Curr Behav Neurosci Rep (2016) 3:193–203
DOI 10.1007/s40473-016-0086-1

CHILD AND DEVELOPMENTAL PSYCHIATRY (M GRADOS, SECTION EDITOR)

Developmental Neuroimaging in Pediatric Obsessive-Compulsive Disorder

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Abstract

Purpose of review This review examines emerging neuroimaging research in pediatric obsessive-compulsive disorder (OCD) and explores the possibility that developmentally sensitive mechanisms may underlie OCD across the lifespan.

Recent findings Diffusion tensor imaging (DTI) studies of pediatric OCD reveal abnormal structural connectivity within fronto-striato-thalamic circuity (FSTC). Resting-state functional magnetic resonance imaging (fMRI) studies further support atypical FSTC connectivity in young patients, but they also suggest altered connectivity within cortical networks for task control. Task-based fMRI studies show that hyperactivation and hypoactivation of task-control networks may depend on task difficulty in pediatric patients similar to recent findings in adults.

Summary This review suggests that atypical neurodevelopmental trajectories may underlie the emergence and early course of OCD. Abnormalities of structural and functional connectivity may vary with age, while functional engagement during task may vary with age and task complexity. Future research should combine DTI, resting-state fMRI, and task-based fMRI methods and incorporate longitudinal designs to reveal developmentally sensitive targets for intervention.

Keywords Pediatric OCD · DTI · Resting-state · fMRI · Executive function · Task-control network

Introduction

Obsessive-compulsive disorder (OCD), characterized by intrusive thoughts (obsessions) and related behavioral rituals (compulsions), is a disabling psychiatric illness that begins during childhood or adolescence in 50 % of patients [1]. The prevalence of OCD in pediatric samples is 1–3 % [2], similar to estimates in adults [3]. Among pediatric patients who receive treatment for OCD, approximately half continue to experience full-blown illness into adulthood [4] and, in patients with adult-onset illness, many report subclinical symptoms beginning in childhood [2, 3]. Yet, despite the apparent origin of OCD in early life, neuroimaging studies designed to elucidate the neural underpinnings of the disorder are mostly derived from research with adults. Understanding brain abnormalities in pediatric compared to adult OCD may help to elucidate unique features of illness across the lifespan and ultimately guide the design of therapies most appropriate for different patients at different ages.

FSTC in OCD: a neuroanatomical model

Neuroimaging research has consistently demonstrated abnormalities of fronto-striato-thalamic circuitry (FSTC) in adult OCD [5], and accumulating research in pediatric patients provides evidence for FSTC abnormalities at early stages of the illness. The FSTC system is comprised of parallel, segregated "loops" between distinct portions of the cortex, striatum, and thalamus [6]. FSTC loops of functional relevance for OCD include those passing through dorsal and ventral striatum into the medial dorsal thalamus via topographically organized

This article is part of the Topical Collection on *Child and Developmental Psychiatry*

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projections from cortical centers for cognitive control (e.g., anterior cingulate cortex, dorsolateral prefrontal cortex; [7]) and for emotionally driven evaluative functions, including reward processing and internal mood states (e.g., ventral medial prefrontal cortex; [8]).

The first neuroimaging evidence of FSTC abnormality in OCD came from positron emission tomography (PET) studies showing increased metabolic uptake of radiotracers marking glucose and oxygen metabolism in the anterior cingulate cortex (ACC), orbital frontal portion of the ventral medial prefrontal cortex (vmPFC), and striatum and thalamus in adult patients compared to healthy controls [9]. Initial studies were conducted while patients lay awake in the PET scanner, not performing any particular tasks, thereby demonstrating hyperactivity of FSTC at rest. Follow-up work showed that symptom provocation further increased metabolic hyperactivity in FSTC and that treatment resolved FSTC hypermetabolism [9]. Taken together, these findings suggested a neuroanatomical model of OCD in which excessive signaling through FSTC was hypothesized to underlie symptoms.

An important element of the FSTC system, which is likely relevant to its role in OCD, involves the splitting of each loop into direct and indirect pathways at the level of the basal ganglia (i.e., striatum, globus pallidum, subthalamic nucleus; Fig. 1). In general, the direct pathway facilitates neuronal activity through FSTC, whereas the indirect pathway inhibits it [10]. Neuroanatomical models of OCD suggest that *greater* direct pathway activity through vmPFC-based loops for emotion processing and *lower* indirect pathway activity through dorsal anterior cingulate cortex (dACC)- and dorsolateral prefrontal cortex-based loops for cognitive control may underlie intrusive thoughts, ritualistic behaviors, and related anxiety in OCD [5, 9, 11]. In other words, *hyperactivity* in neural circuitry underlying the affective valuation of thoughts and behaviors (i.e., vmPFC-based FSTC) may couple with *hypoactivity* in neural substrate underlying capacity for task control (i.e., dACC-, dorsolateral prefrontal-based FSTC). A resulting imbalance in FSTC substrate for emotion-processing, relative to task control, could lead to the intrusion of distressing, obsessional thoughts and the repetition of compulsive behaviors to reduce distress, despite insight that such thoughts and behaviors “do not make sense.” Task-based neuroimaging research has supported this possibility, demonstrating deficits of dACC activation during cognitive tasks requiring behavioral adjustment and hyperactivity of vmPFC during emotion-laden evaluative processing in patients, even when OCD symptoms are not directly provoked [5].

MRI-Based Technology Enables Study of FSTC in Pediatric OCD

Despite the pediatric onset of OCD in at least half of all the patients [1], the FSTC model of OCD was first developed based on studies conducted in adults. Initial focus on adult patients was largely due to technical characteristics of PET, the first widely available tool for neuroimaging research, which requires injection of radioactive tracer to reveal brain activity. With the advent of non-invasive magnetic resonance imaging (MRI) technologies, neuroimaging research in children became more feasible and MRI-based neuroimaging studies of pediatric OCD began to emerge. Initial evidence for FSTC abnormality in young patients came from MRI studies showing altered volume of FSTC nodes, including ACC, striatum, and thalamus, but also superior parietal lobule and precuneus (for a review, see [13]). In addition, task-based functional MRI studies began to propagate, revealing abnormalities of activation in FSTC regions during tasks designed to engage OCD-relevant psychological processes (see next section).

