REVIEW

Neurobiological Circuits Regulating Attention, Cognitive Control, Motivation, and Emotion: Disruptions in Neurodevelopmental Psychiatric Disorders

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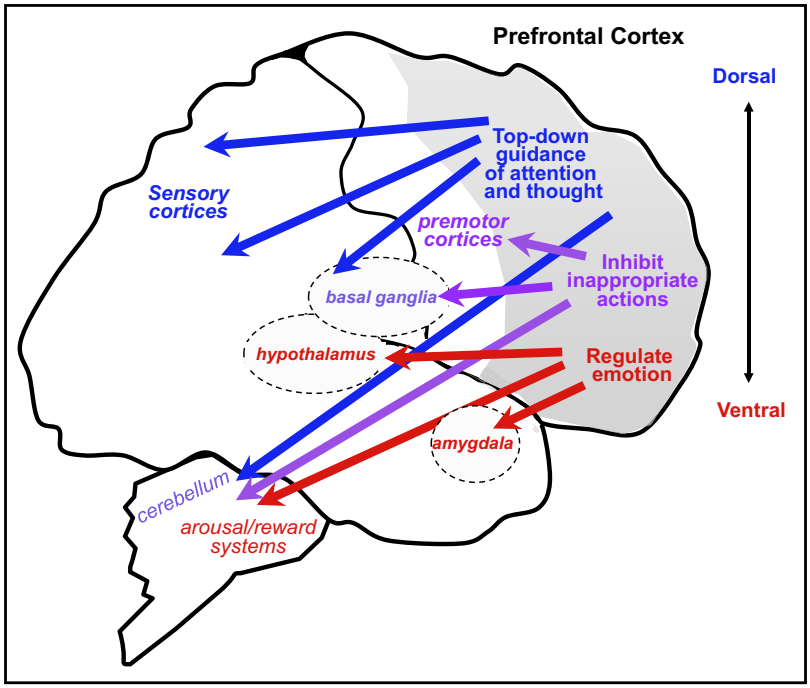
Objective: This article aims to review basic and clinical studies outlining the roles of prefrontal cortical (PFC) networks in the behavior and cognitive functions that are compromised in childhood neurodevelopmental disorders and how these map into the neuroimaging evidence of circuit abnormalities in these disorders. **Method:** Studies of animals, normally developing children, and patients with neurodevelopmental disorders were reviewed, with focus on neuroimaging studies. **Results:** The PFC provides "top–down" regulation of attention, inhibition/cognitive control, motivation, and emotion through connections with posterior cortical and subcortical structures. Dorsolateral and inferior PFC regulate attention and cognitive/inhibitory control, whereas orbital and ventromedial structures regulate motivation and affect. PFC circuitries are very sensitive to their neurochemical environment, and small changes in the underlying neurotransmitter systems, e.g. by medications, can produce large effects on mediated function. Neuroimaging studies of children with neurodevelopmental disorders show altered brain structure and function in distinctive circuits respecting this organization. Children with attention-deficit/hyperactivity disorder show prominent abnormalities in the inferior PFC and its connections to striatal, cerebellar, and parietal regions, whereas children with conduct disorder show alterations in the paralimbic system, comprising ventromedial, lateral orbitofrontal, and superior temporal cortices together with specific underlying limbic regions, regulating motivation and emotion control. Children with major depressive disorder show alterations in ventral orbital and limbic activity, particularly in the left hemisphere, mediating emotions. Finally, children with obsessive-compulsive disorder appear to have a dysregulation in orbito-fronto-striatal inhibitory control pathways, but also deficits in dorsolateral fronto-parietal systems of attention. **Conclusions:** Altogether, there is a good correspondence between anatomical circuitry mediating compromised functions and patterns of brain structure and function changes in children with neuropsychiatric disorders. Medications may optimize the neurochemical environment in PFC and associated circuitries, and improve structure and function. J. Am. Acad. Child Adolesc. Psychiatry, 2012;51(4):356–367. **Key Words:** prefrontal cortex ADHD, OCD, MDD, arousal

There is a remarkable convergence between basic neuroscience studies in animals and imaging studies in humans regarding the brain circuits regulating attention, cognitive control, motivation, and emotion. They show a dissociation of several fronto-striato-cerebellar circuitries that mediate these functions, differing in the precise localization of these functions within the prefrontal cortex and the basal ganglia, and their specific connections to limbic and parieto-temporal association cortices and the cerebellum. Furthermore, there is evidence for relatively late and progressive development of these fronto-cortical and fronto-subcortical "top–down" control systems between childhood and adulthood. Children with neurodevelopmental disorders show deficits in precisely these late developing fronto-cortical and fronto-subcortical circuitries. This article reviews the animal and human imaging literature that delineates these dissociated fronto-striatal circuitries and the functions they mediate, and provides examples of how these

FIGURE 1 The prefrontal cortex (PFC) regulates attention, behavior, and emotion through extensive network connections with other brain regions. Note: Dorsal regions (blue) subserve higher cognitive functions and regulate "top–down" attention through extensive projections to posterior cortical regions. In contrast, ventromedial PFC (vmPFC) regulates emotion through extensive projections to subcortical areas such as the amygdala, nucleus accumbens, and brainstem. In humans, the right inferior frontal cortex (IFC) is specialized for the inhibition of inappropropiate motor responses through projections to the basal ganglia. The PFC also has extensive connections with the cerebellar cortex via the pontine nuclei, which parallel projections through the basal ganglia. Thus, the PFC is positioned to orchestrate all aspects of behavior.



circuitries are compromised in specific neurodevelopmental disorders. We thus review a few very specific "model disorders" that are illustrative for abnormalities in these fronto-cortical and fronto-subcortical circuitries that mediate attention, cognitive control, motivation, and emotion. Thus we review the neuroimaging literature of attention-deficit/hyperactivity disorder (ADHD) as an example of a disruption of inferior fronto-striatal networks of cognitive control and attention; pediatric major depression (MDD) as a model for fronto-limbic disruption mediating emotion control; pediatric obsessive-compulsive disorder (OCD) as a model for disruption of both orbito-frontal inhibitory and fronto-limbic anxiety mediating networks; and conduct disorder (CD) as a model disorder for deficits in fronto-limbic circuits of motivation. A delineation of the dissociated neurofunctional circuitries and their mediating functions based on the basic neuroscience literature, together with the description of abnormalities of these circuitries in these very specific model neurodevelopmental disorders, will hopefully help with a better understanding of the abnormalities and the development of more targeted treatments for these disorders.

