REVIEW

Neuroimaging and neuropsychological findings in pediatric obsessive–compulsive disorder: a review and developmental considerations

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Practice points

- Pediatric obsessive–compulsive disorder (OCD) appears to be distinct from its adult counterpart, especially in preadolescent patients.

- In contrast to the majority of adult imaging studies, a volumetric increase has been identified in the frontal and, in particular, striatal regions in pediatric OCD.

- Imaging research indicates increased frontostriatal metabolism in the pediatric OCD population, but decreased activation in preadolescent young children.

- The decreased activation correlates with OCD symptomatology in young children and increased activation correlates with symptom severity in adolescents.

- Abnormalities in frontostriatal activity tend to normalize following successful treatment.

- Maturational reorganization, including neuronal pruning and myelination, further complicates the isolation of specific neurobiological underpinnings of OCD.

- Even more so than in the adult population, research is inconsistent with regard to the executive function deficits of children with OCD, in part because of hypothesized abnormal maturation processes in this population.

- Studies of executive functioning may be complicated by heterogeneous sample bases that span large developmental ranges.

- More neuropsychological and neurobiological pediatric OCD studies are needed and future studies are advised to incorporate a developmental perspective.

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SUMMARY Obsessive–compulsive disorder (OCD) is one of the most prevalent psychiatric disorders affecting children and adolescents. In the last decade, our knowledge base of pediatric OCD has increased greatly. In examining pediatric OCD, neuropsychological performance may serve as a bridge between brain functioning and the phenomenology of the disorder. Recent advances in neuropsychological and neuroimaging techniques have led to significant interest in the neurobiological underpinnings of OCD. Although considerable research has been conducted on adults with this disorder, relatively little research has been directed towards similarly afflicted youth. Neurobiological research including lesion, structural and functional imaging studies are reviewed, along with the literature on neuropsychological testing and deficits associated with the disorder. Emphasizing both the neural and cognitive developmental processes within the pediatric population, these findings are examined and critiqued within a developmental framework.

Cognitive neuroscience approaches, including neuroimaging and neuropsychological assessment, have demonstrated utility as paradigms for understanding neuropsychiatric disorders, particularly obsessive–compulsive disorder (OCD) [1,2]. An integrative approach may prove especially useful in characterizing the neuropsychological strengths or deficits associated with specific regional brain abnormalities. For example, several studies have suggested that adult OCD is characterized by a prominent impairment in response inhibition [3,4], which could be conceptualized as an adult OCD endophenotype [5,6]. In examining pediatric OCD, neuropsychological performance may serve as a bridge between brain functioning and the phenomenology of the disorder [7]. Until recently, there has been little examination of the applicability of these models to pediatric OCD. However, studies on the developmental progression of neuronal maturation and reorganization, recent imaging and neuropsychological studies together with the extant literature on age-related progress in neuropsychological performance, suggest that neuropsychiatric models of pediatric OCD must consider the developmental context in which abnormal neuropsychological findings are expressed [8].

The goal of this review is to present a developmental perspective on neuroanatomical and neuropsychological findings of OCD in children and adolescents. Following a brief overview of the epidemiology of OCD in youth, we review neuroanatomical theories of OCD, including evidence from structural and functional neuroimaging studies. Furthermore, we examine the neuropsychological correlates of pediatric OCD. Notably, we present a succinct review of findings from adult OCD studies in each section, and where applicable, pediatric–adult comparisons are discussed. Finally, we integrate these findings within a developmental framework that stresses both normal and abnormal processes in the pathogenesis of OCD, and caution the use of adult models in the evaluation of childhood disorders.

Epidemiology

Worldwide prevalence rates of pediatric OCD range from 1 to 3% [9,10], similar to prevalence estimates in adults [11]. As such, this similarity appears puzzling when considering the appearance of new adult cases and in light of reports suggesting that 25–50% of adult OCD patients develop clinically significant OCD in childhood [10,11]. This contradiction may be reconciled by a meta-analysis of long-term pediatric OCD outcome, which found that 41% of pediatric OCD persists into adulthood [12]. While the literature is still without definitive conclusion, OCD appears to exhibit a bimodal incidence across the life span: one peak occurring in pre-adolescent children (mean age: 10 years) [13,14] and a later peak in early adulthood (mean age: 19.5 years) [11].

Neuroanatomy of OCD
■ Anatomy of the frontostriatal systems

Areas of the frontal and prefrontal cortices, including the orbitofrontal cortex and the anterior cingulate cortex, send numerous excitatory projections to the striatum [15]. In turn, regions of the striatum send efferent signals directly and indirectly (through other basal ganglia structures) to the dorsomedial thalamic nuclei, which in turn project back to the prefrontal cortex, stimulating cortical output and completing this feedback loop [2,16].

Several neurotransmitter systems modulate this frontostriatal feedback loop. Specifically, the excitatory amine glutamate is involved in the output from the ventral prefrontal cortex (VPFC),

projecting to the anterior striatum, nucleus accumbens and substantia nigra [17]. Dopamine- and serotonin-containing neurons affect other brain areas implicated in OCD by modulating efferents from the basal ganglia [18]. For example, dopamine D_2 receptors are found in dorsal striatal caudate areas [17] and serotonin receptors are densely located in ventromedial caudate and nucleus accumbens regions [18]. Dopaminergic stimulation of the prefrontal cortex may act by inhibition of pyramidal cells, which in turn reduces glutamatergic excitatory output from these cortical cells to the basal ganglia and other brain regions [19].