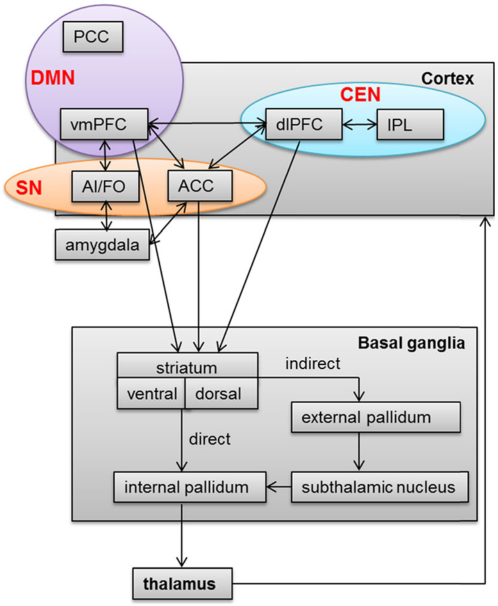

Fig. 1 Simplified illustration of fronto-striato-thalamic circuitry (*FSTC*) and its overlap with salience network (*SN*), central executive network (*CEN*), and default mode network (*DMN*). FSTC model adapted from prior reviews [5, 10–12]. *ACC* anterior cingulate cortex, *AI/FO* anterior insula/frontal opercular, *dlPFC* dorsolateral prefrontal cortex, *IPL* inferior parietal lobule, *vmPFC* ventromedial prefrontal cortex, *PCC* posterior cingulate cortex. Adapted from: Journal of Neural Transmission, Neuroimaging of cognitive brain function in paediatric obsessive compulsive disorder: a review of literature and preliminary metaanalysis, Volume 119, 2012, Silvia Brem, with permission of Springer

Advances in MR-based technology also produced diffusion tensor imaging and resting state functional MRI methods, enabling the measurement of FSTC structural and functional connectivity, respectively, in young patients. Diffusion tensor imaging (DTI) measures the direction and magnitude of water diffusion within white matter tracts [14, 15]. The most commonly studied DTI measure is fractional anisotropy (FA), an index of white matter coherence and thus, the integrity of white matter tracts [16–19]. Resting state functional connectivity MRI (rsfcMRI) measures fluctuations of blood oxygen level-dependent (BOLD) MRI signal. During rsfcMRI data collection, subjects are instructed to "allow your mind to wander" to induce a "resting state" during which low-frequency BOLD signal oscillations throughout the brain are measured. Correlations between oscillations in different brain regions are then calculated to produce a metric of resting-state connectivity. Greater resting state connectivity is believed to reflect a history of co-activation, providing evidence of a functional circuit [20, 21].

Diffusion Tensor Imaging Research in Pediatric OCD

The literature on DTI in pediatric OCD has provided evidence of white matter involvement in the FSTC from early in the course of illness (Table 1). White matter tracts of particular relevance to FSTC include the anterior corpus callosum (CC), anterior cingulum bundle (CB), and anterior limb of the internal capsule (ALIC). The anterior CC contains white matter fibers connecting the right and left prefrontal cortex [22], the anterior CB contains fibers that connect emotion-processing regions such as the amygdala to ACC [23], and the ALIC contains white matter pathways connecting the frontal lobe and thalamus. Several DTI studies have found increased FA and/or axial diffusivity (another DTI metric of white matter integrity) in these tracts in OCD-affected youth compared to healthy controls [24–26], while other researchers have found the reverse [27, 28]. Interestingly, the largest DTI study of pediatric OCD [29••] found *no* overall differences in FA, but rather demonstrated steeper age-related increases of FA in FSTC white matter in patients compared to controls across the ages of 8 to 19. After subdividing the samples into child, early adolescent, and late adolescent groups, lower FA was demonstrated in 8- to 11-year-old child patients, but higher FA was found in 16- to 19-year-old adolescent patients relative to same-aged controls in the anterior CC and anterior CB. These results suggest a possible interaction between FA and age, a finding that may help clarify the discrepant reports of lower FA in OCD compared to healthy youth [27, 28]; the examination of FA in older as compared to younger participants may increase the likelihood of finding abnormally increased or decreased FA in FSTC white matter tracts in pediatric samples (Table 1).

If steeper age-related increases in FSTC structural connectivity in OCD relative to healthy youth [29••] continues beyond adolescence, then abnormally increased FA might be expected in adult patients. Greater FA has been reported in adult OCD in the CC [32, 33], CB [33, 34], and ALIC [32, 34] and in other white matter tracts, including superior longitudinal fasciculus (SLF) and anterior corona radiata in some reports (for a review, see [35]). However, other studies have found decreased FA in these regions in adult patients compared to healthy controls (for a review, see [35]). A meta-analysis of DTI research in adult OCD suggests that conflicting results across studies may derive from sample heterogeneity due to demographics, medication status, illness chronicity, and imaging methodology [35], and the same may be said of DTI research in pediatric OCD with the added complexity of developmental stage. In typically developing individuals, most white matter tracts (e.g., internal capsule, CC, CB) exhibit curvilinear trajectories (i.e., inverted "U" shaped), with age-related increases found during childhood and adolescence followed by decreases in adulthood [36]. DTI research in patients compared to matched controls from childhood into older adulthood will be needed to assess whether shifts in the timing of this curvilinear trajectory (e.g., earlier peaks for healthy, later peaks for OCD) may best describe developmental differences in FSTC structural connectivity over the lifespan.

In summary, the bulk of DTI research in pediatric OCD suggests that increased white matter in FSTC and other white matter tracts occurs in young patients by the time of adolescence and that, from childhood into adolescence, structural connectivity within these tracts may increase at faster rates in patients compared to age-matched healthy youth. Critically, longitudinal research is needed to understand when white matter abnormalities in pediatric OCD emerge to map changes in white matter abnormalities over time and to determine how these changes associate with the course of illness. Moreover, combining DTI and other MR-based imaging methods may elucidate the functional significance of atypical white matter development in pediatric OCD to aid identification of DTI measures as potential targets for intervention and/or intermediate outcomes. Finally, FA abnormalities outside of FSTC have been demonstrated in pediatric (e.g., SLF, corona radiata, posterior limb of internal capsule; see Table 1) and adult patients (for a review, see [37]), prompting a reevaluation of the FSTC model originally theorized to underlie symptoms.