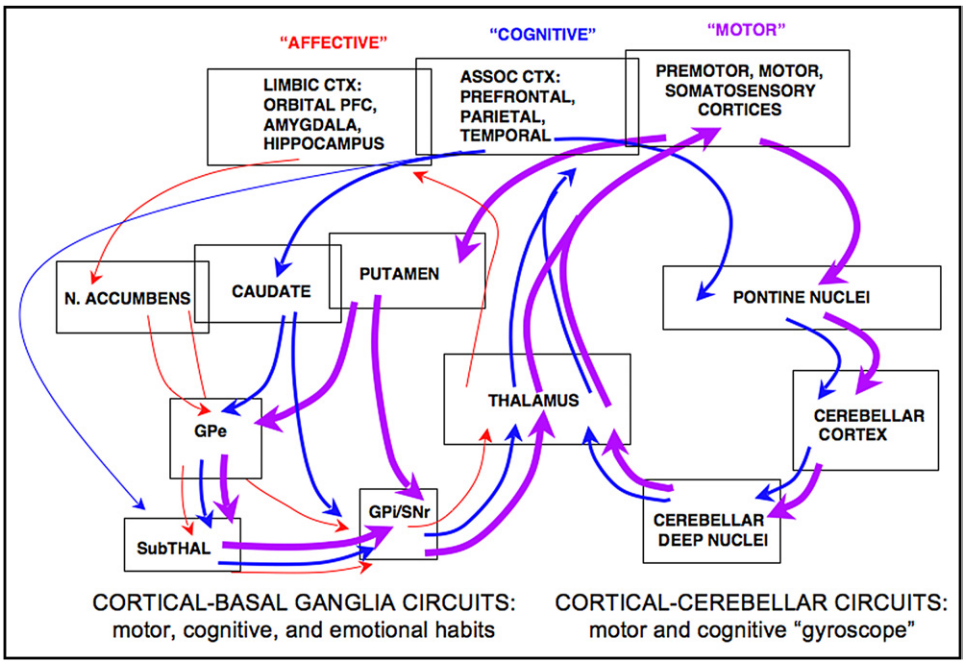
METHOD

The ISI Web of Science and Pubmed were searched using the following search criteria from 1966 onward: "prefrontal cortex", "basal ganglia circuits", "cerebellar circuits", "catecholamines", "serotonin", "neurotransmitters", "ADHD/CD/OCD/MDD and MRI/fMRI", "Methylphenidate/Atomoxetine and MRI/FMRI", "SSRI and MRI/FMRI".

Brain Circuits Regulating Attention, Cognitive Control, Motivation, and Emotion

The prefrontal cortex (PFC) is a highly evolved cortical area that is essential for regulating attention, cognitive control, motivation, and emotion. As shown in Figure 1, distinct regions of PFC regulate this spectrum of functions, with the dorsolateral PFC (DLPFC) regu-

FIGURE 2 The work of Peter Strick (Middleton and Strick[1]) has shown that the prefrontal cortex (PFC) has extensive connections with both the basal ganglia and cerebellar circuits. Note: These form parallel loops for the execution of movement (purple, thick arrows), cognition (blue, medium arrows), and emotion (red, thin arrows). Basal ganglia structures are densely innervated by dopamine, cerebellar structures are innervated by norepinephrine, and cortical structures are innervated by both catecholamines. ASSOC = association; CTX = cortex; GPe = globus pallidus external segment; GPi = globus pallidus internal segment; N. ACCUMBENS = nucleus accumbens; SNr = substantia nigra pars reticulata; SubTHAL = subthalamic nucleus.



lating attention, planning, and working memory, and the inferior frontal cortex (IFC) mediating functions of cognitive control such as inhibitory control, interference control, and cognitive flexibility. The lateral orbitofrontal (OFC) and the ventromedial PFC (including orbital) (VMPFC) regulate emotion and motivation. The anterior cingulate cortex, which many consider to be a PFC subregion, is similarly organized such that the most caudal region regulates movement, more anterior regions regulate attention/cognition, and the most rostral and ventral regions regulate emotion and motivation. Top-down regulation by the PFC arises from its extensive connections to posterior cortical and subcortical structures (Figure 1), including parallel circuits through the basal ganglia and cerebellum specialized for each processing domain (Figure 2).[1] The following is a brief summary of the functional contributions of these brain networks.

Regulation of Attention. More extensive reviews of this topic are provided by Arnsten and Castellanos[2] and Arnsten.[3] Briefly, the association cortices make distinct contributions to our attentional experience. The higher order sensory cortices mediate "bottom–up attention" based on the salience of sensory stimuli. The inferior temporal cortices process sensory features (what things are), and can focus resources on a particular detail, e.g., the color blue, or the perception and recognition of a face. Lesions to the inferior temporal cortices can produce "agnosia," where objects are seen but have no meaning. The posterior parietal association cortices process where visual stimuli are in the visual field, and whether the stimuli are moving. These parietal cortices orient attention in time and space, and are necessary for conscious perception. Lesions to the parietal association cortices produce a syndrome known as contralateral neglect, in which stimuli in the left visual field are not consciously perceived. In contrast, the PFC provides top–down attention, regulating attention based on relevance to the task. The DLPFC/IFC are key for inhibiting the processing of irrelevant stimuli, sustaining attention over long delays, and dividing and coordinating attention. Lesions to the PFC can increase distractibility, impair concentration, and weaken the ability to shift attention appropriately. All of these cortical areas are intricately interconnected, creating both feedforward and feedback loops that optimally work together to provide a unified and tightly regulated attentional experience. These cortical areas all project to the caudate nucleus, which in turn projects through the basal ganglia and thalamus to focus back on the PFC (Figure 2). The PFC and parietal cortices additionally project to the cere-

bellar cortices by way of the pontine nuclei (Figure 2). Thus, lesions in these subcortical areas, or in white matter pathways that connect these circuits, can also disrupt attentional control.

Inhibitory Control (Impulse Control). For a more extensive review of this topic, the reader is referred to Chambers *et al.*[4] A variety of methods, including lesion, imaging and transcranial magnetic stimulation studies have revealed the importance of the inferior PFC in inhibitory as well as cognitive control, especially in the right hemisphere. The right IFC has most prominently been associated with behavioral impulse control and motor inhibition, whereas bilateral IFC is also associated with interference inhibition and cognitive flexibility.[5] The IFC interconnects with a large number of structures involved with cognitive and inhibitory motor control, including the premotor and supplementary motor cortices, the primary motor cortex, as well as basal ganglia, subthalamic nucleus, and parietal and cerebellar cortices.

Regulation of Emotion and Motivation. A more extensive review of this topic is found in Price *et al.* [6] and Best et al.[7] The ventral (orbital) and medial PFC are extensively interconnected with structures involved with emotion, including the amygdala, hypothalamus, nucleus accumbens and brainstem nuclei (Figure 1). The VMPFC is positioned to activate or inhibit these structures, and studies in rats have shown that the vmPFC is essential for inhibition of the fear response. Studies in monkeys have shown the importance of lateral OFC for reward processing and the flexible regulation of emotional responses to reward and punishment.[8,9] In humans, damage to this region produces unregulated emotional behavior, e.g., the famous case of Phineas Gage. Importantly, damage to this area early in childhood has been associated with sociopathy, including reduced response to reward and punishment.[10]

Arousal Pathways Modulate Brain Circuits Mediating Attention and Emotion

The arousal pathways have powerful effects on PFC function, and research in animals suggest that the dorsal and ventral regions of the PFC have differing chemical needs and differing reliance on specific arousal systems.[11] For example, the dorsal regions are especially dependent on catecholamines, whereas the OFC is particularly reliant on serotonin. These differing sensitivities may explain why cognitive disorders are treated with catecholaminergic compounds, whereas affective disorder are commonly treated with serotonergic compounds. This work is reviewed briefly below.

