Neural Correlates of Executive Dysfunction in Attention Deficit Hyperactivity Disorder

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April 24, 2012
Abstract

Executive dysfunction is the defining cognitive and behavioral manifestation of ADHD. Executive functioning is largely mediated by the Cingulo-Fronto-Parietal (CFP) cognitive/attention network, which reaches into subcortical regions. Traditionally, fMRI studies have focused on individual structures of the CFP network, and have reliably found dysfunction in them—though to varying degrees of understanding. Dysfunction in subexecutive cognitive processing has also been correlated with ADHD, and has been shown to contribute to executive deficits. More recently, studies have focused on a more systems-oriented approach towards ADHD. Broader-scale connective and network dysfunction has been found to be central in ADHD pathophysiology, with mounting evidence towards its fundamental role in ADHD etiology. Broad-scale dysfunction has been found in and between the CFP network as well as other networks, such as the Default Mode Network. Dysfunction in localized brain regions may be a result of broader-scale dysfunction—pharmacotherapy is most efficacious in normalizing functional connectivity. Executive dysfunction in ADHD has many etiologies; their relevance, causality, and interrelationships have yet to be determined with certainty.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a highly prevalent neurobehavioral disorder that is a leading cause of morbidity in school-age populations. It is characterized by symptoms of inattention, hyperactivity, and impulsivity, affecting 5-10% of children and 4-6% of adults (Bush et al. 2005). ADHD is divided into three symptomatological subtypes: predominantly hyperactive-impulsive, predominantly inattentive, and combined (APA DSM-IV TR). Behavioral manifestations of ADHD vary dramatically and can even seem contradictory, especially between subtypes (Biederman 2005). Complicating things further are high rates of comorbidity (>30%) with other brain-related disorders, the most prevalent being learning disabilities, affective spectrum disorders, and autism spectrum disorders (Biederman 2005). Currently, ADHD is shown to have clear genetic, neurobiological, and environmental underpinnings, but beyond that much remains unknown. ADHD features a large number of neural correlates that range from the molecular to the systems level, but no cohesive overarching model of has been established. However, there are several correlates that are consistently implicated with ADHD. Dysfunction of catecholaminergic systems seems central to the neurochemistry of ADHD, with all approved pharmacotherapeutic agents directly modulating
dopaminergic and/or noradrenergic function. Another central feature of ADHD is the dysfunction of frontal-subcortical networks, the substrate of executive functions.

The key behavioral features of ADHD—inattention, hyperactivity, and impulsivity—are dysfunctions of cognitive processes that fall under the umbrella term of “executive functions,” which include attention, planning, inhibition, initiation, and task monitoring (Hale et al. 2007). Like other higher-level cognitive processes, the substrates of executive functions are distributed throughout the brain, but the primary structure thought to mediate executive functions is the prefrontal cortex (PFC). Executive functions can be subdivided into “cool” and “hot,” depending on whether a function involves more abstract and decontextualized processing (cold), instead of processing that involves motivation and reward (hot). ADHD subjects show deficits in “cold” and “hot” executive functions, and consequently show abnormal activation patterns in structures associated with these functions (Cubillo et al. 2011). However, dysfunction in higher-level cortical structures may not be the sole cause of executive dysfunction in ADHD, but perhaps are only resultant of dysfunction in other neural networks and structures. There is evidence for more fundamental cognitive processing deficits at the subexecutive level, along with dysfunction in the default mode network (DMN), visual networks, and motor networks (Hale et al. 2007). The past two decades have seen an exponential expansion in the understanding of ADHD, particularly due to the advent of fMRI. However, the small sample sizes of fMRI studies make them particularly vulnerable to the problems that plague all ADHD research: high levels of comorbidity, and widespread use of pharmacotherapeutic agents.