Resting-State Functional Connectivity in Pediatric OCD: from FSTC to Cortical-Cortical Networks

Myelinated neuronal projections (i.e., white matter connections) between FSTC regions were first revealed by chemical tracer studies in laboratory animals [6], but the advent of task-based fMRI and rsfcMRI methods has revealed that functional connectivity between regions can exist in the absence of direct structural connections [38, 39]. These "functional" networks are identified by regions that coactivate in response to task demands and exhibit connectivity at rest [40]. For example, cortical targets of FSTC, particularly dACC, vmPFC, and the dorsolateral prefrontal cortex (dlPFC), are now realized as critical nodes within such networks. As depicted in Fig. 1, functional connectivity of the dACC-bilateral anterior insula, dlPFC-parietal cortex, and vmPFC-posterior cingulate cortex define canonical networks that are now widely believed to

Table 1 Diffusion tensor imaging and resting-state connectivity in pediatric obsessive compulsive disorder

Study	Subject characteristics	Design	Analytic method	Main results
Diffusion tensor imaging				
Rosso et al. [28]	Range: 10–19 OCD: 14.1 ± 2.6, n = 17, 11 M HC: 13.6 ± 2.1, n = 19, 13 M	OCD v HC	TBSS	↓ *FA* in genu, body, splenium of CC, ATR, UF, IFOF, forceps minor, anterior corona radiate. ↑ *RD* in body of CC, ATR, anterior corona radiata, forceps minor. Correlation of lower FA in right thalamus, greater *RD* in right body of CC with earlier age of onset No correlation with OCD severity on CYBOCs.
Fitzgerald et al. [29••]	Range: 8–19 OCD: 14.1 ± 2.9, n = 36, 16 M HC: 14.7 ± 3.1, n = 27, 9 M	OCD v HC Group × age interaction	TBSS, ROI	↑ *FA with increasing age* in anterior CB, ALIC, anterior CC, right splenium, right PLIC, right PTR, bilateral external capsule, anterior & superior corona radiata, right SLF. Correlation of greater FA in anterior CB with greater OCD severity on CYBOCs.
Silk et al. [27]	Range: 8–18 OCD: 12.8 ± 2.8, n = 16, 6 M HC: 11.2 ± 2.1, n = 22, 16 M	OCD v HC	TBSS	↓ *AD* in genu and splenium. No FA differences. Correlation lower AD in left cingulate, left SLF, bilateral *PLIC* with greater OCD severity on CBCL-OCS.
Gruner et al. [25]	Range: 9–17 OCD: 14.3 ± 2.1, n = 23, 13 M HC: 14.2 ± 2.2, n = 23, 12 M	OCD v HC	FSL, SPM8	↑ *FA* in the anterior CB, splenium of CC, right corticospinal tract and left IFOF. Correlation of greater FA in splenium with greater obsession severity in drug-naïve patient subgroup. Correlation of greater FA in anterior CB with better response inhibition and cognitive control performance.
Jayarajan et al. [26]	Range: less than 18 OCD: 14.1 ± 1.8, n = 15, 8 M HC: 14.3 ± 2.2, n = 15, 8 M	OCD v HC	TBSS	↑ *AD* in genu, body, and splenium of CC, bilateral cingulum, bilateral ALIC, bilateral ATR, bilateral SLF, left ILF, left PLIC, and middle cerebellar peduncle. ↑ *RD* in genu of CC, bilateral SLF, left ILF, bilateral UF, bilateral ATR, bilateral IFOF, left PLIC, right superior, middle and right inferior cerebellar peduncle. No correlation with OCD severity on CYBOCs
Zarei et al. [24]	Range: 8–17 OCD: 16.6 ± 1.5, n = 26, 14 M HC: 16.5 ± 1.4, n = 26, 14 M	OCD v HC	TBSS	↑ *FA* in genu and splenium, left cingulum, left inferior longitudinal fasciculus, bilateral superior longitudinal fasciculus, right inferior fronto-occipital fasciculus, bilateral corticospinal tract, bilateral forceps major, bilateral forceps minor, and right uncinate fasciculus Correlation of greater FA in ALIC (and other tracts) with OCD severity on CYBOCs
Resting state connectivity				
Fitzgerald et al. [50]	Range: 8–19 OCD: 13.9 ± 2.6, n = 18, 6 M HC: 14.1 ± 2.7, n = 18, 6 M	OCD v HC	Seed	↓ dACC–right AI/FO, ↓vmPFC–PCC connectivity. No correlation with OCD severity on CYBOCs
Fitzgerald et al. [45]	*Child range*: 8–12 OCD: 11 ± 1.3, n = 11, 6 M HC: 10.7 ± 1.7, n = 13, 6 M *Adolescent range*: 13–17 OCD: 16 ± 1.4, n = 11, 5 M HC: 15.3 ± 1.3, n = 13, 8 M *Young adult range*: 18–25 OCD: 20 ± 1.4, n = 18, 10 M HC: 21 ± 2.3, n = 15, 7 M *Adult range*: 26–40 OCD:32 ± 6.0, n = 13, 6 M HC: 32.3 ± 5.9, n = 17, 7 M	OCD v HC Group × age interaction:	Seed	↓ Dorsal striatum–rACC, left medial dorsal thalamus–left dACC in child group. ↑ Right dorsal striatum–vmPFC across age groups. Correlation of lower dorsal striatum-rACC connectivity with greater OCD severity on CYBOCs in child OCD
Weber et al. [46]	Range: 8–16 OCD: 13.0 ± 2.9, n = 11, 6 M HC: 12.7 ± 3.2, n = 9, 5 M	OCD v HC	ICA	↓ BA 8 (dorsomedial prefrontal cortex) and BA40 (inferior parietal cortex) within cingulate network ↑ BA 43(inferior postcentral gyrus) within auditory network No correlation with OCD severity on CYBOCs

Arrow pointing up means greater in pediatric obsessive compulsive disorder (OCD) than healthy controls (HC); arrow pointing down means lower in OCD than HC. AD measures diffusion in parallel with the primary direction of white matter fibers; as with FA, AD reflects white matter integrity. RD measures diffusion along the radius of a white matter tract, perpendicular its primary direction; in contrast to FA and AD, RD is thought to reflect deficient myelination"

M male, *F* female, *TBSS tract-based spatial statistics*, *ROI* region of interest, *ICA* independent component analysis, *FA* fractional anisotropy, *AD* axial diffusivity, *RD* radial diffusivity, *ATR* anterior thalamic radiations, *UF* uncinate fasciculus, *IFOF* inferior fronto-occipital fasciculus, *CC* corpus callosum, *CB* cingulum bundle, *ALIC* anterior limb internal capsule, *PLIC* posterior limb internal capsule, *PTR* posterior thalamic radiations, *SLF* superior longitudinal fasciculus, *ILF* inferior longitudinal fasciculus, *CYBOCs* Child Yale Brown Obsessive Compulsive Scale [30], *CBCL-OCS* Child Behavior Checklist Obsessive Compulsive Subscale [31], *dACC* dorsal anterior cingulate cortex, *AI/FO* anterior insula/frontal operculum, *vmPFC* ventral medial prefrontal cortex, *rACC* rostral anterior cingulate cortex, *BA* Brodmann area support, respectively, salience detection (salience network, SN), executive functions (central executive network, CEN), and "default" mode processes such as self-reflection, internally directed mentation, and episodic memory requiring task control (default mode network, DMN) [41].