Several frontal cortico-striatal-thalamic circuits have been implicated in OCD patho-physiology [1] and multiple neurotransmitter systems modulate this feedback loop, including the excitatory amine glutamate as well as dopamine and serotonin-containing neurons [18]. Structural imaging research in OCD has yielded somewhat inconsistent results [20]. However, in contrast to the majority of adult imaging studies, pediatric studies indicate a volumetric increase in frontal and especially striatal regions.

It has been proposed that in early onset patients only, OCD symptomatology correlated positively with left orbitofrontal regional cerebral blood flow (rCBF), implying that brain mechanisms in OCD may vary depending on age of symptom onset [21]. However, other studies did not find this association, and a recent review concluded that it is still premature to differentiate between early onset and late-onset OCD based upon brain imaging findings [22].

■ Evidence from lesion studies

Some of the earliest evidence for the role of the prefrontal cortex and basal ganglia comes from studies of patients with brain lesions or other cerebral insult. Obsessive–compulsive symptom onset has been observed following cingulate epilepsy [23]. In fact, a recent review concluded that as many as a quarter of patients suffering from temporal lobe epilepsy exhibit OCD features [24]. Symptoms of OCD are associated with traumatic brain injury (TBI) [25], either more globally [26], or to focal areas such as the basal ganglia [27] or frontal lobe [28]. Nevertheless, it remains unclear whether TBI is associated with OCD-like symptoms or full-scale OCD. In fact, it is suggested that in addition to lesion site location, premorbid status and environmental stressors may influence the presentation of OCD symptoms following

TBI [25]. The high incidence of OCD among patients with basal ganglia disorders, including Sydenham's chorea, has also been described in multiple case studies [29]. Swedo *et al.* examined OCD symptoms using the Leyton Obsessional Inventory–Child Version in 23 children with Sydenham's chorea and a comparison group of 14 children with rheumatic fever [30]. As a group, Sydenham's patients had significantly greater OCD symptoms, as well as more interference from these symptoms.

Structural neuroimaging research
■ Adult studies

Structural examinations of the basal ganglia of adults with OCD, using computerized tomography (CT) or MRI, have yielded somewhat contradictory findings [20]. Some have found decreased caudate nucleus volumes [31,32]. Others have found no group differences in caudate volume or symmetry [33], or even an increase in right caudate nucleus volumes [34]. These inconsistent results have been largely attributed to methodological differences across studies, such as variability in the study populations, treatment effects and specific study procedures (e.g., cortical parcellation), as well as the small sample sizes employed [35]. In addition, demographic factors, such as age or duration of illness, may further complicate cross-study comparisons [20]. However, with some exceptions [32,36], structural scans have generally observed volumetric decreases in cerebral and cerebellar cortical areas in OCD patients [1,31], especially in the lateral frontal gyri.

■ Pediatric studies

Until the last decade, there were almost no neuroimaging studies of children with OCD. Nevertheless, children with OCD may be an especially suitable population in which to study neuroanatomical abnormalities owing to the recent onset of the disorder and limited exposure to psychopharmacological treatment [16]. In one of the first neuroanatomical studies, Behar *et al.* administered CT scans to 16 adolescents diagnosed with OCD and 16 matched controls [37]. They found higher mean ventricular:brain ratios among OCD participants, although ventricular:brain ratios did not correlate with observed neuropsychological deficits [37]. Subsequent pediatric imaging studies, detected abnormalities in the cingulate cortex, basal ganglia and thalami [38].

In an MRI study of 19 treatment-naive pediatric patients with OCD and matched controls (aged 7–17 years), Rosenberg *et al.* observed reduced striatal volumes in OCD patients [39]. Specifically, children with OCD had significantly smaller putamen but not caudate volumes. No significant group differences were found in the total prefrontal cortical gray matter, white matter, lateral ventricular or intracranial volume [39].

In a subsequent study, Rosenberg *et al.* observed significantly larger anterior cingulate volumes in pediatric OCD patients compared with controls, but normal posterior cingulate, dorsolateral prefrontal cortex, amygdala, hippocampal and temporal lobe volumes [39]. They found a positive correlation between the Children's Yale–Brown Obsessive–Compulsive Scale (CY-BOCS) symptom severity and anterior cingulate volumes, and an inverse correlation between CY-BOCS scores and putamen volumes [18,39]. Zarei *et al.* found a positive correlation between CY-BOCS scores and gray matter volume in the right insula, left posterior orbitofrontal cortex, subgenual cingulate cortex, ventral striatum, the cerebellum and brainstem. CY-BOCS scores were negatively correlated with gray matter volumes in the anterior orbitofrontal, ventrolateral and dorsolateral regions [40].

Pediatric OCD has been investigated in the context of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). The PANDAS hypothesis emerged from observations of neurological and behavioral changes that accompany Sydenham's chorea, a sequel of rheumatic fever. An immune response to group A β-hemolytic *Streptococcus* infections leads to cross reactivity with, and inflammation of, the basal ganglia, subsequently resulting in a distinct neurobehavioral syndrome that includes OCD and tics. At this time, the weight of evidence suggests that a subset of children with OCD exhibit both the onset and clinical exacerbation linked to group A β-hemolytic *Streptococcus* [41]. Findings from a series of studies demonstrated that children diagnosed with PANDAS have acute basal ganglia enlargement [42,43]. In an MRI study, Giedd *et al.* examined 34 children with presumed PANDAS and found significantly greater baseline volumes of caudate, putamen and globus pallidus, but not thalamic or total cerebrum volumes when compared with 82 healthy controls [42].