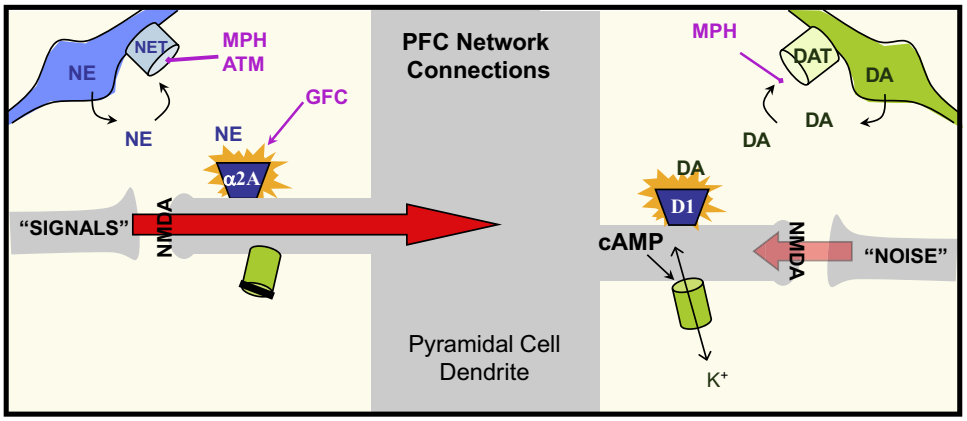
New data also indicate how the arousal systems interact with PFC microcircuits at the level of ion channels to alter network connectivity. The regulatory functions of the PFC are generated by local microcircuits that consist of glutamatergic pyramidal cells and GABAergic inhibitory interneurons.[12] The pyramidal cells excite each other via NMDA synapses on spines (shown schematically in Figure 3) to generate the persistent firing needed for working memory or behavioral inhibition, whereas the GABAergic interneurons provide lateral inhibition to enhance the specificity of information. The activity of these circuits is markedly altered by the arousal systems, which can functionally strengthen or weaken microcircuit connections in a dynamic manner to coordinate cognition with arousal state. A more thorough review is provided by Arnsten.[13]

Catecholamines. The DPFC is especially dependent on the levels of the catecholamines dopamine (DA) and norepinephrine (NE), exhibiting an "inverted U" dose-response to both modulators. Depletion of catecholamines from this region of PFC is as devastating as removing the cortex itself. Similarly, blockade of D1 or alpha-2 receptors in PFC impairs PFC function. NE stimulation of post-synaptic, alpha-2A adrenoceptors on PFC pyramidal cell spines is critical for strengthening appropriate PFC network connections (increasing "signals"), whereas DA D1 stimula tion on a separate set of spines is important for shunting inappropriate network connections (decreasing "noise"). The optimal level of D1 receptor stimulation varies according to task demands, e.g., moderate levels of D1 receptor stimulation are helpful for focused memory and attention, but can be harmful to attentional set-shifting or insight solutions when widespread network inputs may be needed. Thus, medications such as stimulants that increase DA actions may be helpful for some cognitive tasks (e.g., mathematics homework) but interfere with others (e.g., music composition). All PFC functions are impaired by very high levels of DA and NE release—as occurs during stress—through D1 and alpha-1 receptor stimulation, respectively. Under these conditions, all PFC networks disconnect and cell firing is suppressed.

There have been fewer studies of catecholamine actions in other regions of PFC. Emerging data indicate that NE has beneficial effects on ventrolateral and OFC function as well; e.g., stimulation of alpha-2A receptors with guanfacine improves the performance of motor and emotional regulation tasks that depend on these PFC regions. Atomoxetine, a selective noradrenaline transporter inhibitor, has been shown to enhance the activity and inhibitory functions of the right IFC in healthy adults.[14] DA appears to have a complex influence on OFC function; these data are still emerging. A detailed discussion is provided by Robbins and Arnsten.[11]

Serotonin. The OFC is especially sensitive to serotonin, as depletion of serotonin from OFC (but not DLPFC) markedly impairs OFC regulation of emotion and inhibition.[15,16] Given the immense complexity of serotonergic receptors, the receptors mediating these actions are just beginning to be explored. Very high

FIGURE 3 Working model of catecholamine actions on prefrontal cortex (PFC) circuits at the molecular level. Note: The top–down regulatory abilities of the PFC depend on networks of pyramidal cells that excite each other through *N*-methyl-D-aspartate (NMDA) glutamate synaptic connections on dendritic spines, schematically shown in this figure. The catecholamines norepinephrine (NE) and dopamine (DA) have powerful and dynamic influences on the functional strength of network synapses. By increasing or decreasing cyclic adenosine monophosphate (cAMP) signaling, they alter the open state of ion channels on the spine and determine whether a network input is able to get through to reach the cell body. NE engagement of α_{2A} receptors on spines inhibits cAMP production, closes nearby potassium channels, and increases the strength of network connections. Conversely, moderate levels of DA engaging D_1 receptors on a different set of spines can gate out inappropriate network inputs via increased production of cAMP. However, high levels of cAMP production during stress disconnect all network inputs and shut off cell firing. These stress effects may arise from excessive DA D_1, and possibly NE β_1, receptor stimulation. Attention-deficit/hyperactivity disorder (ADHD) medications likely have some of their therapeutic effects by enhancing catecholamine actions in PFC. Stimulant medications such as methylphenidate (MPH) and the nonstimulant medication, atomoxetine (ATM) all block the NE transporter (NET); stimulants also block the DA transporter (DAT). Animal studies show that these agents can improve PFC function by indirectly increasing NE and DA stimulation of the α_{2A} and D_1 receptors, respectively. However, excessive doses of these medications impair PFC function. In contrast, the α_{2A} agonist guanfacine (GFC) appears to have therapeutic effects by mimicking NE at postsynaptic α_{2A} receptors on spines, thereby strengthening PFC network connections.



levels of serotonin release, as occurs during stress, may impair OFC function via the 5HT2 receptor family, and serotonin actions at this receptor family may also disrupt DLPFC function. However, the receptors mediating the beneficial effects of serotonin on OFC are not yet known. Patients with disorders of vmPFC/OFC function show intriguing links to serotonin; e.g., serotonin is altered in patients with uncontrolled aggression,[17] and serotonin medications are the mainstay for treating depression. Thus, understanding serotonin's complex actions will be important for developing additional treatments for disorders of emotional regulation.

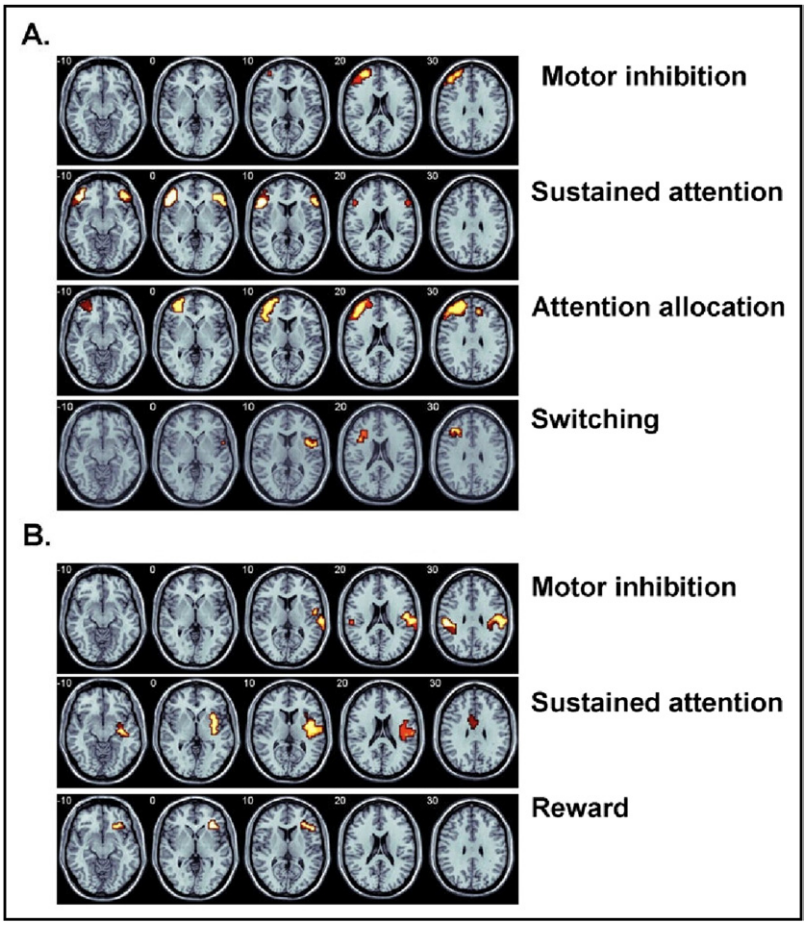
Acetylcholine. Cholinergic projections to the association cortices play an important role in vigilance, and in coordinating attentional processing between anterior and posterior association cortices.[18] Cholinergic actions at nicotinic receptors are known to play an important role in attention and working memory, and nicotinic agonists are being considered as potential treatments for attention disorders. A more detailed discussion of serotonergic and cholinergic actions is provided by Robbins and Arnsten.[11]

In summary, the arousal systems have powerful influences on PFC networks. Understanding these actions will inform new strategies for treating PFC childhood disorders.