Building from rsfcMRI research in adult patients with OCD [42, 43], rsfcMRI research in pediatric OCD initially focused on FSTC. This work tested for temporal correlations of fMRI BOLD signal between anatomically defined regions or "seeds" placed in the striatum and thalamus with voxels across the rest of the brain. Replicating work in adults [42, 44], evidence for distinguishable FSTC loops was demonstrated for seeds placed in the ventral striatum, dorsal striatum, and medial dorsal thalamus [45]. Functional connectivity for each seed was then compared for patients and healthy individuals by developmental stage (child, adolescent, and adult), demonstrating excessive connectivity of dorsal striatum with the medial frontal pole, a subregion of the vmPFC, across the age span. By contrast, the youngest patients exhibited reduced connectivity of dorsal striatum with rostral ACC and of medial dorsal thalamus with dorsal ACC. These child-specific abnormalities of functional connectivity have since been partially replicated in a study of patients with pediatric OCD compared to healthy youth, ages 8 to 16 years; within a "cingulate network" defined by resting-state correlations of striatum, bilateral dlPFC, and dorsal medial prefrontal cortex (dmPFC), patients exhibited reduced connectivity of dmPFC [46].

The relevance of abnormal functional connectivity within FSTC loops in pediatric OCD remains poorly understood, but it can be interpreted in the context of task-based literature. For instance, FSTC running through vmPFC is associated with the processing of emotionally salient stimuli to motivate behavior [8, 47], whereas the maturation of ACC-based FSTC plays a critical role in the development of cognitive control [48]. Thus, excessive connectivity of the FSTC loop running through vmPFC in child, adolescent, and adult patients could drive excessive worry about errors and related attempts at corrective behavior in OCD in patients across the lifespan. By contrast, premature reduction in the connectivity of ACC-based FSTC for cognitive control may contribute to an inability to suppress the contextually inappropriate thoughts and behaviors near illness onset and perhaps, at a critical period of development, give rise to the emergence and progression of OCD in young patients.

In conclusion, interpretation of DTI and rsfcMRI research in pediatric OCD can be informed by neuroimaging work in typically developing youth showing that development of ACC-associated cognitive control and vmPFC-associated emotion processing functions depends not only on the maturation of structural connections between FSTC nodes but also on the developing connectivity of these regions within large-scale, neural networks for salience detection (SN), central executive processes (CEN), and default mode function (DMN) [20, 41, 49]. Indeed, preliminary work in pediatric OCD shows that hyperactivation of dACC and failure to deactivate vmPFC during a simple cognitive task occurs in the context of reduced functional connectivity within the salience (dACC-anterior insula, SN) and default mode (vmPFC-posterior cingulate, DMN) networks [50]. These task-based and rsfcMRI findings extend historical models of altered FSTC connectivity in OCD to include abnormalities in overlapping, resting-state networks in young patients (Fig. 1). In addition, atypical functional connectivity between dACC and vMPFC in pediatric OCD suggests inappropriate interactions of SN and DMN in young patients [50]. In adult OCD, rsfcMRI research has shown that the normally inverse relationship between task-positive networks, namely, the SN and CEN, with DMN is attenuated in patients with OCD compared to healthy controls [51, 52]. These findings suggest a failure to segregate between networks that could lead to deficits in task-control processes due to intrusion of emotional and introspective function of DMN. Task-based fMRI studies may aide examination of the functional significance of altered SN and CEN connectivity and will be further reviewed in the next section.

Functional Activation during Task Control Demands

OCD has long been theorized to stem from core deficits of task control [53, 54]. Task control is a broadly defined term that encompasses a variety of cognitive tasks including interference control, response inhibition, working memory, and cognitive flexibility [55, 56]. Collectively, task-control processes enable the selection of appropriate behavior across a myriad of internal and external inputs and, when impaired, may associate with the repetitive thoughts and behaviors characteristic of OCD. For instance, recurrent intrusive obsessions might be related to an inability to inhibit and select certain stimuli (interference control) and/or an inability to switch attention from one aspect of a stimuli to another depending on environment and context (cognitive flexibility), whereas the repetitive compulsive behavior of OCD might stem from failure to inhibit certain prepotent, but inappropriate, response sets (response inhibition) and/or a deficit in working memory prompting repeated urges to check.

Task-control demands are known to engage "task-positive" salience and central executive networks [55, 57]. These networks were originally defined by task positive coactivations and later found to remain functionally connected, even at rest [40, 41, 57]. As noted above, preliminary evidence suggests reduced functional connectivity between task-positive regions during rest in pediatric OCD [50]. Below, we will review accumulating research from task-based fMRI studies demonstrating abnormal SN and CEN function in both adult (for reviews, see [58•, 59]) and pediatric patients with OCD. Taken together, these studies suggest that altered function of canonical networks for task control in adults with OCD may develop at the early stages of illness.

To frame an understanding of task-based fMRI studies of OCD, it is important to consider the relationship of brain activation to behavioral performance during tasks which, in turn, relates to task difficulty. For example, tasks tapping interference control (e.g., the flanker task) might be less difficult than tasks requiring motor response inhibition (e.g., stop-signal task) since interference control requires inhibition of a *potential* response through the focusing of attention on task-relevant over task-irrelevant stimulus features, whereas motor response inhibition requires the suppression of a behavioral response that has already been triggered and is closer to actually being produced [60]. In some tasks, difficulty can be manipulated by varying parameters within a task; for example, the 3-back working memory task is harder than the 2-back working memory task. Other complex tasks, such as the Wisconsin card sorting test (WCST) and Tower of London (TOL), entail relatively high levels of difficulty by requiring the coordination of multiple task control processes to produce correct performance [61]. In fMRI research, hyperactivation in the context of normal performance in a patient compared to a control group has been interpreted to reflect compensation for underlying neural inefficiency and may be most likely to occur on less difficult tasks [62]. By contrast, as task difficulty increases, hypoactivation may occur as capacity for compensatory activation is exceeded and performance deficits emerge [58•, 63].