**Executive Processing**

The first neural structures found to be implicated in ADHD—and are consequently the most researched—are the structures of the cingulo-frontal-parietal (CFP) cognitive/attention network, which includes the frontostratial and frontoparietal pathways. These are thought to be the primary substrate for most executive functions, especially in attention and cognitive
regulation (Bush 2011). The main nodes of the CFP network include the dorsal anterior midcingulate cortex (daMCC), the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and the parietal cortex—all of which feature significant connectivity with affective subcortical structures, with the primary subcortical node being the striatum (Bush 2011). Not all portions of the CFP are equally relevant to ADHD; for example, the daMCC is currently the most consistently implicated structure in fMRI literature (Cubillo et al. 2012).

The daMCC, previously referred to as the dorsal anterior cingulate cortex (dACC), is thought to modulate reward-based decision making, and features significant connectivity with subcortical ‘reward pathways’ (Bush et al. 2005). This is done by integrating goal and feedback-related information from various sensory, cognitive, and affective modalities, modulating moment-by-moment adjustments in a given task. The daMCC anticipates and signals motivationally-relevant targets, encoding reward values in targets, thus playing a large role in motivational processing and novelty detection. At the executive level, the daMCC modulates response selection, response inhibition, and error detection (Bush 2011). Also, the daMCC’s high connectivity with motor corticies implicates a fundamental role in processing motor
responses (Cubillo et al. 2012). Thus, the daMCC works to increase the efficiency of decision-making and other executive functions, most prominently in the very short-term. Given its functions, dysfunction of the daMCC could produce all the symptoms of ADHD, and provides a neural substrate for one of the most paradoxical ADHD behavioral manifestations: extreme correlation of performance with the motivational value attached to a given task, where ADHD subjects can perform better than controls in tasks associated with high reward or motivation (Bush 2011).

Data from fMRI studies consistently show hypoactive daMCC activation in comparison to healthy controls in a variety of cognitive/attentional tasks. It is one of the few brain regions that consistently show hypoactive activation, both in children and adults (Bush et al. 2005). Hypoactive daMCC activation has been shown in counting stroop, stop-signal, and motor-timing tasks (Cubillo et al. 2012). Hypoactivation seems most prominent in Go-NoGo tasks, where ADHD subjects do not show activation in the daMCC, whereas healthy controls showed significant activation (Bush et al. 2005). There is also anomalous and robust activation in the DLPFC and anterior insula, which has been corroborated in a number of other studies, showing the recruitment of accessory response pathways in ADHD subjects, though further research is needed to determine the nature of this anomalous recruitment (Bush 2011). Additionally, fMRI studies that followed subjects from childhood to adulthood show that hypoactive daMCC activation stays constant with age, unlike with other neural structures (Bush 2011). Given the fine temporal resolution required to analyze daMCC function, fMRI cannot currently show all features of daMCC activation, however, daMCC single-unit and regional electrophysiological recordings in primates have contributed to models of daMCC function, further implicating its role in ADHD symptomology (Cubillo et al. 2012). fMRI data also corroborates nicely with the abnormalities seen in structural and PET imaging, particularly in distribution of dopaminergic availability (Bush et al. 2005). The correlation between daMCC hypofunction and ADHD has
essentially been calcified, but the role of daMCC hypofunction in ADHD etiology still remains unclear (Bush 2011).

Another primary node of the CFP cognitive/attention network is the lateral prefrontal cortices, specifically the DLPFC and VLPFC. These regions are thought to mediate vigilance, selective/divided attention, attention shifting, planning, and working memory functions (Bush 2011). Specifically, the VLPFC is strongly associated with behavioral inhibition. The lateral prefrontal cortices are associated with more “hot” executive functions (Rubia 2011). The lateral prefrontal cortices are strongly implicated with ADHD in non-fMRI studies, spurring fMRI research. Most prominently, a strong association has been found with anomalous thinning of the later PFC and the DRD4 7-repeat allele. The allele results in impaired functioning of the inhibitory dopamine receptor $D_4$, and is one of the strongest genetic correlates of ADHD (Bush et al. 2005). Also, anomalous structural connectivity between the lateral PFC, striatum, and parietal cortex has been established in ADHD subjects (Konrad & Eickhoff 2010). However, fMRI studies of the lateral PFC have not been as conclusive or consistent as in the daMCC; this may be a result of significantly increased anatomical variability in comparison to daMCC (Bush 2011).