Neuro-Imaging of Childhood Disorders

Attention-Deficit/Hyperactivity Disorder. Attention-deficit/hyperactivity disorder (ADHD) is characterized by behavioral features of inattention, impulsiveness, and hyperactivity.[19] Neuropsychological deficits are in tasks of inhibitory control, attention, and timing.[20-22] Neuroimaging studies in patients with ADHD have shown consistent deficits in structure and function as well as interregional structural and functional connectivity in the IFC and DLPFC circuitries that mediate attention and inhibitory control,[22-28] with the most prominent structural deficits in the basal ganglia.[26] Furthermore, longitudinal imaging studies show that the impairment in these late developing DLPFC and IFC fronto-striato-cerebellar and fronto-parietal systems may be due to a late structural cortical maturation.[29] A few recent studies have also

FIGURE 4 (A) Disorder-specific underactivation in attention-deficit/hyperactivity disorder (ADHD) relative to conduct disorder (CD) and healthy children in inferior frontal cortex/dorsolateral PFC (IFC/DLPFC) during four different cognitive tasks.[30-33] (B) Disorder-specific underactivation in CD relative to ADHD and healthy children in areas of the paralimbic system.[30-33]



pointed towards structural and functional deficits in orbitofrontal-limbic circuitries; however, findings are less consistent, do not survive meta-analytic studies and may be confounded by comorbidities with other disorder such as CD and MDD.[22]

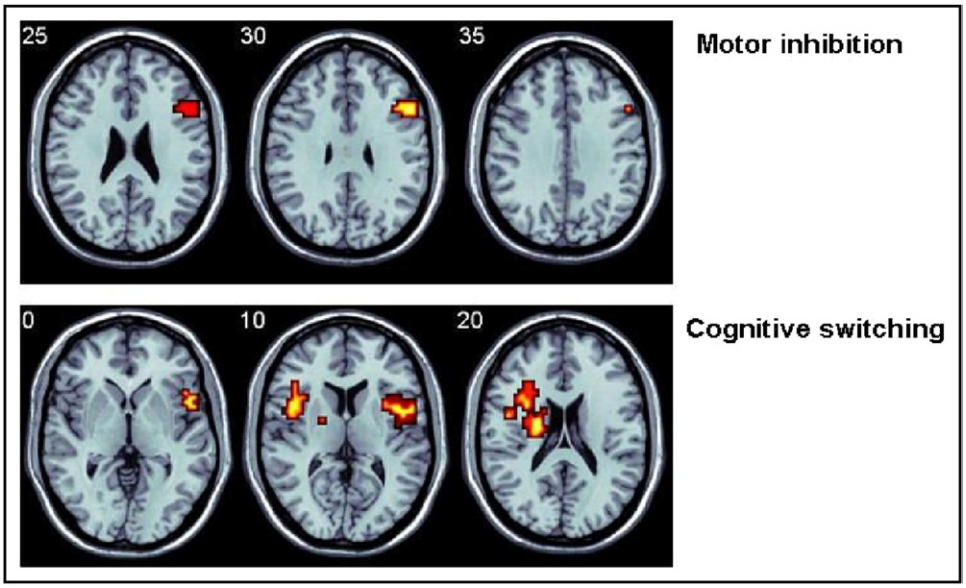
Comparative functional magnetic resonance imaging (fMRI) imaging studies have shown that inferior prefrontal underactivation is disorder specific to patients with ADHD when compared with patients with CD during four different tasks of inhibitory and attention control, as reviewed by Rubia[22] (Figure 4A).[30-33] IFC underactivation during tasks of inhibitory control, furthermore, was also disorder specific compared with patients with obsessive-compulsive disorder (Figure 5)[34] or bipolar disorder,[35] suggesting that IFC dysfunction may be a disorder-specific neurofunctional biomarker for ADHD.

Medications for Treatment of Childhood ADHD. Food and Drug Administration (FDA)–approved medications for the treatment of childhood ADHD all enhance or mimic catecholamine transmission in PFC. Stimulant medications such as methylphenidate (MPH) and amphetamines block both the DA and NE transporters, whereas atomoxetine blocks the NE transporter (which clears DA as well as NE in the PFC). In contrast, guanfacine directly mimics NE beneficial actions at postsynaptic alpha-2A adrenoceptors in PFC.[36]

Therapeutic doses of MPH increase both NE and DA in the PFC, enhance PFC neuronal responses, and improve PFC attention and working memory function.[37,38] Importantly, these doses have less effect on subcortical DA release in areas such as nucleus accumbens,[38] which may explain why they do not cause addiction when they are used as prescribed. PET imaging studies have shown that therapeutic doses of stimulant medications engage DA receptors in striatum,[39] and block DAT levels consistent with the small but significant increases in DA release measured in rodent striatum.[38]

Functional imaging studies have shown that acute and chronic methylphenidate treatment enhances and

FIGURE 5 Disorder-specific underactivation in children with attention-deficit/hyperactivity disorder (ADHD) compared with children with obsessive-compulsive disorder (OCD) and healthy children in inferior frontal cortex (IFC) during motor inhibition and task switching.[34]



even normalizes the activation as well as the functional interregional connectivity of those fronto-striatal networks that are impaired in the disorder during disorder-relevant tasks.[28,40-43] A recent meta-regression analysis showed that long-term stimulant medication in ADHD patients was associated with more normal basal ganglia gray matter as opposed to medication-naive patients who had reduced measures, suggesting "normalization" of brain structure deficits.[26]

Conduct Disorder. Conduct disorder (CD) is defined by the violation of the rights of others and societal rules.[19] CD overlaps clinically, behaviorally and cognitively, with ADHD, with high comorbidity between disorders, although motivation is thought to play a greater role in the disorder.[44] Nevertheless, recent imaging studies in children with CD point toward a relatively distinct underlying neuropathology. Structural and functional imaging studies suggest an abnormality of the paralimbic system that comprises the orbitofrontal cortex, anterior cingulate and superior temporal cortices, and underlying limbic brain regions in children with CD as well as with psychopathy, a more severe subgroup of CD, with a worse adult outcome[30-33,45,46] (reviewed by Rubia[22]). Direct comparison with children with ADHD found disorder-specific dysfunctions in patients with CD in areas of the paralimbic system, including the orbitofrontal cortex, anterior cingulate, insula, hippocampus, and superior temporal lobes during tasks that are compromised in both disorders such as motor inhibition, sustained attention, switching and reward (Figure 4B).[30-33] Similar disorder-specific functional abnormalities in paralimbic regions have been observed in severely disruptive children with psychopathic traits and ADHD when compared with a pure ADHD group.[47,48] These imaging dissociation findings parallel recent dimensional neuropsychological analyses showing that DLPFC and IFC mediated functions of inhibition and attention are associated with ADHD symptoms, while reward-related motivation functions are specifically associated with CD symptoms.[44]

The above-mentioned studies have differentiated between strictly non-comorbid patient groups to identify disorder-specific deficits, Future studies, however, will need to investigate to what extent the more typical comorbid ADHD/CD patients have deficits in both lateral fronto-striato-parietal executive function networks as well as paralimbic networks of motivation and affect control.