Task-Based fMRI Research in Adult OCD

Functional MRI studies of adult OCD have revealed altered activation of SN and CEN during task-control demands [58•, 59] and provide context for interpreting the fMRI literature in pediatric patients. In adults with OCD, *increased* activation in the dlPFC and dACC has been demonstrated during a relatively simple *interference control task* relative to healthy controls [64]; in this study, patients maintained normal performance relative to controls, consistent with the interpretation that hyperactivation may enable compensation for underlying inefficiency of task-control networks [58•, 64]. By contrast, a more difficult task requiring *response inhibition* elicited *decreased* activation in the inferior frontal gyrus (IFG) and parietal regions in OCD relative to healthy control (HC) adults; hypoactivation occurred in the context of performance deficits in patients [65]. The notion that task difficulty impacts the nature of task-control network function in OCD is further supported by fMRI research showing increased activation of dlPFC under low-cognitive demand (e.g, 1- and 2-back working memory task) but decreased-to-normative levels of activation in dACC under increased task demand for patients compared to controls [66–68]. On the more complex tasks of self-shifting/task switching, adult OCD patients showed *decreased* activation in the dlPFC, dACC, and parietal and caudate regions in *cognitive flexibility* relative to HC [69–71]. Similarly, on the TOL task, OCD patients showed *decreased* activation in the dlPFC and parietal lobe during *planning*, relative to controls [72, 73].

Thus, whether task-related brain areas are hypoactivated or hyperactivated in patients compared with healthy controls appears to depend largely on the difficulty of the task and whether compensatory mechanisms are enlisted [58•, 59]. During less difficult tasks, OCD patients may recruit additional neural resources in SN and CEN, possibly to compensate for an underlying inefficiency of these task-control networks. This hyperactivation may explain why individuals with OCD are able to maintain normal behavioral performance, relative to healthy controls, during less complex tasks (e.g., the Flanker task and the Simon task). However, with increasing task demand (e.g., the Go/no-go and the Stop-signal task), these compensatory mechanisms may fail in individuals with OCD, such that behavioral impairments and decreased activity in task-control networks emerge.

Task-Based fMRI Research in Pediatric OCD

Modeling after recent reviews of the adult literature, we consider whether altered activation of task-control networks in pediatric populations also depends on task complexity and/or relates to performance. In contrast to the fMRI literature in adult OCD, only a few studies have examined task-control processing in pediatric samples (Table 2). During simple cognitive tasks with relatively low levels of difficulty (e.g., simplified serial reaction time, interference, 1–2-back working memory tasks), fMRI studies in pediatric OCD reveal *increased* activation in patients compared to healthy youth in task-control regions, including dACC, dlPFC, and the parietal cortex [50, 74, 75]. As with adult studies, hyperactivation of task-control networks in pediatric patients occurred in the context of normal performance relative to controls, suggesting that increased engagement of task-control regions may reflect a compensatory function by which patients maintain appropriate behavioral output. Review of the pediatric OCD literature on brain activation during more difficult/complex cognitive tasks (e.g., motor inhibition, set-shifting, planning) demonstrated that, relative to healthy controls, pediatric patients with OCD showed decreased activation in task-control regions including dlPFC, dACC, IFG, and parietal [76–78].

Thus, consistent with adult OCD literature, a pattern of increased activation during tasks requiring lower cognitive load and decreased activation during tasks with higher level of demand for control characterizes pediatric patients with OCD compared to healthy youth. In line with this notion, Huyser and colleague [79] found decreased activation in conjunction with impaired performance (slower reaction times) in pediatric OCD participants relative to healthy youth on a task

Table 2 Task-control function in pediatric obsessive compulsive disorder

Study	Subject characteristics	Task(s)	Behavior findings	Main imaging findings
Lazaro et al. [74]	Range: 7–18 OCD: 13.1 ± 2.7, $n = 12$, 7 M HC: 13.7 ± 2.8, $n = 12$, 7 M	Simplified SRTT, pretreatment to posttreatment (lower difficulty)	Not reported	*Before treatment:* ↑ Bilateral dlPFC activation for more vs. less complex response options *After treatment:* ↑ Right IPL activation for more vs. less complex response options *Before vs. after:* ↓ Left insula and left putamen activation for more vs. less complex response options within OCD group Correlation of greater Nacc and RSPL activation with greater OCD severity on CYBOCs and greater rSPL and left posterior cingulate activation with greater obsession severity before treatment
Fitzgerald et al. [50]	Range: 8–19 OCD: 13.9 ± 2.6, $n = 18$, 6 M HC: 14.1 ± 2.7, $n = 18$, 6 M	MSIT (lower difficulty)	No group difference	↑ dACC activation for high vs. low interference ↑ vmPFC activation for error vs. correct ↑ dACC–vmPFC connectivity for high vs. low interference (psychophysiological interaction analysis) No correlation with OCD severity on CYBOCs
Fitzgerald et al. [80]	Range: 8–19 OCD: 12.9 ± 3.0, $n = 21$ HC: 14.1 ± 3.1, $n = 25$ (all F)	MSIT (lower difficulty)	Mo group difference	OCD = HC for high vs. low interference. ↓ Left dlPFC activation for error vs. correct No correlation with OCD severity on CYBOCs
Huyser et al. [79]	Range: 8–19 OCD: 14.0 ± 2.5, $n = 25$, 9 M HC: 13.7 ± 2.9, $n = 25$, 9 M	Flanker, pretreatment to posttreatment (lower difficulty)	Mo group difference before or after treatment	*Before treatment***:** ↓ dlPFC and posterior insula activation for high v low interference. ↑ Bilateral insula activation *with age* for high v low interference (OCD relative to HC, group × age interaction) ↑ rACC and bilateral insula activation *with age* for error vs. correct (OCD relative to HC, group × age interaction) *After treatment:* ↑ Bilateral dlPFC and right premotor activation for high vs. low interference. ↑ rACC and right insula activation *with age* for error vs. correct (OCD relative to HC, group × age interaction) Correlation of greater left dlPFC activation to interference with OCD severity on CYBOCs *before treatment* Correlation of greater right insula activation to errors with OCD severity on CYBOCs *before treatment* Correlation of increase in bilateral dlPFC, right dmPFC, and left premotor cortex to interference with decrease in OCD severity on CYBOCs *before-to-after treatment*
Diwadkar et al. [75]	Range: 11–21 OCD: 17.2 ± 3.3, $n = 18$, 11 M HC: 17.4 ± 3.1, $n = 27$, 18 M	n-back (lower difficulty)	Not reported	↑ dlPFC, dACC, and parietal activation to both 1- and 2-back tasks ↑ dACC connectivity with parietal, middle frontal, and BG to 1-back ↑ dACC connectivity with parietal, dmPFC/dACC to 2-back
Wooley et al. [77]	Range: 12–16 OCD: 14 ± 1.7, $n = 10$ HC: 14.5 ± 1.1, $n = 9$ (all M)	Stroop (lower difficulty)	No group difference	↓ Right middle temporal gyrus and bilateral cerebellar vermis activation to high vs. low interference
Wooley et al. [77]	Range: 12–16 OCD: 14 ± 1.7, $n = 10$ HC: 14.5 ± 1.1, $n = 9$ (all M)	Stop-signal (higher difficulty)	No group difference	↓ Right OFC/insula, thalamus, basal ganglia activation to response inhibition. ↓ dmPFC/dACC and dlPFC activation to error vs. correct
Wooley et al. [77]	Range: 12–16 OCD: 14 ± 1.7, $n = 10$ HC: 14.5 ± 1.1, $n = 9$ (all M)	Set-shifting/switch (higher difficulty)	No group difference	↓ Precentral cortex, IFG, TPJ and cerebellar activation to task switch vs. no switch