Thalamic dysfunction has also been implicated in pediatric OCD pathophysiology. Using structural MRI, Gilbert *et al.* measured the thalamic volumes of 21 psychotropic-naive children with OCD, aged between 8 and 17 years, and 21 matched healthy controls [44]. OCD patients exhibited significantly larger thalamic volumes than controls, although baseline thalamic volume was uncorrelated with OCD symptom severity, neuropsychological measures, illness duration or age of OCD onset. Following 12 weeks of effective paroxetine treatment, these same participants demonstrated significant decreases to a normalized level in thalamic volumes, which also correlated highly with parallel reductions in OCD symptom severity [44]. However, using a similar study design, Rosenberg and colleagues found no significant changes in the thalami of pediatric OCD patients treated with 12 weeks of effective cognitive-behavioral therapy (CBT), suggesting that the therapeutic effects of CBT may be mediated through different pathways [45].

Pediatric OCD patients have also exhibited abnormalities of the corpus callosum. Rosenberg *et al.* observed significant abnormalities in the anterior corpus callosum with increased volume of the region connecting the ventral prefrontal cortices and striatum [46]. With the exception of the isthmus, all regions of the corpus callosum were significantly larger in OCD patients than normal controls and these abnormalities correlated significantly with OCD symptom severity. Moreover, OCD subjects did not demonstrate expected age-related increases in corpus callosum size [46].

To examine whether these abnormalities were related to abnormal myelination in pediatric OCD patients, Mac Master *et al.* examined the signal intensity of specific regions of the corpus callosum using midsagittal MRI scan images of 21 treatment-naive pediatric OCD subjects and 21 matched controls [47]. Total raw corpus callosal signal intensity did not differ between OCD and healthy control children, nor were there group differences for the corpus callosal isthmus and splenium regions. However, the mean anterior genu signal intensity was significantly decreased for the OCD group [47]. Furthermore, genu signal intensity was inversely correlated with OCD symptom severity [46]. Since lower signal intensity is related to higher concentrations of white matter, increased myelination in the region of the anterior genu and a concomitant increase in processing speed may, in turn, affect the activity of the associated cortices with which this region is connected [47]. The corpus

callosum receives projections from association and primary motor/sensory cortices, especially the VPFC and striatal circuits [46], lending indirect support for a neurodevelopmental model of abnormal ventral prefrontal–striatal functioning in pediatric OCD.

In summary, while somewhat inconsistent, the empirical literature indicates that compared with age-matched healthy controls, children with OCD exhibit a volumetric increase in the frontal and, in particular, striatal regions. These findings are contrary to observations in the majority of adult studies. As discussed below, owing to maturational processes that characterize young children, it is necessary to evaluate these results with a neurodevelopmental perspective.

Functional neuroimaging research

Several functional neuroimaging techniques, including PET, functional MRI (fMRI), single-photon emission CT (SPECT) and proton magnetic resonance spectroscopy have been employed to examine differences between OCD patients and healthy controls [48]. These techniques have been employed to examine group differences at rest, during symptom provocation and following treatment [49,50] (for a review see [51]).

■ Adult studies

At rest, OCD patients demonstrate hypermetabolism in the orbitofrontal [52–55], medial-frontal [56] and anterior cingulate cortex [55]. Abnormal activity in the striatum (caudate) has also been detected [53,54] and abnormalities in the anterolateral prefrontal cortex have been implicated in the depression that often accompanies OCD [52]. More recently, functional connectivity studies have reported increased frontostriatal connectivity [54,57]. Resting state activation was found to positively correlate with OCD symptom severity [54,58]. Symptom provocation paradigms have also yielded increased activation in the bilateral orbitofrontal cortex, right caudate nucleus, anterior cingulate cortex and bilateral temporal cortex [10,48,53,59]. Activation of the orbitofrontal cortex during symptom provocation has been observed to correlate with the severity of obsessional symptomatology [10].

Specific patterns of brain activity may be associated with different OCD subtypes/symptom dimensions [60,61]. However, activation of the anterior orbitofrontal cortex and caudate nucleus appears to be specific to OCD [35], whereas areas of the paralimbic belt, right inferior frontal cortex and subcortical nuclei may mediate symptoms across different anxiety disorders [35].

fMRI studies of treatment effects have shown that increased activity in the orbitofrontal cortex, thalamus, caudate nucleus and anterior cingulate cortex are normalized following effective pharmacotherapy or CBT [62–67]. The magnitude of this effect is such that post-treatment OCD patients are indistinguishable from controls in orbitofrontal cortex and caudate nucleus metabolic rates [68,69].