Pharmacological Treatment for CD. CD is not usually treated pharmacologically, although recent data suggest that guanfacine may reduce oppositional symptoms in ADHD.[49] As guanfacine can improve OFC function in monkeys,[50] it is possible that it ameliorates aggressive symptoms by strengthening OFC regulation of emotion.

Pediatric Major Depressive Disorder. Compared with the other developmental psychiatric disorders, the onset of major depressive disorder (MDD) in the pediatric population is relatively late, with rare onset among young children but with a sharp rise in incidence during adolescence. As opposed to ADHD or

CD, where males predominate, a 2:1 female:male ratio emerges in MDD in adolescence. MDD is characterized predominantly by structural, biochemical and functional alterations in OFC and vmPFC-limbic circuitries, including pituitary gland, amygdala, and hippocampus, that mediate motivation and emotion.[51-56] There is evidence for predominantly left OFC abnormalities in structural studies of children with depression,[57] in line with evidence for a lateralization of positive emotions and appetitive approach in left prefrontal brain regions[58,59] as well as with the left–right prefrontal imbalance hypothesis of adult MDD, which postulates a hypoactive left PFC mediating positive emotions together with a hyperactive right PFC mediating negative emotions.[60] The laterality differences between predominantly left frontal deficits in MDD,[57] as opposed to predominantly right frontal deficits in ADHD,[25,26] are interesting to note. fMRI studies of executive functions in pediatric MDD, in line with adult MDD fMRI studies,[61] observed abnormal activation in attention areas of DLPFC, anterior cingulate and caudate.[62] Interestingly, during motivated but not unmotivated attention, we found underfunctioning of a right hemispheric network of inferior fronto-striato-thalamic attention and limbic reward processing areas, suggesting that in MDD patients there is an abnormal interplay between motivation and attention.[63]

Comparison studies between patients with MDD and comorbid ADHD or CD are needed to establish to what extent the motivational circuit deficits differ from those in CD or to what extent the DLPFC attentional circuits differ from those in ADHD. Although no direct comparisons in fMRI are available, our deficit findings in both disorders during the same sustained attention task suggest that, whereas deficits are marked in IFC-striatal circuitries in ADHD patients,[31,41] deficits in these circuits are observed in MDD only when motivation comes into play,[63] suggesting that attention network dysfunction is caused by underlying motivation network deficits. This would also be in line with differences in attention performance between disorders, with fast, erratic responses in ADHD, reflecting impulsiveness, versus slow, erratic responses in MDD, suggesting sluggishness.[64]

Pediatric Obsessive-Compulsive Disorder. Obsessive-compulsive disorder (OCD) in the pediatric population is characterized by poor inhibition over intrusive, unwanted obsessive thoughts and compulsions.[19] At the neuropsychological level, patients with OCD have deficits in tasks of inhibitory control, including motor response inhibition, cognitive inhibition, reflex inhibition, and verbal inhibition.[65]

In adult OCD, there appears to be a dysregulation within orbitofronto-striatal systems with poor control of orbitofrontal regions over overactive and hyperdopaminergic subcortical striato-thalamic activity, presumably causing poor control over intruding compulsions and obsessions, as well as deficits in DLPFC-parietal cortices that mediate executive and attention functions.[65] In children with OCD, structural, and functional imaging findings point toward abnormalities in similar areas of DLPFC, OFC, and ACC, striatal, and thalamic regions (reviewed in Huyser *et al.*[61]). Two meta-analyses of whole-brain structural morphology studies converge in the finding that prefrontal gray matter density and volumes are decreased in OCD patients, including medial, dorsal, inferior, and orbital frontal areas, whereas there is enhanced gray matter density in bilateral lenticular nucleus and thalamus.[66-68] Both studies observed no age effects. The findings support the notion of an imbalance between frontal and subcortical striato-thalamic structures in patients with OCD.[65,69] The relatively few fMRI studies in pediatric OCD show reduced OFC and lPFC, striato-thalamic, and temporo-parietal activation during inhibition and planning tasks,[70-72] as well as in limbic areas during emotion processing.[70]

Few imaging studies have compared OCD to other childhood disorders. Biochemical abnormalities of the thalamus have been observed in OCD, but not MDD, suggesting that this may be a disorder-specific abnormality.[69] The presence of enhanced gray matter volumes in bilateral lenticular nuclei was specific to OCD relative to anxiety, who had enhanced volumes,[66] whereas anterior cingulate volume abnormalities were shared between disorders.[68] fMRI comparisons with children with ADHD showed that, whereas inferior prefrontal and caudate dysfunction was disorder specific to patients with ADHD and healthy controls during two inhibitory tasks (Figure 5), the brain dysfunctions in other frontal regions, including DLPFC and OFC, were shared.[34] Activation in the caudate, in particular, showed disorder-specific activation deficits. Specifically, caudate activation was reduced in ADHD relative to patients with OCD, and was, respectively, negatively and positively correlated with symptom severities.[34,73] In ADHD versus OCD, the inverse associations between caudate activation and symptoms could be consistent with evidence from positron emission tomography (PET) studies for reduced striatal dopamine availability in ADHD versus enhanced dopamine availability in patients with OCD.[74-80] The findings thus are in line with theories of a dysregulation of orbitofronto-striatal activation in OCD, with poor orbitofrontal control over overactive basal ganglia activation,[65] which is different from the evidence in ADHD for a delayed maturation of inferior fronto-striatal networks.[29]

Medications for Treatment of Pediatric MDD and OCD. The mechanism of action of selective serotonin reuptake inhibitors (SSRIs) for the treatment of depression as well as for OCD is still being explored. Given the important role of serotonin for OFC function,[81] it is tempting to speculate that these agents normalize vmPFC regulation of emotion in both disorders, as well as lateral OFC-striatal regulation of inhibitory control in OCD. However, the great complexity of

serotonin receptor pharmacology has slowed progress in this arena. It is also not understood why the therapeutic effects of SSRIs take several weeks to develop. Research in animals has suggested that growth factors may play a role in the antidepressant response.[82] The fact that the OFC develops rapidly in this age group[83] may also be a factor in childhood depression and in its response to antidepressant medications.

Few studies have directly tested the effects of SSRIs on brain activation in pediatric MDD. Meta-analyses and reviews of treatment effects on functional activation in adult depression show that SSRIs upregulate lateral fronto-cortical regions while reducing abnormally enhanced activation in ventromedial frontal, striatal, and limbic brain regions, suggesting better frontal control within fronto-limbic circuitries.[61,84,85] In pediatric OCD, chronic treatment with SSRIs has been shown to normalise abnormal thalamus.[86] amygdala,[87] and parietal structure,[88] as well as medial frontal function[89] and abnormally enhanced striatal glutamate levels,[54] suggesting improvement of an imbalanced interaction between fronto-striatal and fronto-limbic serotonergic and glutamatergic systems.[90]

Many childhood psychiatric disorders likely arise from insults to PFC-basal ganglia or fronto-limbic circuits, which develop slowly and relatively late in adolescence and are thus particularly susceptible to injury.[91,92] Differences have emerged with respect to laterality, exact location, and specific fronto-striatal pathways involved. Inferior prefrontal and striatal dysmorphology and dysfunction is key to the cognitive control deficits in ADHD, with evidence for inferior prefrontal dysfunction being disorder-specific when compared with patients with CD, PBD, and OCD. CD patients, on the other hand, appear to have more predominant abnormalities in the paralimbic system, comprising vmPFC, and lateral OFC, the temporal lobes and underlying limbic areas, that mediate affect and motivation. These abrnomalities in CD seem relatively disorder-specific, when compared with children with ADHD but without comorbid CD. Orbitofronto-striato-limbic abnormalities in the context of abnormal affect and motivation seem to be characteristic for pediatric MDD. In children with OCD, there appears to be a dysregulation within orbitofronto-striatal systems with poor control of orbitofrontal regions over overactive and hyperdopaminergic subcortical striato-thalamic activity, presumably causing poor control over intruding compulsions and obsessions. Although some differences have emerged, there are also significant overlaps in affected circuitries, such as in DLPFC-striato-parietal systems of attention and EF which are compromised in ADHD, OCD, and MDD, in line with shared neuropsychological deficits in these functions.