Table 2 (continued)

Study	Subject characteristics	Task(s)	Behavior findings	Main imaging findings
Britton et al. [76]	Range: 10–17 OCD: 13.5 ± 2.4, *n* = 15, 9 M HC: 13.6 ± 2.4, *n* = 20, 13 M	Set-shifting/switch (higher difficulty)	No group difference	↓ IFG activation to task switch vs. no switch ↓ Right caudate activation with shift costs IFG–caudate connectivity only in HC, but not in OCD
Huyser et al. [78]	Range: 8–19 OCD: 14.0 ± 2.5, *n* = 25, 9 M HC: 13.7 ± 2.9, *n* = 25, 9 M	Tower of London, pretreatment to posttreatment (higher difficulty)	OCD slower than HC before treatment, but no group difference after treatment	*Before treatment*: ↓ Left dlPFC/premotor and right parietal cortex activation to planning ↑ dlPFC, left dACC, right dmPFC, left insula with increased task load *After treatment:* No group difference; no group × task load interaction Correlation of before-to-after treatment decrease in the left dlPFC and parietal to planning with decrease in OCD severity on CYBOCs

Arrow pointing up means greater in pediatric obsessive compulsive disorder (OCD) than healthy controls (HC); arrow pointing down means lower in OCD than HC

M male, *F* female, *SRTT* serial reaction time task, *MSIT* multisource interference task, *dlPFC* dorsal lateral prefrontal cortex, *IPL* inferior parietal lobule, *Nacc* nucleus accumbens, *rSPL* right superior parietal lobule, *dACC* dorsal anterior cingulate cortex, *vmPFC* ventral medial prefrontal cortex, *rACC* rostral anterior cingulate cortex, *dmPFC* dorsal medial prefrontal cortex, *IFG* inferior frontal gyrus, *TPJ* temporoparietal junction, *CYBOCs* Child Yale Brown Obsessive Compulsive Scale [30]

requiring higher levels of control (TOL). However, this study stands out as an exception since, in other fMRI studies of pediatric OCD, patients performed as well as healthy youth on relatively difficult tasks (e.g., [76, 77]), despite decreased activation in task-control network. Finally, patients with pediatric OCD have been found to exhibit normal performance in the context of decreased dlPFC activation during incorrect [80] and correct [79] trials on relatively low-load, interference tasks. These findings are in conflict with the theory that, during less difficult tasks, hyperactivation of task-control regions is necessary to support the maintenance of performance in OCD [58•].

Several factors may contribute to the discrepancies observed in the pediatric OCD fMRI literature. First, most of the pediatric OCD fMRI studies employed small sample sizes (ranging from 10 to 25 pediatric OCD participants). Small samples in neuroimaging studies often yield low reproducibility of results [81] and may contribute to the observed inconsistencies. Future studies should include larger sample sizes to increase the external validity of the findings. Second, fMRI studies in pediatric OCD have typically included children and adolescents across a wide age range, spanning 8 to 19 years. The function and connectivity of task-control networks develop dramatically from early childhood into adolescence and early adulthood [20, 49]. Thus, different studies may produce different findings depending on the specific ages of each study sample. That is, developmental variability within age groups may outweigh the between-group (OCD versus healthy) variability in brain function and/or performance. Future studies should further stratify by age and recruit more subjects at each age, differentiating effects for young children from adolescents [82].

Conclusions

In conclusion, there is strong evidence demonstrating abnormalities of both FSTC and canonical networks for task control (SN, CEN) in pediatric OCD. Emerging works suggests that these abnormalities may vary with age and performance in young patients. Understanding this variation will be important for elucidating the neurodevelopmental trajectories that may underlie the emergence and early course of OCD. Additional research combining DTI and rsfcMRI studies with task-based fMRI methodologies will also be needed to elucidate the relationships between developing connectivity and interactive cognitive and emotional functions served by FSTC and cortical-cortical networks. Such knowledge would guide efforts to develop brain stimulation (e.g., transcranial magnetic stimulation (TMS) or transcranial direct-current stimulation (tDCS)) to potentiate/modulate activity in the relevant neural circuits or cognitive training paradigms to target the brain regions involved in cognitive and emotional dysfunction specific to pediatric OCD. Longitudinal imaging designs will be especially important in reaching these goals. By following patients over time, neuroimaging research may reveal developmentally sensitive MR metrics, as well as functional activation and connectivity patterns, to serve as targets or intermediate outcomes, by which to measure the effect of cognitive training and neuromodulatory therapies. Ultimately, this line of research may identify personalized strategies for adjusting neurodevelopment to treat (and even prevent) OCD in different patients, at different ages.