In ADHD subjects, hypoactivation of the DLPFC has been seen consistently in tasks that require motor inhibition, interference inhibition, memory inhibition, sensorimotor timing, and working memory (Bush 2011). Furthermore, concurrent hypoactivation of the VLPFC is seen in tasks that require temporal processing (Cubillo et al. 2012). However, several studies have seen increased activation of the DLPFC in working memory and inhibition tasks (Bush et al. 2005). The contradictory results may result from the aforementioned anatomical variability in the lateral PFC, however there have been preliminary studies that have attempted to account for the contradictory data (Bush 2011). One study showed hypoactivation of the DLPFC during gain anticipation in a monetary incentive delay task, but hyperactivation during delay outcome (Strohle et al. 2008), but other studies have been inconclusive (Bush 2011). Anomalous
functional connectivity and the lateral PFC in ADHD subjects have also been found. In Go/NoGo tasks, anticorrelation has been found between the VLPFC, IFG, and the caudate nucleus (Konrad & Eickhoff 2012). This corroborates well with structural connectivity studies showing reduced connectivity between the lateral PFC and striatum, but further research is necessary. Anomalous activation of the lateral PFC is strongly associated with ADHD, but the nature and implications of this anomalous activation remains unclear, and further research is necessary.

The parietal cortex remains the least-studied CFP region in relation to ADHD (Bush 2011). The parietal cortex plays an important role in attention, specifically in attention allocation. Also, the parietal cortex mediates spatial processing and features polymodal sensory convergence areas (Cubillo et al. 2012). Hypoactivation of the parietal activation in ADHD subjects has been seen in a number of tasks, not all involving significant use of executive functions (Hale et al. 2007). Specifically, hypoactivation has been seen in visual oddball tasks, spatial working memory mental rotation tasks, task switching, and sequential finger tapping; thus, there is a relatively strong correlation between ADHD and abnormal parietal function (Bush 2011; Cubillo et al. 2012). However, it remains unclear whether abnormal parietal activation is a primary or secondary result of ADHD—a popular theory is that parietal hypoactivation is a result of abnormal input from other regions instead of abnormalities within the parietal cortex itself; structural and connectivity data do not correlate anomalies with ADHD as strongly as other regions of the CFP network (Konrad & Eickhoff 2012; Bush 2011). fMRI data from the parietal cortex also reveals anomalous activation in non-executive tasks, giving credence to sub-executive deficits playing a role the in executive deficits seen in ADHD—this will be discussed further in a later section of this paper (Hale et al. 2007).

The CFP cognition/attention network extends into subcortical regions, with the striatum as the primary subcortical node (Bush 2011). The striatum is the primary source of affective afferents in cortical regions of the CFP network; namely, the striatum is the source of reward, novelty, and salience that is integrated to tasks/objects in cortical regions (Rubua 2011; Cubillo
et al. 2012). Specifically, the ventral striatum is thought to act as an interface between motivation and attention (Rubia 2011). The striatum and other subcortical areas also feature significant dopaminergic and noradrenergic activity, both central neurochemical correlates of ADHD (Bush et al. 2005). In a monetary incentive delay task, hypoactivation of the ventral striatum is seen during gain anticipation during a monetary incentive delay task, but hyperactivation throughout the striatum is seen during gain outcome. In temporal discounting tasks, hypoactivation is seen in the ventral striatum and amygdala during delayed choices, but hyperactivation is seen during immediate choices (Bush 2011). Interestingly, the stratum seems particularly sensitive to slight alterations in a given task; this has been seen in a number of studies using Go/NoGo tasks (Cubillo et al. 2012). Overall, the ventral striatum displays the most prominent hypoactivation in ADHD subjects, corroborating with the functions of the ventral stratum, which are integral in ADHD symptomology (Bush 2011).

