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

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## Abstract

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 (CFP) 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. ADHD imaging data related to CFP 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.



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## INTRODUCTION

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 which 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).

### Cingulo-Frontal-Parietal 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 cingulo-frontal-parietal [CFP] cognitive-attention network (see Figure 1). These areas, along with striatum, premotor areas, thalamus and cerebellum have been identified as nodes within parallel networks of attention and cognition (9–21).

**Dorsal Anterior Midcingulate Cortex: Cognition, Attention and Motivation/Reward—**The most consistent cross-study and cross-modality data identifying a region as dysfunctional in ADHD has been provided for the dorsal anterior midcingulate cortex (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 (dACC). 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 may 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 comprised of 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 fMRI, PET and event-related potential (ERP) studies have reported daMCC hypofunction in ADHD using a variety of tasks and techniques. Zametkin and colleagues (29) reported that even after normalization for an observed 8.1% global reduction of cerebral glucose metabolism in 25 treatment-naïve ADHD adults (compared to 50 adult controls), 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 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 to controls. These have included an fMRI study of adolescent boys with ADHD using a Go/NoGo task (31) (see Figure 3), as well as others using response inhibition and timing tasks (32–39).

Importantly, a meta-analysis of neuroimaging studies by Dickstein and colleagues (40), shown in Figure 4, found daMCC to be among a limited number of brain regions that were hypoactive in ADHD relative to healthy controls. Using an activation likelihood estimate meta-analytic method (41), this review provided a relatively unbiased overview of ADHD imaging findings. 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 and colleagues (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 prefrontal 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 (DTI) by Makris and colleagues (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 pharmacoimaging has begun to identify alterations in the CFP neural circuitry that may underlie ADHD and to characterize the mechanisms-of-action of medications used to treat it. Pharmacoimaging 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 may work in part by increasing and therefore by possibly “normalizing” the generally observed hypoactivation of the CFP cognitive/attention network and striatum in ADHD.

Specifically, a recent study by Bush and colleagues (24) used fMRI in conjunction with a specialized cognitive task, the Multi-Source Interference Task (MSIT) (49), to determine if methylphenidate would increase activation in the daMCC and other fronto-parietal regions that subserve attention. This randomized, placebo-controlled, 6-week, pre/post study found a group x scan interaction and t-test confirmation of higher activation in the daMCC at 6

weeks in the MPH group, as compared to the placebo group. Moreover, the MSIT enabled single subject daMCC volume-of-interest analyses which confirmed the group-averaged findings and suggested that daMCC activity might be related to clinical response (see 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 may act, in part, by helping to normalize daMCC and wider CFP hypofunction in ADHD.

Biochemical and electrophysiology studies mesh well with these pharmacoimaging findings. A magnetic resonance spectroscopy study found decreased choline and increased N-acetyl-aspartate (NAA) levels in daMCC following treatment of ADHD with 5–6 weeks of MPH, indicating biochemical changes occur in daMCC with MPH treatment (50). Pliszka and colleagues (51) found stimulant treatment increases ACC activity in ADHD using 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 and colleagues (53) provided new evidence on how genetic variations of the dopamine system dopamine transporter gene [SLC6A3] may be linked to alterations of daMCC function. In 42 adults with ADHD performing the Multi-Source Interference Task (MSIT) during fMRI, ADHD subjects homozygous for the 10R allele showed significant hypoactivation of left daMCC compared to 9R-carriers. Clearly, the accumulated data from these fMRI, PET and ERP studies, along with the biochemical, genetic, cortical thickness and volumetric data reviewed above, provide compelling evidence that daMCC dysfunction likely contributes to the pathophysiology of ADHD.

**Lateral Prefrontal Cortex—**While 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, as 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). Though speculative, it may be that some of the inconsistency surrounding lateral prefrontal findings may 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 do lateral/peripheral regions such as DLPFC or VLPFC). Despite this though, 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 to 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 controls, though 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. Though 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 and colleagues (61) used fMRI maps from a go/nogo task to 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 fronto-striatal connections may play a role in ADHD. The work of Silk and colleagues (62) further indicates fronto-striatal 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). Fronto-temporal 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 above, the PET study by Zametkin and colleagues (29) also showed regional hypoactivity of superior prefrontal cortex and premotor cortex.