Compliance with Ethical Standards

Conflict of Interest Dr. Yanni Liu, Dr. Emily L. Bilek, and Dr. Kate D. Fitzgerald declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Kessler RC et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):593–602.
2. Pauls DL et al. A family study of obsessive-compulsive disorder. Am J Psychiatry. 1995;152(1):76–84.
3. Ruscio AM et al. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol Psychiatry. 2010;15(1):53–63.
4. Stewart SE et al. Long-term outcome of pediatric obsessive-compulsive disorder: a meta-analysis and qualitative review of the literature. Acta Psychiatr Scand. 2004;110(1):4–13.
5. Menzies L et al. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. Neurosci Biobehav Rev. 2008;32(3):525–49.
6. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci. 1986;9:357–81.
7. Ridderinkhof KR et al. The role of the medial frontal cortex in cognitive control. Science. 2004;306(5695):443–7.
8. Haber SN, Knutson B. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology. 2010;35(1):4–26.
9. Baxter Jr LR et al. Brain mediation of obsessive-compulsive disorder symptoms: evidence from functional brain imaging studies in the human and nonhuman primate. Semin Clin Neuropsychiatry. 1996;1(1):32–47.
10. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci. 1989;12(10):366–75.
11. van den Heuvel OA et al. Frontal-striatal abnormalities underlying behaviours in the compulsive-impulsive spectrum. J Neurol Sci. 2010;289(1-2):55–9.
12. Brem S et al. Neuroimaging of cognitive brain function in paediatric obsessive compulsive disorder: a review of literature and preliminary meta-analysis. J Neural Transm (Vienna). 2012;119(11):1425–48.
13. Radua J, Mataix-Cols D. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. Br J Psychiatry. 2009;195(5):393–402.
14. Dell'Acqua F, Catani M. Structural human brain networks: hot topics in diffusion tractography. Curr Opin Neurol. 2012;25(4):375–83.
15. Hagmann P et al. Understanding diffusion MR imaging techniques: from scalar diffusion-weighted imaging to diffusion tensor imaging and beyond. Radiographics. 2006;26 Suppl 1:S205–23.
16. Beaulieu C. The basis of anisotropic water diffusion in the nervous system—a technical review. NMR Biomed. 2002;15(7-8):435–55.
17. Bonekamp D et al. Diffusion tensor imaging in children and adolescents: reproducibility, hemispheric, and age-related differences. Neuroimage. 2007;34(2):733–42.
18. Paus T. Growth of white matter in the adolescent brain: myelin or axon? Brain Cogn. 2010;72(1):26–35.
19. Walhovd KB, Johansen-Berg H, Karadottir RT. Unraveling the secrets of white matter—bridging the gap between cellular, animal and human imaging studies. Neuroscience. 2014;276:2–13.
20. Fair DA et al. Development of distinct control networks through segregation and integration. Proc Natl Acad Sci U S A. 2007;104(33):13507–12.
21. Ernst M et al. fMRI functional connectivity applied to adolescent neurodevelopment. Annu Rev Clin Psychol. 2015;11:361–77.
22. Hofer S, Frahm J. Topography of the human corpus callosum revisited—comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. Neuroimage. 2006;32(3):989–94.
23. Jones DK, Knosche TR, Turner R. White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. Neuroimage. 2013;73:239–54.
24. Zarei M et al. Changes in gray matter volume and white matter microstructure in adolescents with obsessive-compulsive disorder. Biol Psychiatry. 2011;70(11):1083–90.
25. Gruner P et al. White matter abnormalities in pediatric obsessive-compulsive disorder. Neuropsychopharmacology. 2012;37(12):2730–9.
26. Jayarajan RN et al. White matter abnormalities in children and adolescents with obsessive-compulsive disorder: a diffusion tensor imaging study. Depress Anxiety. 2012;29(9):780–8.
27. Silk T et al. White matter abnormalities in pediatric obsessive-compulsive disorder. Psychiatry Res. 2013;213(2):154–60.
28. Rosso IM et al. Brain white matter integrity and association with age at onset in pediatric obsessive-compulsive disorder. Biol Mood Anxiety Disord. 2014;4(1):13.
29. •• Fitzgerald KD et al. Atypical frontal-striatal-thalamic circuit white matter development in pediatric obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 2014;53(11):1225–33. **As the first study to examine the effect of age on structural connectivity in pediatric OCD, this paper highlights the relevance of atypical brain development in pediatric OCD**.
30. Scahill L et al. Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. J Am Acad Child Adolesc Psychiatry. 1997;36(6):844–52.
31. Nelson EC et al. Obsessive-compulsive scale of the child behavior checklist: specificity, sensitivity, and predictive power. Pediatrics. 2001;108(1):E14.
32. Yoo SY et al. White matter abnormalities in drug-naive patients with obsessive-compulsive disorder: a diffusion tensor study before

and after citalopram treatment. Acta Psychiatr Scand. 2007;116(3): 211–9.