Figure 2 (Cubillo et al. 2012): Hypoactivation during a variety of executive tasks in ADHD subjects
In the most recently published reviews, there is great similarity in the postulated functions of the CFP network and its relation to ADHD. Broadly speaking, the DLPFC mediates overall planning and goal-setting, while the parietal cortex assists with target detection and attention shifts, with the VLPFC and daMCC mediating inhibition of excessive or inappropriate behavior (Bush 2011). Additionally, the daMCC integrates information from sensory, cognitive, and affective inputs and modifies behavior moment-by-moment in a trial-by-trial basis (Cubillo et al. 2012). In ADHD subjects, executive tasks tend to broadly and robustly recruit lateral areas of the CFP network that are more associated with ‘hot’ executive functions, in contrast to normal controls which feature less robust activation in specialized areas like the daMCC. In corroboration with the latest neuroimaging data, it is postulated that dysfunction within the CFP network seen in ADHD leads to inattention primarily by faulty target detection and inadequate filtering of extraneous information (Bush 2011). Additionally, impaired reward and error feedback, alongside dysfunctional encoding of motivational goals, can result in inadequate behavioral (especially motor) inhibition, and an impaired ability to pursue less salient long-term goals versus short-term goals (Bush 2011; Cubillo et al. 2012). Of course, the outlined mechanism is highly simplistic and speculative; much more research is needed to conclusively detail the relationship between the CFP network and ADHD.

Subexecutive Processing

A landmark fMRI study done by Hale et al. in 2007 aimed to decompose the role of executive versus subexecutive processing in ADHD. This study used the forwards (FDS) and backwards (BDS) digit span task; both require subexecutive cognitive processing, but the BDS requires extensive executive processing as well. Slight performance deficits were found for FDS, with significant deficits for BDS. More significantly, similar anomalous activation patterns were found for both FDS and BDS, implying cognitive dysfunction at the subexecutive level as well. Before this study, ADHD has only been thought to affect higher-level executive processing
rather than basic cognitive processing, however the relation between the two still remains unclear.

During the simpler FDS, hyperactivation was found along the ventral border of the left angular gyrus (AG), along with a left occipital region. This suggests anomalous verbal contributions to numeric processing in ADHD. Specifically, ADHD subjects seem less efficient at combining surface features of stimuli, such as visual form and phonological name codes; more ventral activation of the left AG may indicate ‘unnecessary’ processing of abstract identity codes. The FDS task also saw hyperactivation in the right hemisphere IPFC, DLPFC, posterior and midline parietal regions, implying compensatory visual/spatial processing, though increased right hemisphere activation is also associated with increased mental effort. However, ADHD subjects activated the right precuneus, which is thought to mediate attentional orientation to a mental number line. Overall, this indicates compensatory use of visual/spatial processing in simple numerical tasks as a correlate of ADHD (Hale et al. 2007).

