Withdrawn/Depressed Behaviors and Error-Related Brain Activity in Youth With Obsessive-Compulsive Disorder

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Objective: The pathophysiology of obsessive-compulsive disorder (OCD) involves increased activity in corticostriatal circuits connecting the anterior cingulate cortex with other brain regions. The error-related negativity (ERN) is a negative deflection in the event-related potential after an incorrect response that is believed to reflect anterior cingulate cortex activity. This study examined the relation of the ERN to OCD symptom dimensions and other childhood symptom dimensions.

Method: The ERN, correct response negativity, and accuracy were measured during a flanker task to assess performance monitoring in 80 youth with a lifetime diagnosis of OCD and 80 matched healthy comparison participants ranging from 8 to 18 years old. The relation of the ERN to OCD symptom dimension scores and Child Behavior Checklist Syndrome Scale scores was examined in multiple linear regression analyses.

Results: Accuracy was significantly decreased and ERN amplitude was significantly increased in patients compared with controls. ERN amplitude in patients was significantly correlated with accuracy, but not with OCD symptom dimensions, severity, comorbidity, or treatment. In a multiple linear regression analysis using age, accuracy, OCD, and Child Behavior Checklist Syndrome Scale scores as predictors of ERN amplitude, the ERN had significant associations only with Withdrawn/Depressed Scale scores and accuracy.

Conclusion: An enlarged ERN is a neural correlate of pediatric OCD that is independent of OCD symptom expression and severity. The finding of lower accuracy in pediatric cases requires replication. The relation between an enhanced ERN and withdrawn/depressed behaviors warrants further research in youth with OCD and other internalizing disorders.

Key words: error-related negativity, biomarker, obsessive-compulsive disorder, Child Behavior Checklist, symptom dimensions

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Obsessive-compulsive disorder (OCD) is a heterogeneous psychiatric syndrome, with lifetime prevalence estimates ranging from 1% to 3% and a median age at onset of approximately 19 years.[1,2] OCD is characterized by recurrent intrusive thoughts and repetitive behaviors or mental acts that vary in their content and are often associated with other psychiatric disorders.[2,3] Brain imaging studies have indicated the pathophysiology of OCD involves increased activity in corticostriatal circuits connecting the anterior cingulate cortex with other brain regions.[4,5] However, it is unclear whether the phenotypic heterogeneity of OCD reflects distinct or partially distinct disease mechanisms.[6] OCD symptom dimensions can have specific relations to genetic variation, comorbid psychiatric disorders, and treatment response.[6,7] Hence, further research is warranted on the relation of putative OCD biomarkers to OCD symptom dimensions and other symptom dimensions often associated with OCD.

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The error-related negativity (ERN),[8] or error negativity,[9] is a negative deflection in the response-locked event-related potential that peaks within 100 ms after an incorrect response. It is believed to be generated mainly by the dorsal anterior cingulate cortex and to reflect an alarm signal to increase cognitive control and adjust behavior.[10] The ERN has a heritability of 47% in youth, suggesting it might serve as an endophenotype in genetic studies of childhood psychopathology.[11] The ERN is a unit of analysis in 3 domains of the Research Domain Criteria project: cognitive systems (cognitive control: performance monitoring), negative valence systems (sustained threat), and positive valence systems (reward learning).[12] Its placement in 3 separate domains suggests that it reflects variance in each domain, but further research is required to delineate the behaviors associated with the ERN across the lifespan.[12]

Increased ERN amplitudes have been demonstrated in most studies of patients with OCD using tasks eliciting response conflict.[5,6,12-24] An enlarged ERN has been detected in unaffected first-degree relatives of probands with OCD, indicating that overactive performance monitoring can occur in relatives at risk for developing OCD.[18,24] An enhanced ERN has been shown to remain unchanged in patients with

OCD, whereas symptom severity has been shown to decrease significantly with cognitive-behavioral therapy, demonstrating that increased error-related brain activity does not necessarily maintain OCD symptoms.[21,22] Most studies reporting an enlarged ERN in patients with OCD have detected no correlation between ERN amplitude and OCD symptom severity.[5,6,12,13,15-24] A recent study of performance monitoring in adults with OCD found overactive performance monitoring was independent of OCD symptom severity and lifetime symptom dimension scores.[6] However, for current symptom dimension scores, an association with mental rituals and superstitious behaviors was found, with higher scores associated with more error-related brain activity. Thus, studies suggest the ERN is a state-independent measurement that could serve as a biomarker or endophenotype for OCD.[12,13,18,21,22,24]

Because the relation between the ERN and OCD symptom dimensions has not been examined in pediatric OCD, the present study was conducted in 80 youth with a lifetime diagnosis of OCD and 80 age-matched healthy controls using a flanker task.[5,23,24] The aims of the study were to examine the relation of the ERN to the OCD symptom dimensions noted earlier and Child Behavior Checklist (CBCL) Syndrome Scales.[6,7,25] The CBCL Syndrome Scales were examined because they provide a dimensional classification of psychopathology without reference to traditional categorical diagnoses that might account for a significant amount of the variance in the ERN independent of lifetime OCD diagnosis.[12,25]