Importantly, the aforementioned meta-analysis by Dickstein and colleagues (40) provided confirmatory evidence of wider CFP neurocircuitry dysfunction in ADHD (cf. Figure 4). Also, by limiting their focus to response inhibition task studies, as suggested by the work of Durston et al (33) and Aron & 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 may contribute to ADHD in different ways.

Pharmacoimaging studies have further supported the conclusion that CFP hypofunction in occurs in ADHD. In the previously mentioned study by Bush and colleagues (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). Non-stimulant 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 and colleagues (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 controls in multiple areas of parietal cortex, DLPFC and putamen. A lack of a difference in daMCC in this study may have been attributable to higher error rates in the ADHD group, since 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, while 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 while 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 has 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 PFC, 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 and colleagues 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 which serves to interrupt and reset ongoing

activity. Further, they hypothesize that when attention for a specific task is required, the ventral network is suppressed to prevent reorienting to distracting events (78). Distinct and separable roles for DLPFC, daMCC and parietal cortex in cognitive processing have also been suggested by Liston et al. (79). Dosenbach and colleagues have suggested that parallel "hybrid" control systems are possible in which transient activity of a fronto-parietal network reflects trial-by-trial adjustments, while sustained activity of cingulo-opercular regions throughout trials may indicate that it is more responsible for set maintenance (80, 81). Recent work has utilized 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 subserve resting state and vigilance functions (85, 86) may interfere with CFP-modulated attention systems. Castellanos and colleagues (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 and colleagues recently reported that psychosocial stress reversibly and selectively impairs attention control and disrupts functional connectivity within a frontoparietal network that mediates attention shifts (89). While admittedly speculative, it would be interesting to extend beyond these findings to determine if the chronic stress within those with ADHD could (1) parametrically contribute to the disruption of functional attention network integrity in ADHD and (2) if 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 may play in the pathophysiology of ADHD (92-94). Dopamine plays roles on 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 may adversely affect performance at lower or higher levels (92). Volkow and colleagues showed specific activity of methylphenidate in basal ganglia (99), that it blocks the dopamine transporter (DAT) (100), and that methylphenidate increases extracellular dopamine in striatum (101). Spencer et al (102) confirmed how striatal effects of methylphenidate match behavioral effects using immediate and extended release formulations. Studies of the dopamine transporter (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 and colleagues (7, 105–111).

In conclusion, functional, structural, biochemical and connectionist imaging data have identified abnormalities of brain regions within CFP networked functional systems, and pharmacoimaging 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.

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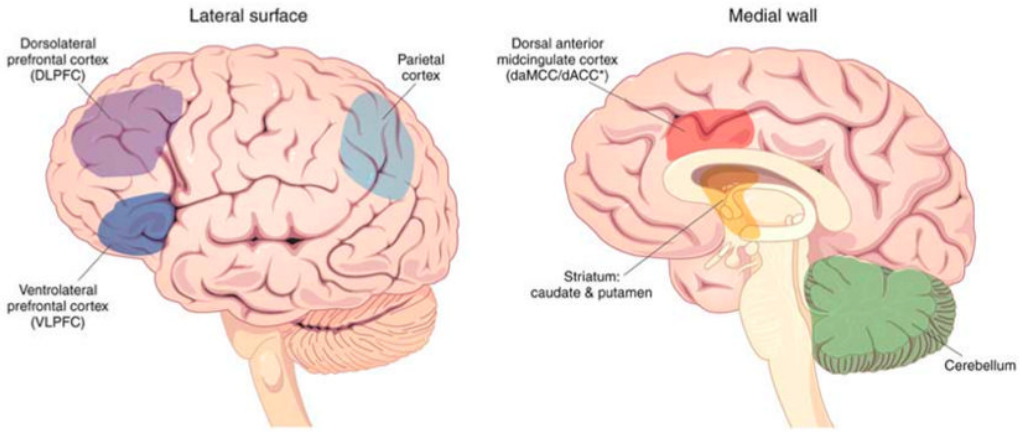


**Figure 1. The Cingulo-Frontal-Parietal Cognitive/Attention Network**

The dorsal anterior midcingulate cortex [daMCC], dorsolateral prefrontal cortex [DLPFC], ventrolateral prefrontal cortex [VLPFC] and parietal cortex comprise the CFP network. 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 ADHD.

