

# Cingulate, Frontal, and Parietal Cortical Dysfunction in Attention-Deficit/Hyperactivity Disorder

George Bush

Functional and structural neuroimaging have identified abnormalities of the brain that are likely to contribute to the neuropathophysiology of attention-deficit/hyperactivity disorder (ADHD). In particular, hypofunction of the brain regions comprising the cingulo-frontal-parietal cognitive-attention network have been consistently observed across studies. These are major components of neural systems that are relevant to ADHD, including cognitive/attention networks, motor systems, and reward/feedback-based processing systems. Moreover, these areas interact with other brain circuits that have been implicated in ADHD, such as the “default mode” resting state network. The ADHD imaging data related to cingulo-frontal-parietal network dysfunction will be selectively highlighted here to help facilitate its integration with the other information presented in this special issue. Together, these reviews will help shed light on the neurobiology of ADHD.

**Key Words:** ADHD, attention, cingulate, cognition, decision, frontal, imaging, parietal, reward

Dysfunction of cingulate, frontal, and parietal cortical regions has been implicated in the pathophysiology of attention-deficit/hyperactivity disorder (ADHD) by convergent data from a variety of sources, including neuroimaging, neuropsychological, neurochemical, and genetics studies (1–7). Earlier in this special issue, the groundwork has been laid that shows how cingulate, frontal, and parietal cortical regions interact with striatal, cerebellar, and other brain regions in healthy humans and animals during cognitive processes relevant to ADHD. This review will highlight studies that have found functional and structural abnormalities of the cingulo-frontal-parietal (CFP) cognitive-attention network in ADHD. However, at no time should the narrow focus of this review be taken to suggest that CFP network abnormalities are the only factors responsible for ADHD. Clearly, they are only part of the pathophysiology of ADHD. To fully characterize the disorder, the findings herein will need to be integrated with the wider literature on neurocircuitry models of ADHD—such as data on possible dysfunction of a proposed “default mode” network of the brain and/or reward/motivation networks—as reviewed in this issue and elsewhere (8).

## CFP Attention Network

Imaging studies have attempted to identify the pathophysiology of ADHD by looking for abnormalities of brain regions that are normally involved in attention, cognition, executive function, motor control, response inhibition, and working memory. This typically led to investigations centered on dorsal anterior midcingulate cortex (daMCC), dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and to a lesser extent, parietal cortex. Together, these regions comprise the main components of the CFP cognitive-attention network (Figure 1). These areas, along with striatum, premotor areas, thalamus, and cerebellum, have been

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Received May 21, 2010; revised Jan 21, 2011; accepted Jan 21, 2011.

0006-3223/\$36.00  
doi:10.1016/j.biopsych.2011.01.022

identified as nodes within parallel networks of attention and cognition (9–21).

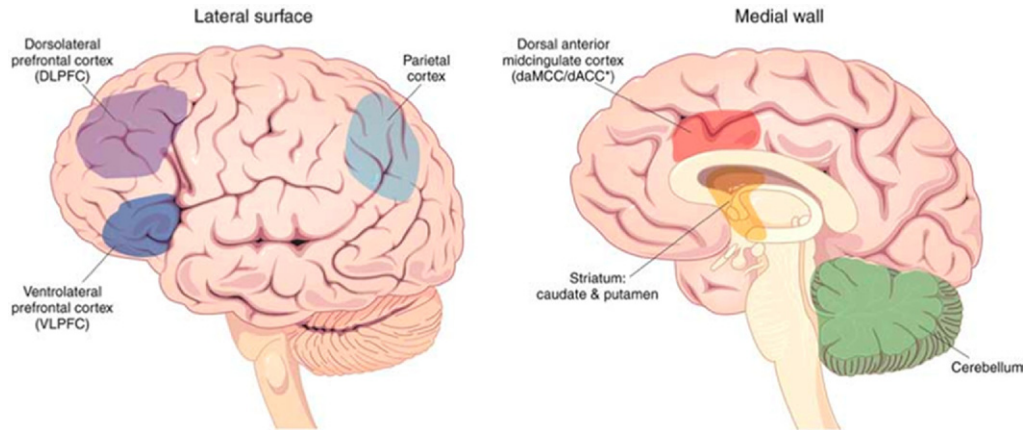
## daMCC: Cognition, Attention, and Motivation/Reward