■ Pediatric studies

A handful of functional imaging studies conducted with children with OCD at rest and following treatment have yielded results comparable to those found in adult studies. Fitzgerald *et al.* used magnetic resonance spectroscopic imaging to measure thalamic *N*-acetyl-aspartate (NAA), creatine and choline levels in 11 pediatric OCD patients and 11 matched controls [70]. They found a significant reduction in NAA/choline and NAA/creatine/phosphocreatine levels bilaterally in the medial thalami of affected children compared with controls. Furthermore, reductions in the left medial thalamic NAA levels were inversely correlated with OCD symptom severity [70]. In a follow-up study of these youths, Rosenberg *et al.* obtained absolute measures of NAA (a putative marker of neuronal viability), cytosolic choline and creatine [71]. Following treatment, NAA and creatine levels no longer differed significantly between children with OCD and controls in either the medial or lateral thalamus [71].

In a larger paroxetine treatment study of 11 psychotropic drug-naive children aged 8–17 years with OCD and 11 control children, Rosenberg *et al.* found significantly greater caudate glutamate concentrations in the OCD group [72]. As reported in an earlier case report [72], the authors concluded that following paroxetine treatment, glutamate levels decreased significantly in parallel with reduction in OCD symptoms [73].

In a SPECT study of 13 adults with early onset OCD (onset age <10 years old), 13 adults with late-onset OCD (onset age >12 years old), and 22 healthy controls, the early onset cases showed decreased cerebral blood flow in the right thalamus, left anterior cingulate cortex and bilateral inferior prefrontal cortex relative to later-onset subjects. Compared with controls, early onset

OCD patients exhibited decreased left anterior cingulate and right orbitofrontal rCBF. Later-onset subjects showed reduced right orbitofrontal rCBF and increased rCBF in the left precuneus. In early onset subjects only, the severity of obsessive–compulsive symptoms correlated positively with left orbitofrontal rCBF. These results provide preliminary evidence that brain mechanisms in OCD may differ depending on the age of symptom onset [21].

As suggested by similar adult OCD studies, pediatric OCD resting-state investigations found frontostriatal hypermetabolism. In a SPECT study of 18 medication-free 11–15-year-olds with OCD and 12 matched healthy controls, Diler and colleagues found significantly elevated resting state rCBF in the bilateral dorsolateral prefrontal cortex, anterior cingulate cortex and caudate nucleus [68].

Only a few pediatric OCD fMRI studies have been published. Lazaro et al. examined 12 children and adolescents with OCD and matched healthy controls before and after 6 months of pharmacological treatment [69]. The authors reported that pretreatment, the OCD group showed increased activation in the middle frontal gyrus compared with healthy controls. Subsequently, after 6 months of pharmacotherapy, reduced activity was found in the left insula and left putamen, which was associated with reduction of obsessive–compulsive symptoms [69].

Brain activity during task performance was also assessed in pediatric OCD. Reduced frontostriatal activation in the inferior frontal cortex was found during the performance of set-shifting tasks [74] and during stop–signal tasks [75]. In fact, Huyser et al. found reduced frontostriatal activation during the Tower of London task, which normalized after 16 CBT sessions [76]. These studies are in accordance with adult OCD studies that suggest disorder-specific elevated resting-state frontostriatal metabolic activity and reduced activity during executive function tests [77,78]. However, findings in other functional imaging studies in pediatric OCD are in direct contrast to findings in adult OCD. In the only pediatric OCD symptom-provocation study we are aware of, Gilbert et al., examined 18 children with OCD, aged 11–17 years, and 18 matched healthy controls [79]. The authors reported reduced activity in the right insula, putamen, thalamus, dorsolateral prefrontal cortex and left orbitofrontal cortex in the contamination condition and in the right thalamus and right insula in the symmetry-related condition. Moreover, symptom severity was found to correlate significantly with reduced activity in the right dorsolateral prefrontal cortex [79]. The authors concluded that their findings suggest developmental effects on neuronal systems associated with OCD symptoms in pediatric patients. More recently, Fitzgerald et al. compared 60 patients with OCD with 61 healthy controls using a resting-state MRI protocol [80]. Participants recruited for this study were children, adolescents and adults. Overall, the authors found increased frontostriatal activation. Reduced connectivity in the fronto-thalamic-striatal network was found only in the pediatric group (mean age: 11.0 years). In addition, reduced frontostriatal activity was significantly correlated with symptom severity only in the pediatric group [80]. Specifically, reduced left dorsal striatum-rostral anterior cingulate cortex connectivity was correlated with a CY-BOCS score in the youngest age group (mean age: 11.0 years), although no correlation was found for adolescents (mean age: 15.3 years) [80].

Neurobiological model of OCD: a developmental perspective

OCD may be associated with an imbalance in tone between the direct and indirect striato-pallidal pathways, which in turn leads to increased activity in orbitofrontal-subcortical circuits [51,81]. Involuntary thoughts, sensations and actions are normally suppressed with little conscious effort, partially via the action of the indirect basal ganglia pathway, which in turn inhibits thalamic activity [17,82]. Dysfunction in the striatopallidal circuits, in addition to insufficient inhibition of the thalamocortical pathways, may result in the sustained activity of a 'worry' circuit involving the orbital cortex, caudate and thalamus. This may lead to deficient gating of cortical function and the experience of intrusive thoughts and sensations [17].