Several limitations of the imaging literature needs to be noted. The majority of imaging studies (expect for the direct comparisons in our lab) have included patients with comorbidities. For example, the CD/ADHD imaging literature is mostly confounded by presence of ADHD/CD symptoms, the OCD literature by co-presence of affective problems and MDD imaging studies are counfounded by anxiety symptoms. Comorbid conditions are likely to share more overlap in their underlying neurobiology then non-comorbid disorders. Future large-scale structural and functional neuroimaging studies that compare between very clearly defined comorbid and non-comorbid disorders need to further disentangle shared and disorder-specific neurobiological abnormalities, and to clarify to what extent the comorbid presentation shares the aetiopathophysiology of the non-comorbid disorders or whether it is a more complex disorder, characterized by a qualitatively different underlying pathology.

Furthermore, the majority of structural imaging studies are biased by region of interest analyses, that restrict the search to *a priori* hypothesized regions, for example targeting fronto-striatal regions in ADHD and fronto-limbic areas in MDD. More whole brain imaging analyses or meta-analyses comparing between disorders will be necessary for a more unbiased picture. Functional imaging using fMRI is not measuring neuronal activation directly but metabolic processes. Therefore, activation clusters may reflect metabolic input into these regions from other activated areas rather than activation of these areas directly. Also, the subtraction method in fMRI analysis is less than perfect and typically co-measures several cognitive functions other than the target functions. Finally, fMRI is highly task dependent and the fMRI literature of disorders is biased by the choice of tasks, with more cognitive tasks being tested in cognitive disorders like ADHD and more affective paradigms been measured in affective disorders. A challenge also resides in the design or appropriate paradigms that map into core behavioral problems. Future studies of disorder comparisons will need to test a range of cognitive and affective paradigms to obtain a comprehensive picture of shared and disorder-specific deficits in PFC circuitries.

Longitudinal studies should clarify differences in neurodevelopmental trajectories which may likely be more elucidating than a comparison between disorders in any cross-sectional moment in time. Longitudinal studies would also shed light on the currently unknown relationship between the onset of disorders and neurobiological circuit deficits. Although all neurodevelopmental disorders are characterized by deficits in the top–down control of specific PFC circuitries that develop late in life, it is currently not understood why some disorders develop earlier than others, and how or whether this relates to the developmental timecourse of the specific PFC circuitries affected in the specific disorders. In ADHD, for example, there is

evidence for a delay in normal brain maturation which manifests relatively early in life.[29] Pediatric MDD, however, manifests relatively late in adolescence, despite the fact that orbitofrontal-limbic areas develop earlier than the inferior fronto-striatal circuitries implicated in ADHD. It is likely that earlier developing disorders such as autism and ADHD are more strongly determined by genetic or perinatal factors than later developing disorders such as MDD and OCD, where environmental factors may be more prominent and take longer to interact with neurobiological and genetic systems, thus causing disruption.

Animal studies have begun to reveal the neurochemical needs of these PFC networks affected in childhood disorders, but pharmacological imaging studies are needed to elucidate the effects of medications on brain networks in these neurodevelopmental disorders. Catecholaminergic and serotoninergic medications for disorders such as ADHD, MDD, or OCD appear to help normalize neuromodulation of these circuits, enhancing PFC regulation of abnormal behavior and cognition, but their mechanisms of action still need to be better understood. A more thorough understanding of disorder-specific neuroimaging correlates and trajectories and their underlying neurotransmitter abnormalities may ultimately help with a more objective neuroimaging-based differential diagnosis or prognosis. &

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REFERENCES

1. Middleton FA, Strick PL. Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Res Brain Res Rev. 2000;31:236-250.
2. Arnsten AFT, Castellanos FX. Neurobiology of attention regulation and its disorders. In: Martin A, Scahill L, Charney DS, Leckman JF, eds. Pediatric Psychopharmacology: Principles and Practice. New York, NY: Oxford University Press; 2003.
3. Arnsten AFT. The emerging neurobiology of attention deficit hyperactivity disorder: the key role of the prefrontal association cortex. J Pediatr. 2009;154(5 Suppl 1):S22-S31.
4. Chambers CD, Garavan H, Bellgrove MA. Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. Neurosci Biobehav Rev. 2009;33:631-646.
5. Derrfuss J, Brass M, Neumann J, von Cramon DY. Involvement of the inferior frontal junction in cognitive control: meta-analyses of switching and Stroop studies. Hum Brain Mapp. 2005;25:22-34.
6. Price JL, Carmichael ST, Drevets WC. Networks related to the orbital and medial prefrontal cortex; a substrate for emotional behavior? Prog Brain Res. 1996;107:523-536.
7. Best M, Williams JM, Coccaro EF. Evidence for a dysfunctional prefrontal circuit in patients with an impulsive aggressive disorder. Proc Natl Acad Sci USA. 2002;99:8448-8453.
8. Iversen SD, Mishkin M. Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. Exp Brain Res. 1970;11:376-386.
9. Dias R, Robbins TW, Roberts AC. Dissociation in prefrontal cortex of affective and attentional shifts. Nature. 1996;380:69-72.
10. Anderson SW, Bechara A, Damasio H, Tranel D, Damasio AR. Impairment of social and moral behavior related to early damage in human prefrontal cortex. Nat Neurosci. 1999;2:1032-1037.
11. Robbins TW, Arnsten AF. The neuropsychopharmacology of fronto-executive function: monoaminergic modulation. Annu Rev Neurosci. 2009;32:267-287.
12. Goldman-Rakic PS. Cellular basis of working memory. Neuron. 1995;14:477-485.
13. Arnsten AF. Stress signalling pathways that impair prefrontal cortex structure and function. Nat Rev Neurosci. 2009;10:410-422.
14. Chamberlain SR, Del Campo N, Dowson J, *et al*. Atomoxetine improved response inhibition in adults with attention deficit/hyperactivity disorder. Biol Psychiatry. 2007;62:977-984.
15. Clarke HF, Walker SC, Dalley JW, Robbins TW, Roberts AC. Cognitive inflexibility after prefrontal serotonin depletion is behaviorally and neurochemically specific. Cereb Cortex. 2007;17:18-27.
16. Rubia K, Lee F, Cleare AJ, *et al*. Tryptophan depletion reduces right inferior prefrontal activation during response inhibition in fast, event-related fMRI. Psychopharmacology (Berl). 2005;179:791-803.
17. Lee R, Coccaro E. The neuropsychopharmacology of criminality and aggression. Can J Psychiatry. 2001;46:35-44.
18. Sarter M, Hasselmo ME, Bruno JP, Givens B. Unraveling the attentional functions of cortical cholinergic inputs: interactions between signal-driven and cognitive modulation of signal detection. Brain Res Brain Res Rev. 2005;48:98-111.
19. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders DSM-IV*. Washington, DC: American Psychiatric Association; 1994.
20. Langley K, Fowler T, Ford T, *et al*. Adolescent clinical outcomes for young people with attention-deficit hyperactivity disorder. Br J Psychiatry. 2010;196:235-240.
21. Easton N, Shah YB, Marshall FH, Fone KC, Marsden CA. Guanfacine produces differential effects in frontal cortex compared with striatum: assessed by phMRI BOLD contrast. Psychopharmacology (Berl). 2006;189:369-385.
22. Rubia K. "Cool" inferior frontostriatal dysfunction in attention-deficit/hyperactivity disorder versus "hot" ventromedial orbitofrontal-limbic dysfunction in conduct disorder: a review. Biol Psychiatry. 2011; 69:e69-e87.
23. Cubillo A, Halari R, Taylor E, Rubia K. A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with attention deficit hyperactivity disorder (ADHD) and new

