Reduced Error-Related Activation of Dorsolateral Prefrontal Cortex Across Pediatric Anxiety Disorders

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Objective: Abnormalities of cognitive control functions, such as conflict and error monitoring, have been theorized to underlie obsessive-compulsive symptoms but only recently have been considered a potentially relevant psychological construct for understanding other forms of anxiety. The authors sought to determine whether these cognitive control processes elicit the same abnormalities of brain function in patients with pediatric obsessive-compulsive disorder (OCD) as in those with non-OCD anxiety disorders. **Method:** Functional magnetic resonance imaging of the Multisource Interference Task was used to measure conflict- and error-related activations in youth (8–18 years) with OCD (n = 21) and non-OCD anxiety disorders (generalized anxiety disorder, social phobia, separation anxiety disorder; n = 23) compared with age-matched healthy controls (n = 25). **Results:** There were no differences in performance (accuracy, response times) among groups. However, a significant effect of group was observed in the dorsolateral prefrontal cortex (dlPFC) during error processing, driven by decreased activation in patients with OCD and those with non-OCD anxiety compared with healthy youth. Between patient groups, there was no difference in error-related dlPFC activation. **Conclusions:** Hypoactive dlPFC response to errors occurs in pediatric patients with OCD and those with non-OCD anxiety. These findings suggest that insufficient error-related engagement of the dlPFC associates with anxiety across traditional diagnostic boundaries and appears during the early stages of illness. J. Am. Acad. Child Adolesc. Psychiatry, 2013;52(11):1183–1191. **Key Words:** conflict, dorsolateral prefrontal cortex, errors, pediatric anxiety disorders, pediatric obsessive-compulsive disorder

Traditional diagnostic categories have led researchers to attempt to distinguish between the anxiety disorders, particularly obsessive-compulsive and other forms of anxiety[1]; however, distinct categories do not clearly map onto real-world clinical presentations. The overlapping phenomenology of obsessive-compulsive disorder (OCD) and non-OCD anxiety disorders presents diagnostic challenges, particularly in pediatric patients, because the boundary between obsession and worry can be especially blurry in children.[2] This challenge is further complicated by high rates of comorbidity and developmental fluidity between OCD and non-OCD anxiety disorders, with early-onset OCD and specific phobias predicting other forms of anxiety at later stages of development.[3] Collectively, these lines of evidence suggest that OCD and non-OCD anxiety may occur along a single dimension and derive from common causal pathways, whereas expression may be shaped by developmental stage.[4] Understanding whether the same psychological processes and their underlying neural substrate are shared across OCD and non-OCD forms of pediatric anxiety will inform mechanism-based strategies to prevent and treat anxiety from the early stages of illness.

Theoretically, failure to resolve conflict between intrusive worries and actual circumstance could contribute to OCD[5] and non-OCD anxiety disorders. Strictly defined, conflict processing involves the detection of competition between conflicting response options and signaling for

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increased cognitive control to optimize performance when conflict is high.[6] Errors represent a form of response conflict owing to competition between the actual and desired response.[7] Given the key role of conflict and error processing in mediating behavioral adjustments,[6] abnormality of these functions might contribute to the repetition of anxious thoughts and behaviors. Patients experience obsessions and worry as intrusive, unwanted, and difficult to control,[8] despite evidence from the environment (e.g., reassurance from family and friends) and patients' own insight[9] that such thinking is not justified by circumstance. Common security concerns tend to evoke anxiety, even in healthy children, and might be especially potent in anxiety disorders,[10] producing higher levels of conflict that can overwhelm cognitive control resources to drive repetitive thoughts (e.g., obsessions and/or worries) and related behaviors (e.g., compulsions and/or avoidance). Conversely, patients typically endorse insight that their anxiety-provoking thoughts "do not make sense,"[8,9] raising the possibility that feared outcomes are appropriately detected as "thinking errors,"[11] but that error detection fails to sufficiently engage cognitive control, so that anxious thoughts and behavior continue, without correction.

Conflict and errors activate a task control network that mediates the allocation of attentional resources to enable behavioral adjustments in response to these events.[12] The posterior medial frontal cortex (pMFC) and dorsolateral prefrontal cortex (dlPFC) are key nodes within this network, interacting to optimize performance. In healthy individuals, conflict and errors are detected by the pMFC, which signals for dlPFC engagement to increase cognitive control and optimize goal-directed behavior.[6] Failure to adjust obsessive thinking and compulsive behavior, despite insight that feared outcomes are unlikely, suggests abnormalities of this network in OCD. Indeed, tasks requiring cognitive control have been associated with pMFC hyperactivation[5,13-16] and decreased engagement of dlPFC[17] in patients with OCD, even when OCD symptoms are not specifically triggered. Given the expected role of these regions,[6] pMFC hyperactivation could reflect inefficient conflict or error detection, whereas dlPFC hypoactivation might reflect failure to appropriately engage the neural substrate for cognitive control[18]—either of which might lead to difficulty in adjusting the repetitive thoughts and behaviors characteristic of OCD.

In patients with non-OCD anxiety disorders, functional neuroimaging research has traditionally used emotion-inducing, rather than cognitive, conflict tasks, showing anxiety to associate with increased amygdala reactivity to threat.[19] Some studies of non-OCD anxiety have examined cognitive control over emotion, showing excessive pMFC activation to emotional conflict[20] but decreased dlPFC recruitment during tasks requiring the regulation of emotional response.[21] During "pure" cognitive conflict, higher levels of trait anxiety in healthy adults associate with an exaggerated electrophysiologic response in an area of the midline prefrontal cortex that may localize to the pMFC[22,23] but decrease dlPFC recruitment based on a study using functional magnetic resonance imaging (fMRI).[24] In addition, errors on cognitive conflict tasks induce an exaggerated, pMFC-localized electrophysiologic signal, the error-related negativity, in OCD and non-OCD anxiety disorders.[25] Taken together, these findings raise the possibility that excessive pMFC engagement and impoverished dlPFC engagement by conflict and errors may generalize across OCD and non-OCD anxiety disorders.

To determine whether conflict and/or error monitoring represent useful constructs for characterizing the neural circuitry underlying a spectrum of pediatric anxiety, fMRI was used to measure pMFC and dlPFC responses to these cognitive control functions during the Multi-source Interference Task (MSIT)[26] in pediatric patients with OCD and non-OCD anxiety disorders compared with healthy youth. The MSIT induces high levels of cognitive conflict and reliably engages the pMFC and dlPFC[26]—including in children.[27] Based on extant literature, the authors hypothesized that patients from the 2 groups would exhibit pMFC hyperactivation and dlPFC hypoactivation during conflict and errors compared with healthy youth. By studying pediatric patients, the authors sought to determine whether the neural substrate for conflict and error monitoring is affected early in the illness course.

METHOD

Participants

Subjects were female, ranged in age from 8 to 19 years, and included 21 patients with OCD, 23 patients with non-OCD anxiety disorders, and 25 healthy youth. Anxiety disorders occur more commonly in female