The most consistent cross-study and cross-modality data identifying a region as dysfunctional in ADHD have been provided for the daMCC (22). The daMCC, located on the medial surfaces of the frontal lobes, refers to areas 24c'/32' in humans. The nomenclature of cingulate subdivisions has evolved over the past few decades (22–24). To clarify, the more recent term, daMCC, is equivalent to dorsal anterior cingulate cortex (ACC). As monkey connection studies have shown, it maintains strong reciprocal connections with other cognitive/attention and motor regions, including DLPFC, parietal cortex, premotor cortex, and striatum, and these differential connections might be correlated with different cognitive, motor, and reward functions (25,26).

The daMCC plays critical roles in attention, cognitive processing, target detection, novelty detection, response selection, response inhibition, error detection, and motivation. Particularly relevant to reward/motivation and cognitive theories of ADHD, the daMCC is a key modulator of moment-to-moment adjustments in behavior via its primary role in feedback-based decision-making. As detailed elsewhere (22,27,28), this feedback-based decision-making conceptualization of daMCC is based on evidence from single unit studies in monkeys and humans as well as on human neuroimaging studies. The daMCC encompasses a local intracortical network comprising functionally heterogeneous cells that variously anticipate and signal motivationally relevant targets, indicate novelty, encode reward values, signal errors, and influence motor responses. The daMCC integrates goal- and feedback-related information from various sources and uses this information to modulate activity in executive brain regions that direct attention and produce motor responses. The daMCC thus acts within cognitive-reward-motor networks to increase the efficiency of decision-making and execution, and its proper function is therefore germane to ADHD.

Numerous functional, structural, connectionist, neurochemical, and pharmacological imaging studies have identified abnormalities of daMCC in ADHD. Specifically, many functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and event-related potential studies have reported daMCC hypofunction in ADHD with a variety of tasks and techniques. Zametkin *et al.* (29) reported that, even after normalization for an observed 8.1% global reduction of cerebral glucose metabolism in 25 treatment-naïve ADHD adults (compared with 50 adult control subjects), regional metabolism was specifically lower in ADHD in daMCC, premotor, and somatosensory areas during a continuous performance task. As shown in Figure 2, the first fMRI study to specifically interrogate daMCC integrity in ADHD found that daMCC

BIOL PSYCHIATRY 2011;69:1160–1167  
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**Figure 1.** The cingulo-frontal-parietal (CFP) cognitive/attention network. The daMCC, DLPFC, VLPFC, and parietal cortex comprise the CFP network (8). These regions work in concert with each other and other regions such as striatum and cerebellum to support normal cognition, attention, and motor control processes. All of these brain regions have been found to display functional and structural abnormalities in attention-deficit/hyperactivity disorder. Reprinted with permission from (8).

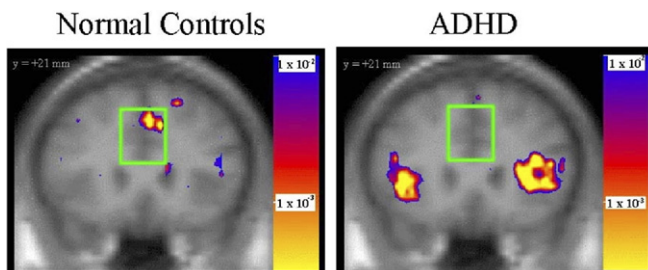
was hypoactive in ADHD adults during cognitive/attention task performance (30). Subsequent fMRI studies using a variety of tasks have similarly found relative daMCC hypofunction in ADHD compared with control subjects. These have included an fMRI study of adolescent boys with ADHD using a Go/NoGo task (31) (Figure 3) as well as others using response inhibition and timing tasks (32–39).

Importantly, a meta-analysis of neuroimaging studies by Dickstein *et al.* (40)—shown in Figure 4—found daMCC to be among a limited number of brain regions that were hypoactive in ADHD relative to healthy control subjects. With an activation likelihood estimate meta-analytic method (41), this review provided a relatively unbiased overview of ADHD imaging findings. The ADHD was additionally found to be associated with significant hypoactivity of DLPFC, VLPFC, superior parietal cortex, caudate, and thalamus.