Cells within the orbital cortex and anterior cingulate seem to play a role in 'error detection responses' [66] and are involved in the mediation of stimulus–reward associations by modifying behavior when reinforcement contingencies change, modulating emotional, autonomic and endocrinological responses to meaningful stimuli and inhibiting responses to irrelevant stimuli [83]. The orbitofrontal cortex may also be involved in fear conditioning and anticipatory

anxiety [83]. Abnormalities in orbitofrontal and cingulate cortices may therefore be linked to both the persistent feeling in OCD that 'things are not what they should be' and also the intrusive quality of OCD symptoms. The caudate and other striatal regions, central structures in terms of OCD pathophysiology, have been implicated in numerous affective, learning and memory processes, including conditioned behavioral responses that occur rapidly without allocation of conscious thought or awareness [66]. The temporal lobe and amygdala also play a role in the emotional appraisal of stimuli characteristic of OCD, such as perception of danger and risk.

The consistent lack of association between illness duration, age of onset and morphological findings for both adults and children, argues against a neurodegenerative process in OCD. However, differences in the neuroanatomical findings between youths and adults with OCD point to the importance of developmental factors in the pathogenesis and maintenance of this disorder. In youths with OCD, enlarged structure size accounts for most structural abnormalities. By contrast, several adult studies have suggested smaller volume for the basal ganglia and thalamic structures. It is possible that increased structure size reflects increased metabolic activity and blood flow in these regions, without indicating a pathogenic process. Instead, structural and metabolic differences may represent an attempt to cope with the OCD symptoms themselves [71]. Notably, the autoimmune hypothesis associated with PANDAS suggests that acute enlargement of brain regions, predominantly in the basal ganglia, may be a consequence of inflammation. This may be followed by scarring and shrinkage of the structure that may later result in a decrease in structure size [84].

In addition, the specificity of the above neuroimaging and neuropsychological findings in OCD has been questioned. For example, several of the deficits displayed by children diagnosed with OCD on neuropsychological tests of frontostriatal functioning have also been observed among ADHD youths (i.e., executive functioning and working memory impairments [for a review see [85,86]]). Similarly, neuroimaging studies of ADHD youths have also reported abnormalities in the prefrontal cortex, anterior frontal cortex, corpus callosum and basal ganglia regions [87]. Since OCD may co-occur with ADHD in pediatric populations, care must be taken to disentangle the neuropsychological findings in OCD youth from those that result from comorbid ADHD.

Thus, converging evidence indicates that pediatric OCD may represent a neurodevelopmentally distinct disorder from adult OCD, characterized by specific anatomic and metabolic features attributable to developmental factors, including neuronal pruning and myelination. Research has found that the brain undergoes significant reorganization during childhood and adolescence [19,88–91]. Early in development the brain overproduces neural connections (synaptogenesis) followed by a period of synaptic pruning. These cyclical growth processes appear to be largely under the influence of the frontal lobes.

Accompanying synaptic loss is an increase in the capacity for discrete focal activation of the brain, with less widespread activation during task performance [92]. Cerebral glucose metabolic rates change significantly as children mature. Functional neuroimaging studies demonstrate that rates of glucose metabolism peak above adult levels by the age of 3–4 years, then progressively decrease prepubertally to reach adult levels by the end of the second decade of life [93,94]. This sequence is especially pronounced in the neocortical, basal ganglia and thalamic brain regions, in which childhood glucose metabolism rates peak at almost twice the adult values [93,94]. Similarly, in cortical gray matter regions, ratios of NAA:choline peaked at 10 years and decreased thereafter. By contrast, in white matter, ratios of NAA:choline increased with age. The observed nonlinear age-related changes of NAA:choline in frontal and parietal cortices resemble related changes in rates of glucose utilization and cortical volumes, and may be associated with dendritic and synaptic development and regression. Similarly, linear age-related changes of NAA:choline in white matter follow age-related increases in white matter volumes, and may reflect progressive increases in axonal diameter and myelination [90].

Development is also considered to be domain specific [91], so that the course of synaptic production and pruning depends upon the particular brain region [92]. Neural systems that undergo development during adolescence include serotonergic systems [95], glutamatergic receptors in regions such as the hippocampus [96] and dopaminergic projections to the prefrontal cortex and to mesolimbic brain regions

implicated with reward systems [19]. Dopamine innervation of the prefrontal cortex undergoes significant change during adolescence, whereas the serotonergic innervation of the prefrontal cortex attains adult levels much sooner in childhood [18]. These observations provide a plausible hypothesis to explain why, compared with adults, selective serotonin reuptake inhibitor medications are equally effective in young children with OCD whereas dopaminergic and noradrenergic agents frequently are not.

Mesocortical dopaminergic fiber density increases in the prefrontal cortex and undergoes significant reorganization during adolescence, including an age-related decline in dopamine synthesis in mesocortical brain regions [19]. Dopamine receptors in the striatum undergo significant pruning, with a third to a half of D_1 and D_2 receptors in basal ganglia structures lost between adolescence and adulthood [97]. Evidence suggests that during adolescence, a shift occurs in the balance between subcortical and cortical dopamine systems. Specifically, subcortical dopamine activity is lower in adolescence than adulthood, and inhibitory dopamine input to the prefrontal cortex is highest during early adolescence [19].