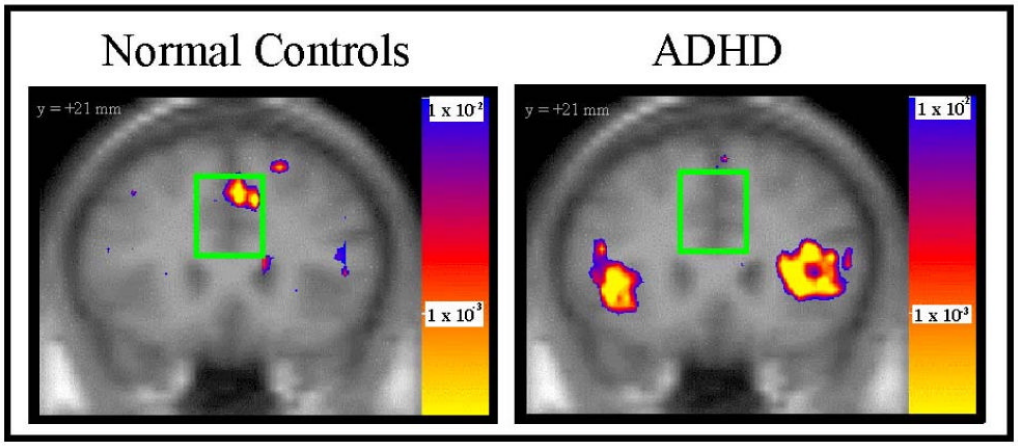


**Figure 2. The daMCC Shows Hypofunction in ADHD during Counting Stroop**
Dorsal anterior midcingulate cortex (daMCC) activated in healthy controls, but not in subjects with ADHD, during the Counting Stroop (30).

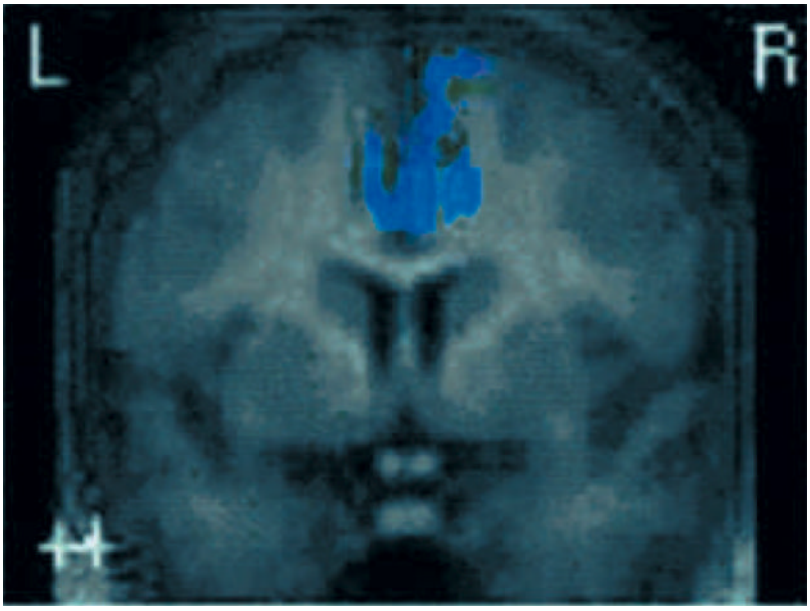


**Figure 3. The daMCC Shows Hypofunction in ADHD during Response Inhibition**

Tamm and colleagues (31) showed that daMCC was hypoactive in an ADHD group relative to control group during a response inhibition Go/NoGo task.