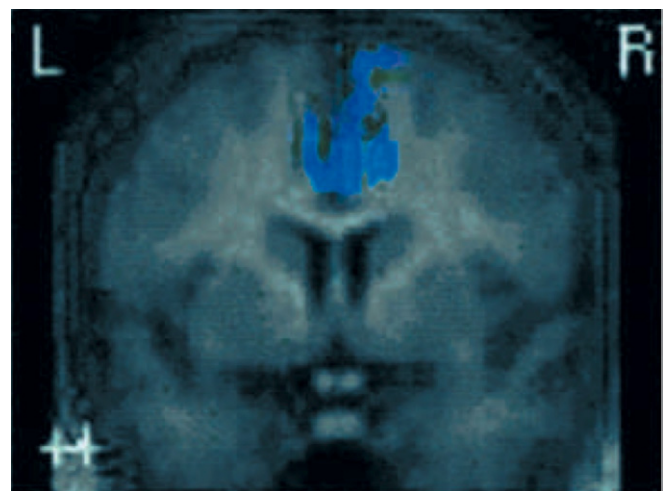
Structural studies have also reported abnormalities within defined regions of cingulate cortex and lateral prefrontal cortex in ADHD. Smaller cingulate cortical volumes have been reported in adults (42) and children (43) with ADHD. More recently, Makris *et al.* (44) reported pilot study results showing that both treatment-naïve as well as treated adults with ADHD displayed significantly reduced ACC volumes. An earlier study of ADHD children, relevant to default mode network studies, showed a reduction in posterior cingulate volume in ADHD (45). Cortical thickness quantification via high-resolution MRI structural scans has been recently applied to the study of ADHD. Children with ADHD had significant global thinning of the cortex, most prominently in the cingulate and superior pre-

frontal regions (46). These data in children were generally consistent with the findings Makris *et al.* (47) that showed selective cortical thinning of the daMCC and CFP attention networks in adults with ADHD. Connection studies using diffusion tensor imaging by Makris *et al.* (48) have also identified abnormalities of cingulum bundle and superior longitudinal fascicle II in adults with ADHD—connection pathways that subserve attention and executive functions and are thus highly relevant to ADHD.

Functional pharmaco-imaging has begun to identify alterations in the CFP neural circuitry that might underlie ADHD and to characterize the mechanisms-of-action of medications used to treat it. Pharmaco-imaging studies using fMRI complement dopaminergic imaging studies (discussed elsewhere in this issue) by highlighting the cingulate and frontal effects. Such reports now suggest that stimulant medications might work in part by increasing and therefore by possibly “normalizing” the generally observed hypoactivation of the CFP cognitive/attention network and striatum in ADHD.



**Figure 2.** The daMCC shows hypofunction in attention-deficit/hyperactivity disorder (ADHD) during counting Stroop daMCC activated in healthy control subjects but not in subjects with ADHD, during the counting Stroop. Reprinted from (30) with permission from Elsevier, copyright 1999. Abbreviations as in Figure 1.



**Figure 3.** The dorsal anterior midcingulate cortex (daMCC) shows hypofunction in attention-deficit/hyperactivity disorder (ADHD) during response inhibition. Tamm *et al.* (31) showed that daMCC was hypoactive in an ADHD group relative to control group during a response inhibition Go/NoGo task (figure reprinted with permission from Elsevier, copyright 2004).



**Figure 4.** Meta-analysis shows daMCC and CFP dysfunction in ADHD. Dickstein *et al.* (40), via an activation likelihood meta-analysis, found daMCC to be among a limited number of brain regions that were hypoactive in ADHD relative to healthy control subjects (figure reprinted with permission from John Wiley and Sons). The CFP network abnormalities were also reported. Abbreviations as in Figures 1 and 2.

Specifically, a recent study by Bush *et al.* (24) used fMRI in conjunction with a specialized cognitive task, the Multi-Source Interference Task (MSIT) (49), to determine whether methylphenidate would increase activation in the daMCC and other fronto-parietal regions that subservise attention. This randomized, placebo-controlled, 6-week, pre/poststudy found a group  $\times$  scan interaction and *t* test confirmation of higher activation in the daMCC at 6 weeks in the MPH group, compared with the placebo group. Moreover, the MSIT enabled single-subject daMCC volume-of-interest analyses that confirmed the group-averaged findings and suggested that daMCC activity might be related to clinical response (Figure 5). Beyond daMCC, 6 weeks of MPH also increased activation of many structures implicated in ADHD pathophysiology, including DLPFC, VLPFC, parietal cortex, caudate, thalamus, and temporal lobe. These findings indicated that MPH might act, in part, by helping to normalize daMCC and wider CFP hypofunction in ADHD.