These developmental changes in the adolescent brain may be correlated with both the maturation-related behavioral features of adolescence (e.g., impulsive behaviors [19]), as well as the psychophysiological underpinnings of complex neurobehavioral disorders, such as OCD. Rosenberg and Keshavan propose that in adolescence, there may be a relative excess of dopamine and serotonin, which may account for the increase in OCD symptoms [18]. Increased regional blood flow in VPFC circuits could lead to increased volume whereas increased activity in mesocortical/mesolimbic dopamine circuits lead to feedback inhibition of frontostriatal glutamatergic pathways and, in turn, striatal volumes [18]. The environment of the adolescent and the onset of puberty may also play a role in influencing synapse elimination during this period. Such pruning may also exemplify developmental plasticity, whereby the brain is sculpted not only by genetic influences, but also in response to environmental exposures and experience. In summary, child-onset OCD may be distinguished from the adult-onset OCD by increased white matter and enlargements of the basal ganglia, frontal lobes and thalamus. Moreover, early childhood OCD may be differentiated from adolescent and adult OCD by distinct reduced frontostriatal activity.

Neuropsychological findings in pediatric OCD

Given the potential involvement of frontostriatal systems in OCD, several aspects of neuropsychological functioning have been especially relevant to study, specifically measures of attention and executive functions, short-term memory and visuospatial abilities. Of these, executive functioning and especially response inhibition have received the greatest attention in the literature [5,98]. Executive functioning is primarily characterized by the ability to consider all aspects of a situation and use this knowledge to prioritize goals and plans, implement behavior strategically and shift behavior as the environmental context changes [99]. Executive functions also involve the ability to maintain a problem set to attain a future goal by inhibiting or delaying potent but inappropriate responses and maintain a mental representation of the task in memory [100,101]. Although executive functions may be difficult to assess directly, they may be tapped by tasks that require the individual to tolerate boredom, function independently and actively solve problems.

Executive functioning impairments have been associated with lesions to the frontal cortex (e.g., the dorsolateral and orbitofrontal regions) and its basal ganglia–thalamic connections [102]. Tasks involving executive functioning skills that are sensitive to frontostriatal lesions include the Wisconsin Card Sorting Test (WCST) [103], Stroop test [104], Rey-Osterrieth Complex Figure Test (ROCF) [105] and Tower of Hanoi test [106]. Tasks that specifically tap response inhibition (e.g., Go–No Go and the stop–signal task) assess the ability to inhibit prepotent motor responses in accordance with changing situational demands [107]. These tasks are similar in that they require the participant to select among competing response alternatives and then select the correct, less prepotent response [101].

■ Adult studies

A number of neuropsychological studies of adults with OCD have found deficits across several different cognitive tasks including measures of information processing speed [3,108], nonverbal memory [109,110] and verbal memory [111]. Executive function studies have found impairments in reasoning and planning [78], response

inhibition [3,112] and set-shifting [113,114] (for a review, see [5,98]). However, these findings are highly inconsistent. For example, whereas a number of studies revealed impaired performance on response inhibition tests [3,4,112], other studies did not find deficient performance on these tests [115,116], or in other executive function tests such as planning [117] and set-shifting [118]. In fact, some studies administering comprehensive neuropsychological batteries reported only minor or no impairments in OCD [119,120]. Similarly, whereas impairments in verbal and nonverbal memory performance among OCD patients have also been well documented [3,110,111], other studies reported normative performance on memory tests in adult OCD [121,122]. A number of explanations for this inconsistency have been suggested including failure to control for the impact of depression [123], confounding demographic factors and other statistical or methodological issues [98]. However, others still suggested theoretical accounts for this discrepancy. Studies suggested that OCD is characterized by problems in memory confidence rather than memory functions *per se* [124,125]. Others suggest that the underlying impairment in memory functions may be poor strategic processing and encoding ability [7,126].

A broader account suggests that OCD is characterized by a slower processing speed that may impact performance on the majority of neuropsychological tests and may specifically impact performance on tests of executive function [108,127]. More recently, it has been proposed that situational or state-dependent factors have a significant impact on neuropsychological performance particular to OCD [3,128]. For example, Abramovitch *et al.* suggested that situational or state-dependent factors are particularly relevant in traditional pencil–paper neuropsychological testing settings [129]. The authors emphasize the need for reassurance and the significant impact that reassurance has on reduction of obsessive–compulsive-related distress. Traditional pencil–paper neuropsychological testing involves numerous informal interactions between examiner and examinee and may result in variability between studies [3]. Finally, the question whether neuropsychological impairments in adult OCD is an integral primary phenomenon [98] or an epiphenomenon that is contingent upon the executive overload caused by the consistent surge of unwanted thoughts [129], is yet to be resolved.

■ Pediatric studies

Despite the ample research in adult OCD, few studies have examined neuropsychological functioning among pediatric samples. As seen with the adult population, the majority of pediatric OCD samples have revealed various neuropsychological impairments, yet the overall body of research still suffers from highly inconsistent results. In the first study examining the neuropsychological performance of children, Behar *et al.* compared 16 children with OCD (mean age: 13.7 years) with 16 matched controls [37]. Participants were evaluated through several neuropsychological tests of frontal lobe functioning (e.g., Money's Road Map Test). Compared with healthy control participants, OCD patients demonstrated poorer performance on tasks assessing the ability to mentally rotate themselves in space and tasks assessing maze learning. The authors noted that deficits in performance in the OCD group were not attributable to attentional deficits or obsessiveness during task performance. Moreover, neuropsychological test results were not correlated with ventricular enlargements on the CT scan [37]. A review of more recent research implicates executive function and nonverbal memory deficiencies in pediatric OCD. In the nonverbal memory domain, a handful of studies reveal impaired performance on the ROCF [130,131]. Whereas this test is designed to assess nonverbal memory, performance on the copy condition enables inference regarding visual construction abilities. In addition, analysis of performance on subsequent retrieval conditions provides insight regarding coding strategies, which were found to be impaired in adult OCD samples [7]. Similarly, impairments on the three test conditions were found in pediatric OCD samples [130,132]. Others found impairment only on the copy condition [131] and others reported intact performance on this test [133].