METHOD

Participants

Patients with OCD were recruited from the Department of Psychiatry at the University of Michigan and surrounding community. Comparison participants were recruited from the surrounding community and were matched to patients by age and sex. After a complete description of the study, written informed consent was obtained from at least 1 parent of the participant and written informed assent was obtained from the participant. Participants were paid for their interviews and psychophysiologic recordings. All tasks and procedures were approved by the University of Michigan Medical School Institutional Review Board. Some participants were excluded based on poor electroencephalographic data (n = 2), accuracy level lower than 65% during the task (n = 1), or commission of fewer than 10 errors (n = 3), leaving 160 participants. The final sample consisted of 67 boys and 93 girls 8.0 to 18 years old (mean 13.5, standard deviation 3.0), with an ethnic and racial breakdown that was 86.9% Caucasian, 1.9% Black, 4.4% Latino, 3.7% Asian, and 3.1% Native American.

All 80 patients had a lifetime diagnosis of OCD. Patients were excluded if they had a lifetime diagnosis of autistic disorder, schizophrenia, other psychotic disorder, bipolar disorder, substance-related disorder, or anorexia nervosa. All 80 comparison participants had no history of a specific Axis I disorder. Lifetime and current Axis I diagnoses were made independently by 2 clinicians using all sources of information according to *DSM-IV* criteria. Participants were excluded if they had a history of intellectual disability, head injury with a loss of consciousness, or chronic neurological disorder other than tics. All participants lived with at least 1 English-speaking biological parent willing to participate in the research.

All 160 participants were interviewed with the Schedule for Schizophrenia and Affective Disorders for School-Aged Children-Present and Lifetime Version[26] and the Schedule for Obsessive-Compulsive and Other Behavioral Syndromes (SOCOBS).[27] The lifetime and current severity of OCD was assessed in patients with a modified version of the Children's Yale-Brown Obsessive Compulsive Disorder Scale (CY-BOCS), with patients and their parents providing item scores retrospectively for the most severe episode of OCD and item scores for current severity.[28] OCD symptom dimension scores were derived for patients using the SOCOBS checklist, with assignment of items to symptom dimensions based on the largest item-level factor analysis of OCD symptoms.[7] The 5 symptom dimensions were taboo, contamination/cleaning, doubt, rituals/superstitions, and hoarding/symmetry. Each patient was described by 5 dimensional scores ranging from 0 to 1 for current and lifetime symptoms, respectively. Parents completed the CBCL[25,29] and Social Communication Questionnaire[30] about their children. Patients and controls completed the Children's Depression Inventory[31] about themselves.

Table 1 presents the demographic, clinical, behavioral, and event-related brain potential data for the patients with OCD and healthy controls ranging in age from 8 to 18 years. The OCD group had 31 boys and the comparison group had 36 boys ($p = .42$). Age at onset of OCD symptoms in the patients ranged from 2 to 16 years. Current and lifetime CY-BOCS scores in the patients with OCD ranged from 0 to 37 and 11 to 38, respectively. Although all patients had a lifetime diagnosis of OCD, 54 had a current diagnosis, 26 a past diagnosis with OCD symptoms that no longer met the criteria for diagnosis, and 61 had a history of at least 1 other specific Axis I disorder. Because studies have found that treatment with a serotonin reuptake inhibitor has no effect on the ERN,[12,13,16,18,21] 34 patients were enrolled taking a stable dose of a serotonin reuptake inhibitor but no other psychotropic medications.

Task and Procedure

Participants performed a modified Eriksen flanker task in which arrows appeared on a computer display with congruent (e.g., →→→→→) and incongruent (e.g., →→←→→) conditions.[32] They were instructed to respond by pressing 1 of 2 buttons indicating the direction of the central arrow (i.e., right versus left) while ignoring the adjacent arrows and to respond as quickly and accurately as possible, placing equal emphasis on speed and accuracy. The stimuli remained on the screen for 250 ms, with an interval of 1,500 ms between consecutive stimuli. Each participant was seated 0.65 m directly in front of the computer monitor. After 32 practice trials, each participant completed 8 blocks of 64 trials, with the number of completed trials ranging from 256 to 512. Performance feedback was provided after every block to yield an error rate of approximately 10%, with encouragement to focus on speed if there were fewer than 4 errors or to focus on accuracy if there were more than 10 errors.[5,23,24]

Electrophysiologic Recording, Data Reduction, and Analysis

The electroencephalogram was recorded from DC-104 Hz with 64 Ag/AgCl scalp electrodes, 2 mastoid electrodes, and 2 vertical and 2 horizontal electro-oculogram electrodes using the BioSemi Active-Two system. Data were digitized at 512 Hz, referenced to a ground formed from a common mode sense active electrode and driven right leg passive electrode (http://www.biosemi.com/faq/cms&drl.htm), and re-referenced offline to the average of the 2 mastoid electrodes. Data were bandpass filtered at 0.1–30 Hz using 0-phase shift filters. Electroencephalographic data were screened using