Biochemical and electrophysiology studies mesh well with these pharmaco-imaging findings. A magnetic resonance spectroscopy study found decreased choline and increased N-acetyl-aspartate levels in daMCC after treatment of ADHD with 5–6 weeks of MPH, indicating biochemical changes occur in daMCC with MPH treatment (50). Pliszka *et al.* (51) found stimulant treatment increases ACC activity in ADHD with event-related potentials. Data on subsets of children from a 1-year follow-up fMRI study of ADHD suggested long-term effects of MPH on cingulate cortex, insula, and putamen (52).

Recently, Brown *et al.* (53) provided new evidence on how genetic variations of the dopamine system dopamine transporter (DAT) gene (SLC6A3) might be linked to alterations of daMCC function. In 42 adults with ADHD performing the MSIT during fMRI, ADHD subjects homozygous for the 10R allele showed significant hypoactivation of left daMCC compared with 9R-carriers. Clearly, the accumulated data from these fMRI, PET, and event-related potential studies along with the biochemical, genetic, cortical thickness, and volumetric data reviewed in the preceding text provide compelling evidence that daMCC dysfunction likely contributes to the pathophysiology of ADHD.

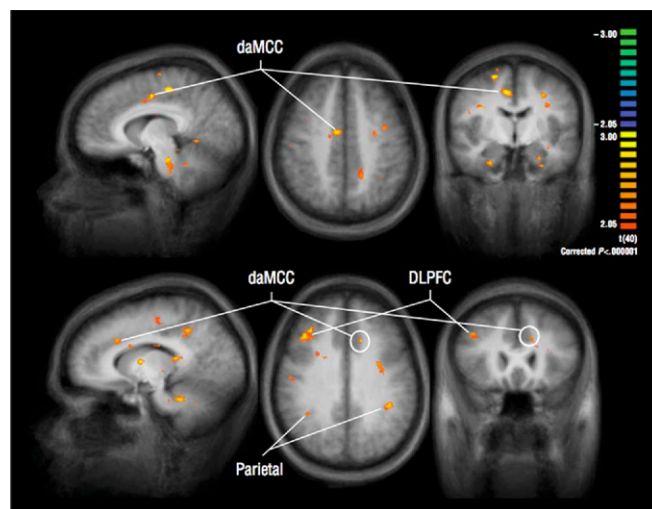
### Lateral Prefrontal Cortex

Although daMCC dysfunction likely contributes to the pathophysiology of ADHD, many brain regions have also been implicated, including other areas within the CFP cognitive/attention network. Research has focused mainly on DLPFC and VLPFC, because these regions are thought to support vigilance, selective and divided attention, attention shifting, planning, executive control, and working memory functions (10,21). Also, VLPFC in particular

has been associated with behavioral inhibition (32,54). Although speculative, it might be that some of the inconsistency surrounding lateral prefrontal findings might be due in large part to the relatively increased spatial variability in the anatomic locations of these structures between subjects (i.e., centromedial brain structures, such as daMCC, show relatively less morphologic variability in probabilistic atlases than lateral/peripheral regions such as DLPFC or VLPFC). Despite this, however, structural and functional data support the conclusion that lateral prefrontal cortex abnormalities contribute to ADHD.

Structural imaging studies of ADHD have identified both 3%–4% smaller global cerebral volumes in ADHD as well as specifically smaller prefrontal volumes in ADHD (55,56). More recently, Monuteaux *et al.* (57) found that, among adults with ADHD, subjects with the 7-repeat allele of the dopamine D4 receptor (DRD4) gene had a significantly smaller mean volume of superior frontal cortex and cerebellum compared with subjects without this allele. Cortical thickness maturation delays have been found in ADHD, with delays most prominent in lateral prefrontal cortex, especially the superior and DLPFC regions (58). In a separate study combining cortical thickness and genetics by the same group, cortical thinning of multiple regions—including orbitofrontal cortex, inferior prefrontal cortex, and posterior parietal cortex—was associated with possession of the DRD4 7-repeat allele in both healthy children and those with ADHD (59). These brain regions were generally thinner in ADHD than control subjects, although a complicating factor was that ADHD patients with the DRD4 7-repeat allele did better clinically. Cortical thickness results have not, however, always been consistent. Although Wolosin *et al.* (60) reported overall decreases of total cerebral and cortical volumes and a significant decrease in cortical folding bilaterally in ADHD children, they did not find significant differences in cortical thickness between ADHD and healthy children.