The majority of neuropsychological studies on pediatric OCD, however, investigated performance on executive function tests. Ornstein *et al.* reported that children required significantly more moves to complete the Tower of London task [134], whereas Huyser *et al.* found that the OCD group was slower on this task but otherwise performed comparably to controls [76]. Impaired performance was also found in two studies examining performance on the WCST [132,135], whereas others reported intact performance [136].

Interestingly, whereas response inhibition was suggested as an endophenotype in adult individuals with OCD [5], only three studies investigated response inhibition in pediatric OCD. In the first study investigating inhibitory abilities, Rosenberg and colleagues examined cognitive functions associated with the prefrontal cortex using an occulomotor paradigm [137]. They examined the participants' ability to suppress reflexive responses to external cues (e.g., a target light), volitionally execute delayed responses and anticipate predictable events [137]. Results showed that pediatric OCD subjects demonstrated more response suppression failures than controls. In turn, these impairments were correlated with impairments on other measures of frontostriatal functioning. Overall, controls developed the ability to suppress occulomotor responses (a function of prefrontal cortex development) approximately 5 years younger than OCD patients [137]. By contrast, two imaging studies reported no difference between healthy control and pediatric OCD samples in performance on switching and stop tasks [57,75]. A similar discrepancy was found between studies examining performance on the Stroop test, where two studies reported impaired performance on this task [132,135], while others did not [75].

Inconsistent results were also found on studies employing a comprehensive neuropsychological battery, which largely yields intact performance among pediatric OCD samples as compared with healthy controls [134,136]. For example, Beers *et al.* examined cognitive functioning in 21 treatment-naive children with OCD (mean age: 12.3 years) and 21 matched control participants [138]. Children were assessed using a comprehensive neuropsychological battery, including multiple measures of frontal lobe functioning (e.g., Stroop test, WCST, and the California Verbal Learning Test) and subtests of the Wechsler Intelligence Scale for Children. Children in the OCD group did not demonstrate cognitive impairment on any measures of executive functioning. By contrast, Andres *et al.* examined 35 7–18-year-olds with OCD and 35 gender- and age-matched healthy controls [132]. Participants completed the revised Wechsler Intelligence Test for Children, selected tests from the Wechsler Memory Scale III, the ROCF, the Rey Auditory Verbal Learning Test, the Trail Making Test, the WCST, the Controlled Oral Word Association Test and the Stroop test. After controlling for depressive severity, the authors reported extensive neuropsychological impairments on most constructs including impaired performance on delayed verbal memory, visual reproduction, Rey Auditory Verbal Learning Test, coding, ROCF time, block design, Trail Making Test, Stroop test and WCST [132]. Notably, application of statistical correction eliminated the effects found on the Stroop test, delayed verbal memory tests, coding and WCST.

Three studies examined neuropsychological functioning among participants diagnosed with PANDAS. Apart from poor performance on the ROCF reported in one study [139], these studies reported no significant neuropsychological impairments among the OCD groups [136,138,139]. Finally, association between OCD symptom severity and neuropsychological impairments in pediatric OCD was found in two studies [132,139], but not in others [18,134].

Several methodological explanations may be offered for the inconsistency that characterizes neuropsychological studies in pediatric OCD. First, most studies use small sample sizes [57,75,139]. This issue is of specific concern to the field of neuropsychology as the majority of neuropsychological studies use comprehensive batteries of tests, thereby resulting in a large number of dependent variables. To maintain a satisfactory ratio between sample size and the number of dependent variables, future studies are encouraged to increase sample size or alternatively combine several tests to a single score representing a neuropsychological domain [3,127]. Notably, employing a statistical correction to avoid inflation of type-I errors in the analyses of large neuropsychological batteries is warranted and was rarely employed in the studies reviewed.

Neuropsychological tests may not be sensitive to dysfunction in the frontostriatal systems implicated in OCD [134], or children with OCD may not display cognitive deficits early in their illness [138]. Prefrontal functions presumed to be related to OCD symptoms, including neurobehavioral inhibition, continue to develop throughout adolescence and early adulthood [18]. Age-related changes in neuropsychological performance depend on the particular task observed and the specific executive function tapped by each task [87,140–142]. Attentional control, for example, develops rapidly in early childhood. This is followed by the critical period of maturation between 7 and 9 years of age, in which children develop cognitive flexibility, goal setting and information processing [88].

Developmental consideration and evidence from studies exemplifying differences between young children and adolescents with OCD should be taken into account. As noted above, young children with OCD show frontostriatal hypoactivation, as opposed to the increased activity seen in adolescents and adults that may be attributable to maturational processes of prefrontal regions that may be disorder specific [79,80].

