Altered Function and Connectivity of the Medial Frontal Cortex in Pediatric Obsessive-Compulsive Disorder

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Background: Exaggerated concern for correct performance has been linked to hyperactivity of the medial frontal cortex (MFC) in adult obsessive-compulsive disorder (OCD), but the role of the MFC during the early course of illness remains poorly understood. We tested whether hyperactive MFC-based performance monitoring function relates to altered MFC connectivity within task control and default mode networks in pediatric patients.

Methods: Eighteen pairs of OCD and matched healthy youth underwent functional magnetic resonance imaging during performance monitoring and at rest. Task-related hyperactivations in the posterior and ventral MFC were used as seeds for connectivity analyses during task and resting state.

Results: In posterior MFC, patients showed greater activation of dorsal anterior cingulate cortex (dACC) than control subjects, with greater activation predicting worse performance. In ventral MFC, control subjects exhibited deactivation, whereas patients activated this region. Compared with control subjects, patients showed increased dACC-ventral MFC connectivity during task and decreased dACC-right anterior operculum and ventral MFC-posterior cingulate connectivity during rest.

Conclusions: Excessive activation and increased interactions of posterior and ventral MFC during performance monitoring may combine with reduced resting state connectivity of these regions within networks for task control and default mode to reflect early markers of OCD. Alteration of reciprocal interactions between these networks could potentiate the intrusion of ventral MFC-based affectively laden, self-referential thoughts, while disrupting posterior MFC-based performance-monitoring function in young patients.

Key Words: Default mode network, medial frontal cortex, pediatric obsessive-compulsive disorder, performance monitoring, resting state connectivity, task control network

Hyperactivity of the medial frontal cortex (MFC) has been posited to underlie repetitive thoughts and behaviors in obsessive-compulsive disorder (OCD) (1). One MFC function of relevance for OCD is performance monitoring, because OCD symptoms are often associated with excessive concern for correct performance (2,3). Performance monitoring involves the detection of interference between competing response options, and the processing of errors, to enable behavioral adjustments. Hypothetically, the repetitive thoughts and behaviors of OCD could stem from failure to resolve interference from prepotent response sets or hypersensitivity to errors in security concern domains (e.g., contamination/washing, aggression/checking, symmetry/ordering) that make up the typical symptoms of OCD (4). Indeed, interference and error processing elicit MFC hyperactivity in adults with OCD (5–9), even when not overtly triggering OCD symptoms. Given the role of the posterior MFC (pMFC) in detecting interference between competing response options (10) and of the ventral MFC (vMFC) in affective response to errors (11), performance-related hyperactivation of these regions in adult OCD has been alternately interpreted to reflect inefficient interference monitoring (pMFC) (5–7) or exaggerated valuation of correct performance (vMFC) (8). Building on these insights from functional neuroimaging studies of adult patients, we sought to determine whether MFC hyperactivity during performance monitoring represents an early marker of illness and if/how it relates to altered MFC connectivity within the brain in pediatric OCD.

The characterization of MFC-based neural networks in healthy adults provides context for understanding MFC hyperactivity during performance monitoring in OCD. Interference and error processing are facilitated by interactions between the pMFC (dorsal anterior cingulate cortex [dACC] into presupplementary motor area) and lateral frontal cortex (LFC) (10,12), contributing to a task control network that is engaged by cognitive effort but remains connected even at rest (13). The effective regulation of performance by this network depends on concurrent deactivation in the vMFC (14), which, along with the posterior cingulate cortex (PCC), contributes to a default mode network (DMN) in which activity increases during rest and decreases during the performance of cognitively demanding tasks (15). In adults with OCD, hyperactivation of both the posterior (5–7) and ventral (6,8) MFC has been reported during performance monitoring, suggesting a disruption of the normal, reciprocal relationship between these MFC subregions.

To explore the possibility that performance-related abnormalities of the MFC in OCD may be associated with the alteration of task control and default mode networks, we examined performance monitoring function using the Multisource Interference Task (MSIT) (16) and connectivity of the MFC in pediatric patients compared with healthy youth using functional magnetic resonance imaging (fMRI) and functional connectivity magnetic resonance imaging (fcMRI). Based on previous work in adult OCD, we predicted pMFC and vMFC hyperactivation during performance monitoring would define areas with altered function and connectivity in task control (e.g., pMFC-LFC) and default mode (e.g., vMFC-PCC) networks. By

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Received Apr 7, 2010; revised Aug 2, 2010; accepted Aug 4, 2010.

0006-3223/$36.00
doi:10.1016/j.biopsych.2010.08.018

studying pediatric OCD, we sought to characterize MFC function and connectivity as early markers of illness.

Methods and Materials

Participants

Subjects ranged in age from 8 to 18 years and included 18 patients with pediatric OCD and 18 age- and gender-matched healthy youth (Table S1 in Supplement 1). All subjects were evaluated using the Kiddie-Schedule for Affective Disorders-Present and Lifetime Version (17), the Multidimensional Anxiety Scale for Children (18), and the Child Depression Inventory (19), and for patients, the Children's Yale-Brown Obsessive Compulsive Scale (20). Serious medical/neurological illness, head trauma, and mental retardation were not allowed. Among patients, comorbid diagnoses were separation anxiety disorder ($n = 5$), generalized anxiety disorder ($n = 1$), anxiety NOS ($n = 3$), depression NOS ($n = 2$) and tics ($n = 2$). Patients with current or past major depressive disorder were excluded; yet, as seen in most clinical samples of pediatric OCD (21), subthreshold depressive symptoms were higher in patients than control subjects. Children's Yale-Brown Obsessive Compulsive Scale scores indicated OCD symptom severity to be moderate at the time of scanning but more severe in the past. As expected, patients reported higher levels of anxiety on the Multidimensional Anxiety Scale for Children than control subjects. Twelve patients were taking selective serotonin reuptake inhibitors (eight fluoxetine, two sertraline, one fluvoxamine, one citalopram), and six were treatment-naive. After complete description of the study to the subjects and their parents, written informed consent/assent was obtained.