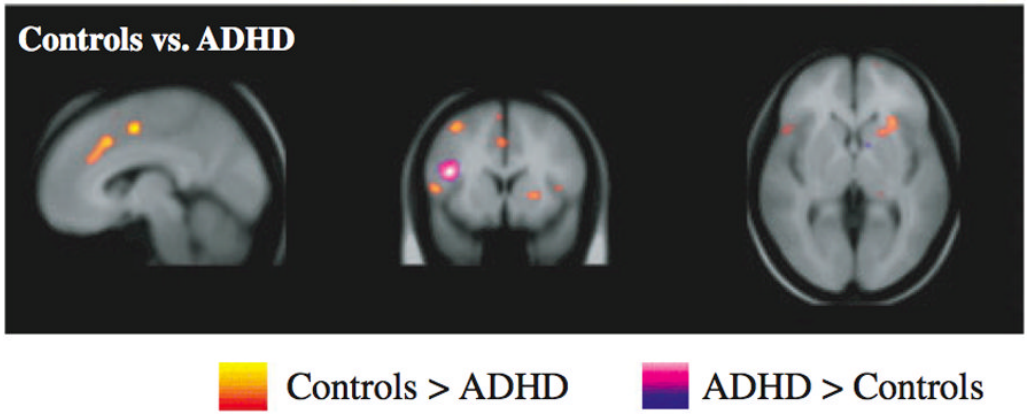


**Figure 4. Meta-Analysis Shows daMCC and CFP Dysfunction in ADHD**

Dickstein and colleagues (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 controls. CFP network abnormalities were also reported.

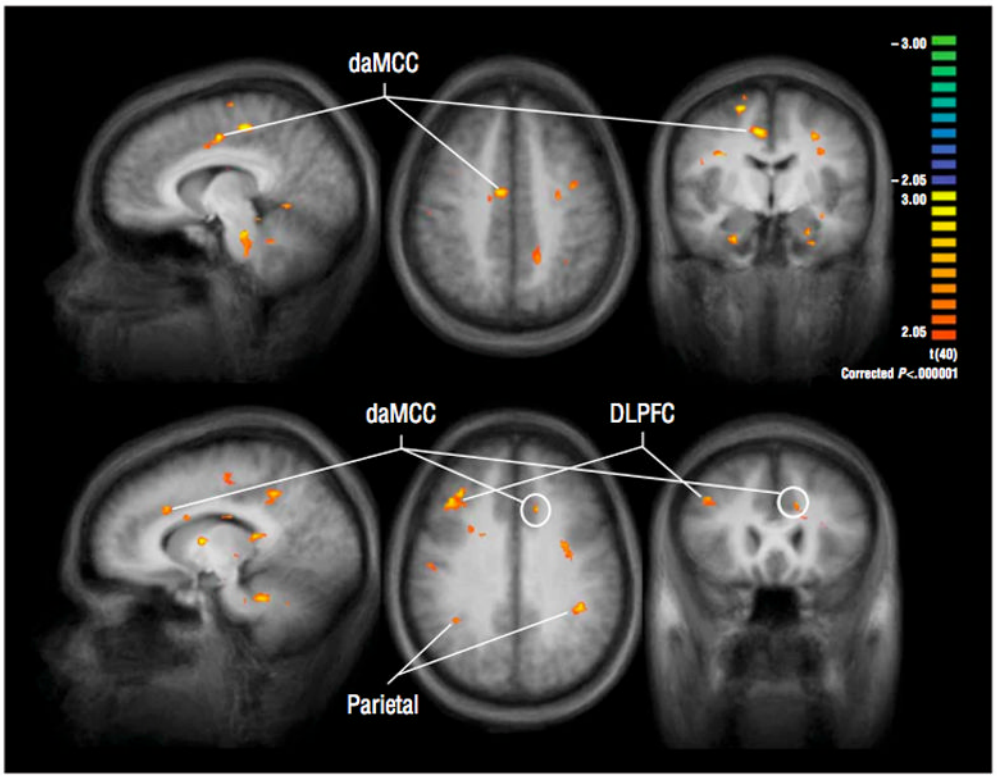


**Figure 5. Methylphenidate increases daMCC and CFP activity in ADHD**

Using the MSIT and fMRI in 21 adults with ADHD, Bush and colleagues (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 dorsolateral prefrontal cortex (DLPFC), parietal cortex and networked regions.