Executive functions, such as sustained attention, planning, abstraction of reasoning, problem solving and semantic organization, also show rapid progression after the age of 12 years [143]. The developmental progression of executive functions throughout childhood has been well documented and performance on several neuropsychological tasks assessing frontal lobe functioning has been found to improve into adolescence [143,144]. For example, performance on tests of planning ability, such as the Porteus Maze Test and Tower of London, has been found to improve well into adolescence [145,146]. In contrast to earlier work indicating that frontal lobe functions (e.g., organization and planning) matured by the age of 4 or 5 years [147], later research has suggested that executive functions continue a multistage developmental process between the ages of 7 years and adulthood [88,148].

With increasing age, children also demonstrated more consistent performance on tasks involving memory demands [149]. Memory functions, including short-term memory, visuospatial memory and meta-memory demonstrate qualitative gains in early childhood. By the age of 7 years, memory function appears similar to that of adults, although changes continue into adolescence [150]. Working memory representations, which are important for inhibiting prepotent responses and performing accurately on tasks of executive functioning, also increase with cognitive development. The automaticity of basic operations improves, thus freeing up processing resources for working memory [101].

In summary, even more so than in adult OCD, research into neuropsychological functioning, and especially executive functions yields inconsistent results, in part because of hypothesized abnormal maturational processes in this population. This is complicated by the fact that most neuropsychological pediatric OCD studies used heterogeneous samples ranging from the ages of 7–18 years. Thus, future pediatric neuropsychological studies are encouraged to analyze and compare young children and adolescent samples separately.

While initial reports suggest some impairment of executive function, visual construction and nonverbal memory, more research is needed to substantiate these claims in pediatric OCD samples and PANDAS-related OCD. In addition, future studies are encouraged to use larger sample groups and further stratify by age, notably aiming to differentiate young children from adolescents.

Conclusion & future perspective

Despite similarities between adults and children with OCD, significant differences in the phenomenological, etiological and neuropsychological correlates of pediatric and adult-onset OCD suggest that neuroanatomical and neuropsychological findings can only be considered within a developmental context. The emergence of childhood OCD symptoms parallels the period of development in which synaptic connections are being actively pruned and reorganized, and the period of time in which prefrontal functions, response inhibition and several brain regions, including the VPFC, are rapidly developing. Due to its significant heritable component, some OCD cases may have abnormalities related to molecular or cellular development in specific brain regions [151]. Environmental events, such as infection, prenatal or perinatal factors or other biological and psychosocial stressors, abnormalities in myelination, synaptic pruning or neuronal organization may lead to the symptoms of OCD. Brain regions including the prefrontal cortex, striatum, cingulate cortex and corpus callosum may be especially sensitive to dysmaturation effects [18,152]. Rosenberg and Keshavan have suggested that environmental stressor(s), genetic abnormality or some interaction of the two may be involved with OCD [18].

Neuropsychological symptoms of OCD may not materialize until prefrontal systems have more fully matured [111]. Thus, impairments on neuropsychological tests may not be evident early in the illness but may become more evident over time. A certain level of prefrontal cortex maturity may also be required for certain OCD symptoms (e.g., pure obsessionality). Given that adult levels of neuropsychological performance are typically not attained until late adolescence, the subtle neuropsychological deficits that often accompany OCD may not be apparent on neuropsychological examination in childhood.

Likewise, pediatric OCD may be associated with distinct neuroanatomical features (e.g., increased myelination, increased structure size and possible frontostriatal hypoactivity) that relate to the particular stage of neurodevelopment during which symptoms emerge.

Additional explanations for the inconsistent neuropsychological findings among youth with OCD must also be considered, including a lack of prospectively obtained data with larger samples of youths, measurement issues associated with neuropsychological tasks (e.g., poor theoretical specification, an inability to identify component processes, questionable reliability and a lack of sensitivity to underlying processes across the range of performance [100]). Pennington and Ozonoff point to a discriminant validity problem common to many neuropsychological tests, whereby symptomatically different behavioral disorders present with similar neuropsychological deficits [100]. For example, executive function impairments were found in nearly every anxiety disorder [153], as well as in eating disorders [154], bipolar disorder [155], major depressive disorder [156], post-traumatic stress disorder [89], schizophrenia [157], antisocial personality disorder [158] and borderline personality disorder [159].

Many tests of prefrontal functioning have been criticized for their inability to differentiate across multiple prefrontal cortical functions, as well as from nonprefrontal cortex deficits. Given that the prefrontal cortex is a large and heterogeneous area, subtle alterations in slightly different regions may result in different behavioral manifestations, but may not be differentiated with tests of gross neuropsychological functioning [100]. Finally, the interpretation of neuropsychological measures in youth is obscured by the fact that several measures of executive functioning have not been widely introduced for use with children [160].

Further research is needed to validate and clarify the applicability of these tests to healthy control and psychiatric child populations. While recent pediatric functional neuroimaging studies have provided greater insight into the developmental aspects of OCD, subsequent research is needed to further elucidate cortical restructuring and metabolic changes. Future efforts should be geared towards greater stratification of demographics, based notably upon age and onset of symptoms. Nevertheless, the fusion of neuroimaging and neuropsychological assessment techniques provides an unparalleled opportunity to examine the multidirectional effects of brain morphology, neuropsychological performance, environmental demands and behavioral manifestations of disorders such as OCD.

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