Task

Participants performed the MSIT (16), which requires identification of the ordinal value of the unique number among three digits—1, 2, or 3 (e.g., for 311, the target is 3)—by pressing a key with one of three fingers (1 for index finger, 2 for middle finger, 3 for ring finger). Interference was enhanced by presenting the target in a position incongruent with its ordinal value (e.g., 3 presented at the first position) and flanked by different numbers (e.g., 11). In the congruent condition, target placement was compatible with its ordinal value (e.g., 1 presented in the first position) and flanked by zeroes (e.g., 100). In contrast to the original blocked version of the MSIT (22), the task was adapted for an event-related design to allow for the separation of fMRI blood oxygenation level-dependent signal associated with correct incongruent, correct congruent, and error trials. The MSIT stimuli appeared for 500 msec, followed by a 2500 msec interstimulus interval (fixation cross) to comprise a trial. A total of 120 incongruent and 120 congruent trials were presented in pseudorandom order, intermingled with 60 fixation trials in which the 500 msec MSIT stimulus was replaced with a fixation cross (Figure S1 in Supplement 1). Trials were presented over five runs (3 min each). Subjects were trained on the task in an magnetic resonance simulator and encouraged to either speed up (accuracy $>$ 95%) or slow down (accuracy $<$ 75%) to maintain individual error rates at approximately 10% to 20% during the experiment.

fMRI Acquisition

Task. A 3.0 T GE Signa scanner was used to acquire an axial T1 image for alignment; a reverse spiral sequence (23) for T2* weighted images (gradient echo, repetition time = 2000 msec, echo time = 30 msec, fractional anisotropy = 90, field of view = 20 cm, 40 slices, 3.0 mm/slice, 64 × 64 matrix); and a high-resolution T1 scan (three-dimensional spoiled gradient, 1.5 mm slices, 0 skip) for anatomic normalization. Subject head movement was minimized through instructions to the participant and packing with foam padding.

Connectivity. The fcMRI data were acquired using the same T2* sequence as above, over 8 min, for a total of 240 volumes, while cardiac and respiratory cycles were recorded. Subjects were instructed to keep eyes open and fixate on a white crosshair on a black background while "allowing the mind to wander." A 9-year old female patient withdrew from the scanner before the completion of the resting state scan, leaving 17 age- and gender-matched pairs of OCD (14.1 ± 2.6, 11 female subjects) and healthy youth (13.9 ± 2.6, 11 female subjects) for inclusion in the connectivity analyses.

Preprocessing

Functional data were sinc-interpolated, slice-time corrected (24), realigned to the first image acquired (MCFLIRT; University of Oxford, Oxford, United Kingdom [25]), and thresholded to exclude extraparenchymal voxels. Functional volumes were warped into common stereotactic space using the Montreal Neurological Institute 152 template in SPM5 (Wellcome Trust Centre, London, United Kingdom) (26). Excessive movement ($>$ 1 mm or degree on average, $>$ 2 mm or degrees for any repetition time) led to the exclusion of several runs (one run: four OCD, two control subjects; two runs: three OCD, one control subject). For fcMRI data, image reconstruction proceeded as above, followed by bandpass filtering (.01–.1 Hz) and the regression of physiological confounds and motion parameters from the time series.

Data Analysis

Behavioral. Accuracy and response times were entered as dependent measures in a two-way analysis of variance using group (OCD vs. healthy) as the between-subjects factor and condition (incongruent vs. congruent) as the within-subjects factor. Average movement parameters for included runs were compared between groups using two-sample *t* tests ($p < .05$, two-tailed).

Task. Functional data were analyzed using a standard random effects analysis within the framework of the modified General Linear Model (27) in SPM5. Correct incongruent, correct congruent, and commission error trials were modeled against fixation trials as implicit baseline. Omission trials were modeled as a covariate of no interest. Activation maps were derived for linear contrasts of interest, incongruent − congruent (correct trials only) and error against implicit baseline (i.e., fixation)[1], including subjects with at least five commission errors across conditions (12). Contrasts were entered into second order random effects analyses to produce activation maps (28) that were examined within and between groups. To test a priori hypotheses concerning vMFC and pMFC function, we used search volumes defined by supergroup (OCD plus healthy youth) activations (pMFC: −12, 24, 30; k = 2448 and vMFC: 0, 60, −9; k = 52). A whole brain search was also performed. Alpha thresholds were $p < .05$, correcting for false discovery rate (FDR) (29).

Connectivity. Task-related areas of group difference in the pMFC and vMFC were used as seed regions in psychophysiological interaction (PPI) analyses testing for task-dependent functional connectivity (30). A PPI variable was created for each subject by multiplying a psychological variable (representing the sequential ordering of incongruent and congruent stimuli)[2] by mean seed

[1] An analysis of error compared with correct trials is included in Supplement 1 to facilitate comparison with some prior work (8).

[2] The PPI analysis focused on interference (incongruent vs. congruent) rather than errors (errors vs. fix, or errors vs. correct), because the imbalanced number of error relative to fixation (or correct) trials precluded the construction of a mean-centered psychological variable, confounding the PPI (30).