Diffusion tensor imaging and fMRI have been combined to help identify abnormalities of connections of prefrontal cortical areas in ADHD. Casey *et al.* (61) used fMRI maps from a Go/NoGo task to



**Figure 5.** Methylphenidate increases daMCC and CFP activity in ADHD with the multi-source interference task and functional magnetic resonance imaging in 21 adults with ADHD. Bush *et al.* (copyright © 2008 American Medical Association. All rights reserved [24]) showed that, at 6 weeks, daMCC activation was higher in the group that received methylphenidate ( $n = 11$ ) than in the group that received placebo ( $n = 10$ ). Similar results were observed in DLPFC, parietal cortex, and networked regions. Abbreviations as in Figures 1 and 2.

identify portions of VLPFC and striatum involved in suppressing an inappropriate action in parent–child dyads with and without ADHD. They reported fractional anisotropy in right prefrontal fiber tracts was correlated with both functional activity in inferior frontal gyrus and caudate nucleus and with performance of a Go/NoGo task in parent–child dyads with ADHD. Prefrontal fiber tract measures were also associated between ADHD parents and their children, suggesting disruption of frontostriatal connections might play a role in ADHD. The work of Silk *et al.* (62) further indicates frontostriatal and fronto-parietal circuitry abnormalities exist in children with ADHD.

A number of functional imaging studies have reported prefrontal cortical abnormalities in ADHD. In particular, dysfunction of DLPFC and VLPFC have been identified (3–5,7,38,39,54,63). Frontotemporal abnormalities were found in ADHD via a working memory task and PET (64). Ernst *et al.* (65), employing a gambling task, provided data implicating VLPFC and daMCC in ADHD and highlighting the need to further examine cognitive, emotional, and motivational interactions in its pathophysiology. Also, beyond the global and daMCC hypometabolism discussed in the preceding text, the PET study by Zametkin *et al.* (29) also showed regional hypoactivity of superior prefrontal cortex and premotor cortex.

Importantly, the aforementioned meta-analysis by Dickstein *et al.* (40) provided confirmatory evidence of wider CFP neurocircuitry dysfunction in ADHD (Figure 4). Also, by limiting their focus to response inhibition task studies—as suggested by the work of Durston *et al.* (33) and Aron and Poldrack (66)—they identified a more limited set of regions, including VLPFC, daMCC, parietal cortex, caudate, and precentral gyrus. Notably DLPFC was not included on this list. These data helped clarify that DLPFC and VLPFC abnormalities might contribute to ADHD in different ways.

Pharmacology-imaging studies have further supported the conclusion that CFP hypofunction occurs in ADHD. In the previously mentioned study by Bush *et al.* (24) it was also reported that, beyond the daMCC findings, 6 weeks of methylphenidate also increased activation of DLPFC and VLPFC (and also parietal cortex, caudate, thalamus, and temporal lobe). Nonstimulant medications used for ADHD have also been studied in healthy male adults with fMRI. Atomoxetine, a selective noradrenaline reuptake inhibitor, was found to increase both inhibitory control on a stop-signal task and right VLPFC activation (67).

### Parietal Cortex

Parietal cortex, a third component of the CFP cognitive-attention network, has long been known to play important roles in attention and spatial processing. Specifically, parietal cortex plays key roles in attention allocation and encompasses polymodal sensory convergence areas (68–71). Although parietal cortex has been the *a priori* focus of only a few ADHD functional imaging studies, it has been identified as displaying altered function in ADHD.