33. Li F et al. Microstructural brain abnormalities in patients with obsessive-compulsive disorder: diffusion-tensor MR imaging study at 3.0 T. Radiology. 2011;260(1):216–23.
34. Cannistraro PA et al. A diffusion tensor imaging study of white matter in obsessive-compulsive disorder. Depress Anxiety. 2007;24(6):440–6.
35. Piras F et al. Brain circuitries of obsessive compulsive disorder: a systematic review and meta-analysis of diffusion tensor imaging studies. Neurosci Biobehav Rev. 2013;37(10 Pt 2):2856–77.
36. Westlye LT et al. Life-span changes of the human brain white matter: diffusion tensor imaging (DTI) and volumetry. Cereb Cortex. 2010;20(9):2055–68.
37. Radua J et al. Multimodal voxel-based meta-analysis of white matter abnormalities in obsessive-compulsive disorder. Neuropsychopharmacology. 2014;39(7):1547–57.
38. Honey CJ et al. Predicting human resting-state functional connectivity from structural connectivity. Proc Natl Acad Sci U S A. 2009;106(6):2035–40.
39. O'Reilly JX et al. Causal effect of disconnection lesions on interhemispheric functional connectivity in rhesus monkeys. Proc Natl Acad Sci U S A. 2013;110(34):13982–7.
40. Fox MD et al. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A. 2005;102(27):9673–8.
41. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci. 2011;15(10):483–506.
42. Harrison BJ et al. Altered corticostriatal functional connectivity in obsessive-compulsive disorder. Arch Gen Psychiatry. 2009;66(11): 1189–200.
43. Sakai, Y., et al., *Corticostriatal functional connectivity in non-medicated patients with obsessive-compulsive disorder*. Eur Psychiatry. 2011;26(7):463–9.
44. Di Martino A et al. Functional connectivity of human striatum: a resting state FMRI study. Cereb Cortex. 2008;18(12):2735–47.
45. Fitzgerald KD et al. Developmental alterations of frontal-striatal-thalamic connectivity in obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 2011;50(9):938–48. e3.
46. Weber AM, Soreni N, Noseworthy MD. A preliminary study of functional connectivity of medication naive children with obsessive-compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2014;53:129–36.
47. Etkin A et al. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron. 2006;51(6):871–82.
48. Rubia K et al. Progressive increase of frontostriatal brain activation from childhood to adulthood during event-related tasks of cognitive control. Hum Brain Mapp. 2006;27(12):973–93.
49. Uddin LQ et al. Dynamic reconfiguration of structural and functional connectivity across core neurocognitive brain networks with development. J Neurosci. 2011;31(50):18578–89.
50. Fitzgerald KD et al. Altered function and connectivity of the medial frontal cortex in pediatric obsessive-compulsive disorder. Biol Psychiatry. 2010;68(11):1039–47.
51. Beucke JC et al. Default mode network subsystem alterations in obsessive-compulsive disorder. Br J Psychiatry. 2014;205(5): 376–82.
52. Stern ER et al. Resting-state functional connectivity between fronto-parietal and default mode networks in obsessive-compulsive disorder. PLoS One. 2012;7(5):e36356.
53. Chamberlain SR et al. The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. Neurosci Biobehav Rev. 2005;29(3):399–419.
54. Snyder HR et al. Obsessive-compulsive disorder is associated with broad impairments in executive function: a meta-analysis. Clin Psychol Sci. 2015;3(2):301–30.
55. Dosenbach NU et al. A core system for the implementation of task sets. Neuron. 2006;50(5):799–812.
56. Diamond A. Executive functions. Annu Rev Psychol. 2013;64: 135–68.
57. Sridharan D, Levitin DJ, Menon V. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proc Natl Acad Sci U S A. 2008;105(34): 12569–74.

58.• van Velzen LS et al. Response inhibition and interference control in obsessive-compulsive spectrum disorders. Front Hum Neurosci. 2014;8:419. **This review paper highlights the importance of considering behavioral/performance measures in interpreting task-based fMRI findings in OCD. It provided a framework that shaped interpretation of fMRI studies in pediatric OCD for the current review.**

59. Eng GK, Sim K, Chen SH. Meta-analytic investigations of structural grey matter, executive domain-related functional activations, and white matter diffusivity in obsessive compulsive disorder: an integrative review. Neurosci Biobehav Rev. 2015;52:233–57.
60. Sebastian A et al. Disentangling common and specific neural subprocesses of response inhibition. Neuroimage. 2013;64:601–15.
61. Miyake A et al. The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. Cogn Psychol. 2000;41(1):49–100.
62. Eysenck MW et al. Anxiety and cognitive performance: attentional control theory. Emotion. 2007;7(2):336–53.
63. Manoach DS. Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. Schizophr Res. 2003;60(2-3):285–98.
64. Marsh R et al. Altered activation in fronto-striatal circuits during sequential processing of conflict in unmedicated adults with obsessive-compulsive disorder. Biol Psychiatry. 2014;75(8): 615–22.
65. de Wit SJ et al. Presupplementary motor area hyperactivity during response inhibition: a candidate endophenotype of obsessive-compulsive disorder. Am J Psychiatry. 2012;169(10):1100–8.
66. Koch K et al. Aberrant anterior cingulate activation in obsessive-compulsive disorder is related to task complexity. Neuropsychologia. 2012;50(5):958–64.
67. de Vries FE et al. Compensatory frontoparietal activity during working memory: an endophenotype of obsessive-compulsive disorder. Biol Psychiatry. 2014;76(11):878–87.
68. Nakao T et al. Working memory dysfunction in obsessive-compulsive disorder: a neuropsychological and functional MRI study. J Psychiatr Res. 2009;43(8):784–91.
69. Gu BM et al. Neural correlates of cognitive inflexibility during task-switching in obsessive-compulsive disorder. Brain. 2008;131(Pt 1): 155–64.
70. Page LA et al. A functional magnetic resonance imaging study of inhibitory control in obsessive-compulsive disorder. Psychiatry Res. 2009;174(3):202–9.
71. Han JY et al. Altered brain activation in ventral frontal-striatal regions following a 16-week pharmacotherapy in unmedicated obsessive-compulsive disorder. J Korean Med Sci. 2011;26(5): 665–74.
72. van den Heuvel OA et al. Frontal-striatal dysfunction during planning in obsessive-compulsive disorder. Arch Gen Psychiatry. 2005;62(3):301–9.
73. den Braber A et al. An fMRI study in monozygotic twins discordant for obsessive-compulsive symptoms. Biol Psychol. 2008;79(1):91–102.

74. Lazaro L et al. Cerebral activation in children and adolescents with obsessive-compulsive disorder before and after treatment: a functional MRI study. J Psychiatr Res. 2008;42(13):1051–9.
75. Diwadkar VA et al. Dysfunctional activation and brain network profiles in youth with obsessive-compulsive disorder: a focus on the dorsal anterior cingulate during working memory. Front Hum Neurosci. 2015;9:149.
76. Britton JC et al. Cognitive inflexibility and frontal-cortical activation in pediatric obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 2010;49(9):944–53.
77. Woolley J et al. Brain activation in paediatric obsessive compulsive disorder during tasks of inhibitory control. Br J Psychiatry. 2008;192(1):25–31.
78. Huyser C, et al. Functional magnetic resonance imaging during planning before and after cognitive-behavioral therapy in pediatric obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 2010; 49(12): 1238-48, 1248 e1-5.
79. Huyser C et al. Developmental aspects of error and high-conflict-related brain activity in pediatric obsessive-compulsive disorder: a fMRI study with a Flanker task before and after CBT. J Child Psychol Psychiatry. 2011;52(12):1251–60.
80. Fitzgerald KD et al. Reduced error-related activation of dorsolateral prefrontal cortex across pediatric anxiety disorders. J Am Acad Child Adolesc Psychiatry. 2013;52(11):1183–91. e1.
81. Button KS et al. Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci. 2013;14(5):365–76.
82. Abramovitch A et al. Neuroimaging and neuropsychological findings in pediatric obsessive-compulsive disorder: a review and developmental considerations. Neuropsychiatry. 2012;2(4):313–29.