evidence for dysfunction in adults with ADHD during motivation and attention. Cortex. 2012;48:194-215.
24. Dickstein SG, Bannon K, Castellanos FX, Milham MP. The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. J Child Psychol Psychiatry. 2006;47:1051-1062.
25. Krain AL, Castellanos FX. Brain development and ADHD. Clin Psychol Rev. 2006;26:433-444.
26. Nakao T, Radua J. Gray matter volume abnormalities in ADHD and the effects of stimulant medication: voxel-based meta-analysis. Am J Psychiatry. 2011;168:1154-1163.
27. Valera EM, Faraone SV, Murray KE, Seidman LJ. Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. Biol Psychiatry. 2007;61:1361-1369.
28. Rubia K, Halari R, Christakou A, Taylor E. Impulsiveness as a timing disturbance: neurocognitive abnormalities in attention-deficit hyperactivity disorder during temporal processes and normalization with methylphenidate. Philos Trans R Soc Lond B Biol Sci. 2009;364:1919-1931.
29. Shaw P, Eckstrand K, Sharp W, *et al.* Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci U S A. 2007;104:19649-19654.
30. Rubia K, Halari R, Smith AB, Mohammad M, Scott S, Brammer MJ. Shared and disorder-specific prefrontal abnormalities in boys with pure attention-deficit/hyperactivity disorder compared to boys with pure CD during interference inhibition and attention allocation. J Child Psychol Psychiatry. 2009;50:669-678.
31. Rubia K, Smith AB, Halari R, *et al.* Disorder-specific dissociation of orbitofrontal dysfunction in boys with pure conduct disorder during reward and ventrolateral prefrontal dysfunction in boys with pure ADHD during sustained attention. Am J Psychiatry. 2009;166:83-94.
32. Rubia K, Halari R, Cubillo A, Mohammad AM, Scott S, Brammer M. Disorder-specific inferior prefrontal hypofunction in boys with pure attention-deficit/hyperactivity disorder compared to boys with pure conduct disorder during cognitive flexibility. Hum Brain Mapp. 2010;31:1823-1833.
33. Rubia K, Halari R, Smith AB, *et al.* Dissociated functional brain abnormalities of inhibition in boys with pure conduct disorder and in boys with pure attention deficit hyperactivity disorder. Am J Psychiatry. 2008;165:889-897.
34. Rubia K, Cubillo A, Smith AB, Woolley J, Heyman I, Brammer MJ. Disorder-specific dysfunction in right inferior prefrontal cortex during two inhibition tasks in boys with attention-deficit hyperactivity disorder compared to boys with obsessive-compulsive disorder. Hum Brain Mapp. 2009;31:287-299.
35. Passarotti AM, Sweeney JA, Pavuluri MN. Neural correlates of response inhibition in pediatric bipolar disorder and attention deficit hyperactivity disorder. Psychiatry Res. 2010;181:36-43.
36. Gamo NJ, Arnsten AF. Molecular modulation of prefrontal cortex: rational development of treatments for psychiatric disorders. Behav Neurosci. 2011;125:282-296.
37. Arnsten AF, Dudley AG. Methylphenidate improves prefrontal cortical cognitive function through a2 adrenoceptor and dopamine D1 receptor actions: relevance to therapeutic effects in attention deficit hyperactivity disorder. Behav Brain Funct. 2005; 1:2.
38. Berridge CW, Devilbiss DM, Andrzejewski ME, *et al.* Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. Biol Psychiatry. 2006;60:1111-1120.
39. Swanson JM, Volkow ND. Pharmacokinetic and pharmacodynamic properties of stimulants: implications for the design of new treatments for ADHD. Behav Brain Res. 2002;130:73-78.
40. Bush G, Spencer TJ, Holmes J, *et al.* Functional magnetic resonance imaging of methylphenidate and placebo in attention-deficit/hyperactivity disorder during the multi-source interference task. Arch Gen Psychiatry. 2008;65:102-114.
41. Rubia K, Halari R, Cubillo A, Mohammad AM, Brammer M, Taylor E. Methylphenidate normalises activation and functional connectivity deficits in attention and motivation networks in medication-naive children with ADHD during a rewarded continuous performance task. Neuropharmacology. 2009;57:640-652.
42. Rubia K, Halari R, Cubillo A, *et al.* Methylphenidate normalizes fronto-striatal underactivation during interference inhibition in medication-naive boys with attention-deficit hyperactivity disorder. Neuropsychopharmacology. 2011;36:1575-1586.
43. Vaidya CJ, Austin G, Kirkorian G, *et al.* Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study. Proc Natl Acad Sci U S A. 1998;95:14494-14499.
44. Hobson C, Scott S, Rubia K. Investigation of cool and hot executive function in ODD/CD independently of ADHD. J Child Psychol Psychiatry. 2011;52:1035-1043.
45. De Brito SA, Mechelli A, Wilke M, *et al.* Size matters: increased grey matter in boys with conduct problems and callous-unemotional traits. Brain. 2009;132:843-852.
46. Decety J, Michalska KJ, Akitsuki Y, Lahey BB. Atypical empathic responses in adolescents with aggressive conduct disorder: a functional MRI investigation. Biol Psychol. 2009;80:203-211.
47. Finger EC, Marsh AA, Mitchell DG, *et al.* Abnormal ventromedial prefrontal cortex function in children with psychopathic traits during reversal learning. Arch Gen Psychiatry. 2008;65:586-594.
48. Marsh AA, Finger EC, Mitchell DG, *et al.* Reduced amygdala response to fearful expressions in children and adolescents with callous-unemotional traits and disruptive behavior disorders. Am J Psychiatry. 2008;165:712-720.
49. Connor DF, Findling RL, Kollins SH, *et al.* Effects of guanfacine extended release on oppositional symptoms in children aged 6-12 years with attention-deficit hyperactivity disorder and oppositional symptoms: a randomized, double-blind, placebo-controlled trial. CNS Drugs. 2010;24:755-768.
50. Steere JC, Arnsten AF. The alpha-2A noradrenergic receptor agonist guanfacine improves visual object discrimination reversal performance in aged rhesus monkeys. Behav Neurosci. 1997;111: 883-891.
51. Caetano SC, Fonseca M, Hatch JP, *et al.* Medial temporal lobe abnormalities in pediatric unipolar depression. Neurosci Lett. 2007;427:142-147.
52. Gabbay V, Hess DA, Liu S, Babb JS, Klein RG, Gonen O. Lateralized caudate metabolic abnormalities in adolescent major depressive disorder: a proton MR spectroscopy study. Am J Psychiatry. 2007;164:1881-1889.
53. MacMaster FP, Russell A, Mirza Y, *et al.* Pituitary volume in treatment-naive pediatric major depressive disorder. Biol Psychiatry. 2006;60:862-866.
54. MacMaster FP, Mirza Y, Szeszko PR, *et al.* Amygdala and hippocampal volumes in familial early onset major depressive disorder. Biol Psychiatry. 2008;63:385-390.
55. MacMillan S, Szeszko PR, Moore GJ, *et al.* Increased amygdala: hippocampal volume ratios associated with severity of anxiety in pediatric major depression. J Child Adolesc Psychopharmacol. 2003;13:65-73.
56. Rosso IM, Cintron CM, Steingard RJ, Renshaw PF, Young AD, Yurgelun-Todd DA. Amygdala and hippocampus volumes in pediatric major depression. Biol Psychiatry. 2005;57:21-26.
57. Nolan CL, Moore GJ, Madden R, *et al.* Prefrontal cortical volume in childhood-onset major depression: preliminary findings. Arch Gen Psychiatry. 2002;59:173-179.
58. Wager TD, Phan KL, Liberzon I, Taylor SF. Valence, gender, and lateralization of functional brain anatomy in emotion: a meta-analysis of findings from neuroimaging. Neuroimage. 2003;19: 513-531.
59. Harmon-Jones E, Gable PA. Neural activity underlying the effect of approach-motivated positive affect on narrowed attention. Psychol Sci. 2009;20:406-409.
60. Davidson RJ, Irwin W. The functional neuroanatomy of emotion and affective style. Trends Cogn Sci. 1999;3:11-21.
61. Thomas EJ, Elliott R. Brain imaging correlates of cognitive impairment in depression. Front Hum Neurosci. 2009;3:30.
62. Halari R, Simic M, Pariante CM, *et al.* Reduced activation in lateral prefrontal cortex and anterior cingulate during attention and cognitive control functions in medication-naive adolescents with depression compared to controls. J Child Psychol Psychiatry. 2009;50:307-316.
63. Chantiluke K, Halari R, Simic M, *et al.* Fronto-striato-cerebellar dysregulation in adolescents with depression during motivated attention. Biol Psychiatry. 2011;71:59-67.