Tamm *et al.* (72) have shown that ADHD subjects performing a visual oddball task had significantly lower activation of parietal cortex, including superior parietal gyrus and multiple areas of inferior parietal lobe. Vance *et al.* (73) reported that ADHD subjects performing a spatial working memory mental rotation task displayed significantly less inferior parietal lobe activation in addition to lower parieto-occipital and caudate activation. In another study, ADHD children showed less activation than control subjects in multiple areas of parietal cortex, DLPFC, and putamen. A lack of a difference in daMCC in this study might have been attributable to higher error rates in the ADHD group, because errors activate daMCC (74). Parietal hypofunction has also been observed in ADHD

in tasks of mental rotation/spatial processing (75), task switching (76), and sequential finger tapping (77).

It has been suggested that such findings of parietal hypofunction might reflect secondary problems rather than primary neuroanatomical abnormalities. For example, hypoactivation during fMRI might occur due to abnormal input from regions that are connected to what would be otherwise normally functional parietal cortex. Although structural (cortical thickness) abnormalities in the parietal cortices of those with ADHD (47) further support the conclusion that parietal cortex functional abnormalities do play a role in ADHD pathophysiology, they do not resolve whether the observed parietal cortex differences are primary or secondary. Thus, although it is clear that hypofunctioning parietal cortical subdivisions likely play roles in ADHD pathophysiology, the challenges ahead will be in specifically parsing how different areas contribute to create the observed symptoms.

### CFP Network Interactions and Conclusions

Advances have been made in identifying hypofunction within the CFP in ADHD. Specifically, it should be noted that—although the data reviewed here strongly support the premises that: 1) the CFP neural circuitry supports attention, cognition, motor control, and motivation/reward processes in healthy humans; and 2) dysfunction of components of the CFP neural circuitry likely contributes to the pathophysiology of ADHD—the exact mechanisms by which such dysfunction leads to the symptoms of ADHD have yet to be determined.

In broad terms, the multiple functions of daMCC, DLPFC, VLPFC, and parietal cortical regions alone provide a great many possibilities. Simplistically, it could be the case that, for healthy humans, DLPFC is more responsible for overall planning and goal-setting, VLPFC and daMCC are responsible for inhibiting excessive or inappropriate motor behavior, heteromodal parietal cortex assists with target detection and attention shifts, and daMCC integrates information from these inputs and helps to execute such plans by modifying behavior on a trial-by-trial basis. Dysfunction within components of the CFP network in ADHD could therefore lead to inattention by failing to detect targets or inadequately filtering noise within the system. Such dysfunction could also lead to hyperactivity by failing to adequately inhibit motor activity that is not in line with motivated goals or by failing to use reward and error feedback to modify behavior. Similarly, impulsivity could be produced by insufficient encoding of motivational goals and/or the impaired ability to preferentially pursue long-term goals over short-term goals.

Of course, the reality is much more complex. Beyond just the CFP intranetwork communications, it has been shown how the CFP network interacts with striatum, premotor cortex, cerebellum, superior temporal sulcus, thalamus, and the brain stem reticular activating system to support cognitive-motor processing. Also, reward/motivational information (encoded by striatum, daMCC, nucleus accumbens, and orbitofrontal cortex) is integrated with information from default mode network regions (perigenual ACC, medial prefrontal cortex, portions of VLPFC, amygdala, and posterior cingulate cortex).

Interactions within such networks and the specific roles of each region are starting to be parsed out experimentally. For example, Corbetta *et al.* (78) have postulated that a “reorienting response” relies on the coordinated action of a dorsal frontoparietal network that links stimuli and responses and helps select actions along with a predominantly right hemispheric ventral frontoparietal network that serves to interrupt and reset ongoing activity. Furthermore,

they hypothesize that, when attention for a specific task is required, the ventral network is suppressed to prevent reorienting to distracting events. Distinct and separable roles for DLPFC, daMCC, and parietal cortex in cognitive processing have also been suggested by Liston *et al.* (79). Dosenbach *et al.* (80,81) have suggested that parallel “hybrid” control systems are possible in which transient activity of a fronto-parietal network reflects trial-by-trial adjustments, whereas sustained activity of cingulo-opercular regions throughout trials might indicate that it is more responsible for set maintenance. Recent work has used event-related fMRI and functional connectivity analyses to identify how different elements of proposed interacting networks are responsible for the maintenance of attention on a target, cued shifts of attention, and reorienting to an unexpected target (82).

