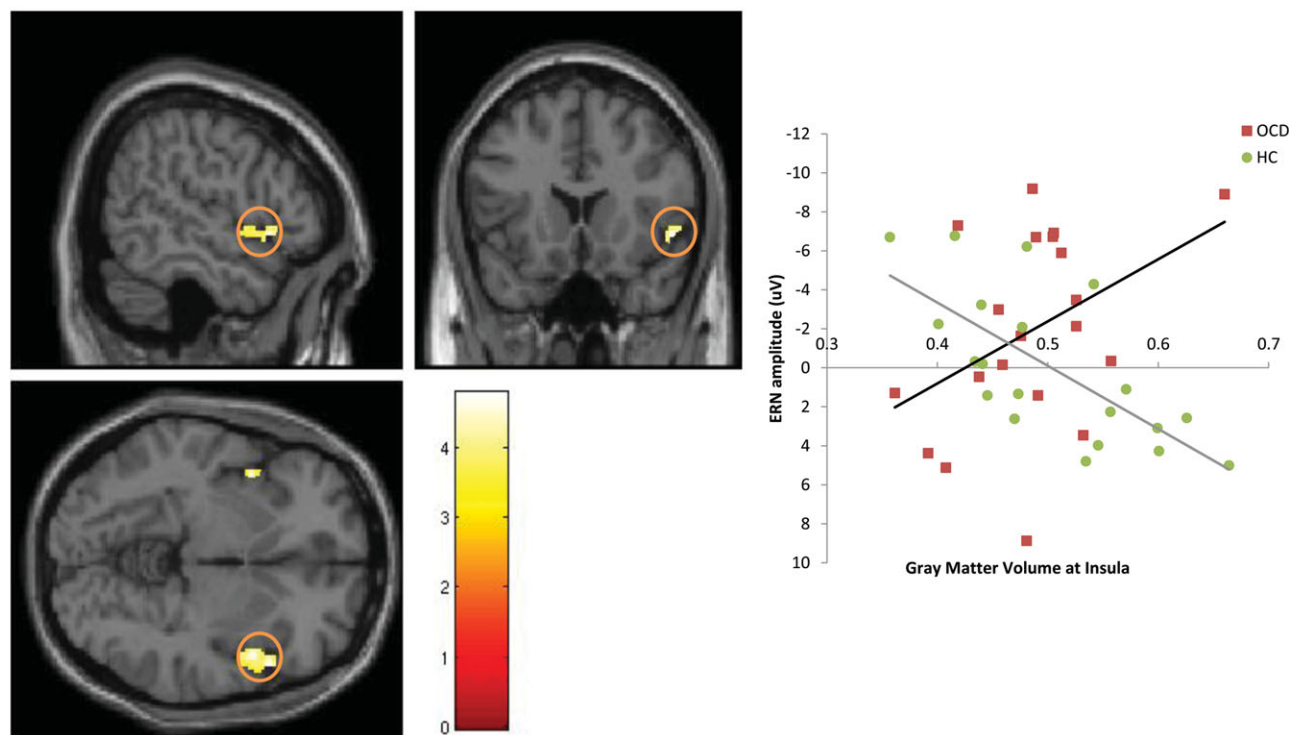
CBCL across all subjects and within the OCD group. dERN, difference of the error-related negativity between error and correct trials; CBCL, child behavioral checklist; OCD, obsessive-compulsive disorder; HC, healthy controls. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

groups, and found a significant correlation of ERN amplitude to right insula gray matter in healthy subjects, but the absence of any ERN-insula association in patients. The insula, together with the pMFC, contributes to a network that activates in response to cognitively relevant events (e.g., errors), but remains connected even at rest, and is believed to mediate salience detection [Menon and Uddin, 2010]. Thus, associations of pMFC and insula gray matter volumes with ERN suggest structural involvement of a network typically associated with salience detection in the generation of the ERN. Prior work has shown reduced gray matter in a network of regions consisting of the pMFC [Radua et al., 2011], as well as excessive pMFC activation to errors in OCD patients in the context of normal performance, which may suggest an underlying inefficiency

of pMFC-based error processing capacity that patients can overcome by additional engagement of this region [Ursu et al., 2003]. Theoretically, association of lower GM volumes in pMFC with larger ERN may also reflect inefficiency. Although speculative, it is possible that the absence of an insula-ERN relationship in OCD could reduce error-processing efficiency, such that patients must generate a larger ERN to maintain normal overall performance.