64. Austin MP, Ross M, Murray C, O'Carroll RE, Ebmeier KP, Goodwin GM. Cognitive function in major depression. J Affect Disord. 1992;25:21-29.
65. Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. Neurosci Biobehav Rev. 2008;32:525-549.
66. Radua J, Mataix-Cols D. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. Br J Psychiatry. 2009; 195:393-402.
67. Radua J, van den Heuvel OA, Surguladze S, Mataix-Cols D. Meta-analytical comparison of voxel-based morphometry studies in obsessive-compulsive disorder vs other anxiety disorders. Arch Gen Psychiatry. 2010;67:701-711.
68. Rotge JY, Langbour N, Guehl D, *et al.* Gray matter alterations in obsessive-compulsive disorder: an anatomic likelihood estimation meta-analysis. Neuropsychopharmacology. 2010;35:686-691.
69. Huyser C, Veltman DJ, de Haan E, Boer F. Paediatric obsessive-compulsive disorder, a neurodevelopmental disorder? Evidence from neuroimaging. Neurosci Biobehav Rev. 2009;33:818-830.
70. Britton JC, Rauch SL, Rosso IM, *et al.* Cognitive inflexibility and frontal-cortical activation in pediatric obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 2010;49:944-953.
71. Huyser C, Veltman DJ, Wolters LH, de Haan E, Boer F. Functional magnetic resonance imaging during planning before and after cognitive-behavioral therapy in pediatric obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 2010;49:1238-48.
72. Woolley J, Heyman I, Brammer M, Frampton I, McGuire PK, Rubia K. Brain activation in paediatric obsessive compulsive disorder during tasks of inhibitory control. Br J Psychiatry. 2008;192:25-31.
73. Rubia K, Cubillo A, Woolley J, Brammer MJ, Smith A. Disorder-specific dysfunctions in patients with attention-deficit/hyperactivity disorder compared to patients with obsessive-compulsive disorder during interference inhibition and attention allocation. Hum Brain Mapp. 2011;32:601-611.
74. Krause J. SPECT and PET of the dopamine transporter in attention-deficit/hyperactivity disorder. Expert Rev Neurother. 2008;8:611-625.
75. Volkow ND, Wang GJ, Newcorn J, *et al.* Brain dopamine transporter levels in treatment and drug naive adults with ADHD. Neuroimage. 2007;34:1182-1190.
76. Volkow ND, Wang GJ, Kollins SH, *et al.* Evaluating dopamine reward pathway in ADHD: clinical implications. JAMA. 2009;302: 1084-1091.
77. Denys D, van der WN, Janssen J, De GF, Westenberg HG. Low level of dopaminergic D2 receptor binding in obsessive-compulsive disorder. Biol Psychiatry. 2004;55:1041-1045.
78. Kim CH, Koo MS, Cheon KA, Ryu YH, Lee JD, Lee HS. Dopamine transporter density of basal ganglia assessed with [123I]IPT SPET in obsessive-compulsive disorder. Eur J Nucl Med Mol Imaging. 2003;30:1637-1643.
79. Kim CH, Cheon KA, Koo MS, *et al.* Dopamine transporter density in the basal ganglia in obsessive-compulsive disorder, measured with [123I]IPT SPECT before and after treatment with serotonin reuptake inhibitors. Neuropsychobiology. 2007;55:156-162.
80. Hesse S, Muller U, Lincke T, *et al.* Serotonin and dopamine transporter imaging in patients with obsessive-compulsive disorder. Psychiatry Res. 2005;140:63-72.
81. Roberts AC. The importance of serotonin for orbitofrontal function. Biol Psychiatry. 2011;69:1185-1191.
82. Tanis KQ, Newton SS, Duman RS. Targeting neurotrophic/growth factor expression and signaling for antidepressant drug development. CNS Neurol Disord Drug Targets. 2007;6:151-160.
83. Giedd JN, Rapoport JL. Structural MRI of pediatric brain development: what have we learned and where are we going? Neuron. 2010;67:728-734.
84. Fitzgerald PB, Laird AR, Maller J, Daskalakis ZJ. A meta-analytic study of changes in brain activation in depression. Hum Brain Mapp. 2008;29:683-695.
85. Murphy SE. Using functional neuroimaging to investigate the mechanisms of action of selective serotonin reuptake inhibitors (SSRIs). Curr Pharm Des. 2010;16:1990-1997.
86. Gilbert AR, Moore GJ, Keshavan MS, *et al.* Decrease in thalamic volumes of pediatric patients with obsessive-compulsive disorder who are taking paroxetine. Arch Gen Psychiatry. 2000;57:449-456.
87. Szeszko PR, MacMillan S, McMeniman M, *et al.* Brain structural abnormalities in psychotropic drug-naive pediatric patients with obsessive-compulsive disorder. Am J Psychiatry. 2004;161:1049-1056.
88. Lazaro L, Bargallo N, Castro-Fornieles J, *et al.* Brain changes in children and adolescents with obsessive-compulsive disorder before and after treatment: a voxel-based morphometric MRI study. Psychiatry Res. 2009;172:140-146.
89. Lazaro L, Caldu X, Junque C, *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: 1051-1059.
90. Rosenberg DR, MacMaster FP, Keshavan MS, Fitzgerald KD, Stewart CM, Moore GJ. Decrease in caudate glutamatergic concentrations in pediatric obsessive-compulsive disorder patients taking paroxetine. J Am Acad Child Adolesc Psychiatry. 2000;39: 1096-1103.
91. Sowell ER, Thompson PM, Toga AW. Mapping changes in the human cortex throughout the span of life. Neuroscientist. 2004; 10:372-392.
92. Power JD, Fair DA, Schlaggar BL, Petersen SE. The development of human functional brain networks. Neuron. 2010;67:735-748.