Translations of such network models into testable predictions about ADHD network circuitry have commenced. For example, it has been hypothesized (83,84) that, in ADHD, abnormal activity in “default mode” brain systems that normally subservise resting state and vigilance functions (85,86) might interfere with CFP-modulated attention systems. Castellanos *et al.* (87,88) have reported abnormal connectivity within default network structures (VMPFC, precuneus, and posterior cingulate cortex) and furthermore altered functional connectivity between the daMCC and default network areas (precuneus and posterior cingulate cortex). Finally, Liston *et al.* (89) recently reported that psychosocial stress reversibly and selectively impairs attention control and disrupts functional connectivity within a frontoparietal network that mediates attention shifts. Although admittedly speculative, it would be interesting to extend beyond these findings to determine: 1) whether the chronic stress within those with ADHD could parametrically contribute to the disruption of functional attention network integrity in ADHD, and 2) whether stress-reduction techniques such as relaxation response training, meditation, or yoga could be used to alleviate some portion of ADHD morbidity by strengthening CFP network connections. For the interested reader, fuller explanations for how such observed CFP cognitive-attention network abnormalities described here might lead to specific ADHD symptoms appear elsewhere within this special issue and also in other sources (8,22,80,81).

Lastly, although this narrow review focuses on CFP network abnormalities, it is important to recall that many other systems have been implicated—most prominently, studies of subcortical dysfunction and dopaminergic modulatory functions have been reported and must be integrated with CFP neurocircuitry models. The interested reader can find reviews of dopaminergic imaging relevant to ADHD (90,91) as well as the roles various neurotransmitters might play in the pathophysiology of ADHD (92–94). Dopamine plays roles in attention, cognition, and reward processes (92,95–97) and can increase the neuronal signal-to-noise ratio both by boosting signal and dampening background noise (98). Dopamine also displays an inverted-U influence such that it optimizes neural transmission within a range but might adversely affect performance at lower or higher levels (92). Volkow *et al.* showed specific activity of methylphenidate in basal ganglia (99), that it blocks the DAT (100), and that methylphenidate increases extracellular dopamine in striatum (101). Spencer *et al.* (102) confirmed how striatal effects of methylphenidate match behavioral effects with immediate and extended release formulations. Studies of the DAT, which is primarily responsible for presynaptic reuptake of dopamine, have shown that methylphenidate blocks striatal DAT and increases extracellular dopamine (90,91,98,103,104). These studies dovetail nicely with imaging studies that illustrate striatum dysfunction in ADHD by Durston, Casey, Vaidya, Epstein *et al.* (7,105–111).

In conclusion, functional, structural, biochemical, and connectionist imaging data have identified abnormalities of brain regions within CFP networked functional systems, and pharmaco-imaging has helped to identify ways that medications used to treat ADHD exert their effects. It remains to be determined how the CFP network functions during cognitive and reward processing and, more specifically, how dysfunction of the component regions contribute to the pathophysiology of ADHD.

*This review was produced without direct support or compensation. Indirect support has been provided to the author for cingulate and attention-deficit/hyperactivity disorder-related work over the past decade in the form of grant or general support by the Centers for Disease Control, the National Institutes of Mental Health, the National Science Foundation, the Mental Illness and Neuroscience Discovery (MIND) Institute, the National Alliance for Research on Schizophrenia and Depression (NARSAD), the Benson-Henry Institute for Mind-Body Medicine at Massachusetts General Hospital, the David Judah Fund, the McIngvale Fund, the Johnson and Johnson Center for the Study of Psychopathology, the Center for Functional Neuroimaging Technologies (P41RR14075), McNeil Pharmaceuticals, Pfizer Pharmaceuticals, and Eli Lilly and Company. The author has, or has had in the past, a relationship with one or more organizations listed as follows: former advisory board member and speaker's honoraria from Eli Lilly and Company and Novartis Pharmaceuticals; and has received speaker's honoraria from Shire U.S., Janssen Pharmaceuticals, Johnson and Johnson, and McNeil Pharmaceuticals. The author does not now and has not at any time had a financial interest in any of these entities.*

*I wish to thank Jennifer Holmes, Scott Rauch, Michael Jenike, Michael Posner, Brent Vogt, Joseph Biederman, Thomas Spencer, and the MGH Pediatric Psychopharmacology Clinic staff for invaluable assistance, support, mentoring, and collaboration related to the topics discussed herein as well as the anonymous reviewers for their many helpful comments.*

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