In contrast to the ERN, which was not correlated with OCD symptom severity in patients, lower pMFC gray matter volumes were associated with greater parent-reported OC symptom severity in the OCD group but not with the CY-BOCS itself. This finding, in conjunction with the relation of lower pMFC gray matter volumes with larger ERN,

(54,18,-5;354;BA 47)



**Figure 4.**

The gray matter volume in insula (BA47) showed group difference in association with ERN amplitude, driven by a correlation in healthy controls (indicated by the gray solid line) and a lack of correlation in OCD patients (indicated by the black solid line). ERN, error-related negativity in error trials; OCD, obsessive-compulsive disorder; HC, healthy controls. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

suggests that reduced pMFC volume may contribute to the increased brain response to errors, as indexed by ERN, as well as to symptom severity in OCD. Other interpretations are possible; however, the association of lower GM volumes in pMFC with more severe OCD suggests that structural alteration of these regions may be critically related to the expression of illness. Similarly, there was nominally inverse correlation of insula with subclinical OC symptoms measured by CBCL in healthy youth and with obsession severity measured by CY-BOCS in patients with OCD, suggesting involvement of insula in the expression of OC symptoms. However, caution should be taken when interpreting the correlation of symptom severity with brain activity because no correction was made for multiple correlation tests.

Across subjects, we also observed the ERN to be associated with gray matter volumes in left lateral orbital frontal cortex, consistent with the notion that the OFC is another possible contributor to the ERN. This notion is supported by intracranial recordings of ERN-like negativity at OFC in humans [Brazdil et al., 2002, 2005] and lesion studies showing association of reduced ERN with OFC lesions

[Stemmer et al., 2004; Ullsperger et al., 2002; see Gehring et al., 2012, for a review]. The lateral OFC, in conjunction with pMFC, dorsolateral prefrontal cortex, and basal ganglia, has been theorized to comprise a brain network involved in cognitive and emotional regulation [see Evans et al., 2004]. Holroyd and Yeung [2012] recently proposed that OFC, together with ventral striatum, modulates goal-directed behavior based on motivational context. Accordingly, lower gray matter volumes in OFC—as previously demonstrated in OCD [Szeszko et al., 1999]—may compromise OFC-based regulatory capacity over errors, driving up activity in other elements of a regulatory network—such as pMFC—and leading to greater amplitude of the ERN. Consistent with this possibility, we found an inverse correlation of OFC gray matter density with subclinical OC symptoms in healthy youth.

Taken together, the association of the ERN with gray matter density in pMFC and orbital frontal cortex, as well as altered association of the ERN with insula in OCD, links electrophysiological response to errors with gray matter volumes in an extended network for error processing, and suggests that structural alterations of this network



may contribute to exaggeration of the ERN in OCD. These findings are also consistent with recent neuroimaging evidence suggesting critical involvement of orbital frontal, dorsal anterior cingulate cortex and insula in OCD pathophysiology in addition to cortico-striatal pathways [Stern et al., 2011; Milad and Rauch 2012].

### Limitations

Our study has several limitations requiring further consideration. (1) The sample size was small. Future study should include more participants to increase the statistical power. (2) No correction was made for multiple correlation tests. Our analysis plan was based on previous findings in both ERN and structural imaging studies; however, the correlations we found between clinical measures with brain activity (ERN amplitude and GM density) should be interpreted with caution due to lack of a correction for multiple comparisons. (3) The treatment and medication of the patients were not controlled, but medications other than selective serotonin reuptake inhibitors were excluded and we did not find any difference in performance, ERN or GM density between medicated and unmedicated patients (see Supporting Information). (4) The age gap between ERP and MRI scan was not controlled during the experiment, but was covaried out in the data analysis when testing gray matter associations with ERN. (5) Patients with a history of tics were excluded, so that the findings in this study may be specific to nontic-related OCD [Leckman et al., 2010].

### CONCLUSION

To our knowledge, this study is the first to use VBM to explore the anatomical correlates of the ERN in either healthy subjects or patients with OCD. Our preliminary results show that patients with pediatric OCD have a hyperactive error processing system indicated by increased ERN, relative to healthy youth, and link greater ERN amplitude to lower gray matter density in pMFC, orbitofrontal cortex, and right insula. These findings suggest that an extended structural network, including but not limited to the pMFC, supports error-processing from early in the course of development. The localization of a group difference in the ERN correlation with right insula gray matter is provisional and requires replication in a larger sample but, nonetheless, suggests that structural alterations within an extended network for error-processing may contribute to the exaggerated electrophysiological response to errors in pediatric OCD.

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