The backwards digit span task is more complex the forwards, and requires the quick generation of internal representations to store and reorder digits. Training for this task encouraged subvocal articulation of stimuli. Hyperactivation was again seen in the left AG, but more dorsally. Also, hyperactivation is seen in Wernicke’s area. These regions are thought to mediate verbal contributions to number processing. The authors postulated that ADHD subjects has difficulty in accessing and storing internally represented information, and thus relied on physical attributes to access semantic representation. Interestingly, ADHD subjects did not show hyperactivation in the right hemisphere regions, instead failing to activate intraparietal and superior parietal regions, which are thought to generate and orient attention to a mental number line. Failure to recruit parietal regions, and their complex executive functions, may be indicative of a fundamental verbal coding deficit, resulting in the overtaxation of downstream regions that are needed transforming stimuli in working memory (Hale et al. 2007).
Overall, it seems that ADHD subjects have deficiencies in verbal processing, particularly in the access and generation of phonetically-encoded information. In the forwards digit span tasks, there is little need for executive processing, however slight performance deficits were found along with the compensatory use of visual/spatial processing in ADHD subjects. In the BDS, which requires the heavy use of executive processing, significant performance deficits were observed; executive regions were not activated, instead subexecutive regions were hyperactivated (Hale et al. 2007). The authors postulate that, in ADHD subjects, verbal processing deficits block the recruitment of executive processing regions, resulting in the compensatory use—and subsequent overtaxation—of accessory subexecutive processes. The lack of performance deficits in subexecutive tasks may be a result of the effectiveness of compensatory processing strategies, which are overtaxed with the additional burden of executive operations. The nature of the verbal processing deficits may be indicative of anomalous connectivity within verbal processing areas (Hale et al. 2007; Konrad & Eickhoff 2012). Failure to recruit executive-related parietal areas also corroborates with deficient parietal connectivity in seen in recent studies (Konrad & Eickhoff 2012; Castellanos & Proal 2012). Subexecutive deficits are apparent yet little investigated in ADHD; thus, much remains to be determined.

**Network Organization and Connectivity**

Recent advances in functional and structural neuroimaging techniques have led to a broad systems-based approach to a variety of psychiatric disorders, including ADHD. Though still preliminary, novel experimental methodologies have given more credence to the notion that dysfunction in more localized regions may just be a result of anomalous connectivity within and between a variety of neural networks. Systems-based paradigms have revealed new insights into the nature of brain regions and circuits that have traditionally been implicated in ADHD (CFP network), as well as implicating other neural systems not traditionally associated with
ADHD, such as the default mode network (DMN), visual networks, and motor networks. The largest study on ADHD functional connectivity found lower levels of connectivity within the dorsal attention network (superior parietal cortex) and DMN. Higher functional connectivity was found within reward-motivation regions (ventral stratum, orbitofrontal cortex). Additionally, the orbitofrontal cortex (salience attribution) had higher connectivity with the stratum and ACC (reward-motivation), and lower connectivity with the superior parietal cortex (attention processing) (Tomasi & Volkow 2012).

The development of resting-state fMRI paradigms along with other experimental techniques have shed much light on the default mode network (DMN), which is a neural network activated during wakeful rest, and is thought to mediate task-independent introspection—inattention (i.e. daydreaming) is a primary symptom of ADHD. Activation of the DMN is characterized by coherent neural oscillations at a rate lower than 0.1Hz. Principal structures of the DMN include the medial temporal lobe (MTL) for memory, medial temporal cortex (MPFC) for theory of mind, and the posterior cingulate cortex (PCC) for integration. The DMN is

Figure 3 (Tomasi & Volkow 2012): Short and Long-Range Functional Connectivity in ADHD versus Control Groups
deactivated during volitional tasks and is replaced by activation of the task-positive network (TPN), a primary constituent of which is the CFP cognitive/attention network (Castellanos & Proal 2012). DMN activation is strongly and consistently anti-correlated with task performance; additionally, DMN fluctuations are 180° out-of-sync with TPN fluctuations, implicating resource competition between the TPN and DMN activation during volitional tasks (Castellanos & Proal 2012).

Studies have shown that decreased DMN coherence and decreased DMN suppression is consistently correlated with ADHD (Konrad & Eickhoff 2012). Also, intrusion of DMN-like activation patterns has been seen during episodes of performance variability in ADHD subjects; high levels of performance variability is characteristic of ADHD (Tomasi & Volkow 2012). Additionally, increased levels of DMN suppression is positively correlated with motivation and incentive in a task (Castellanos & Proal 2012). Decreased anti-correlation between the DMN and a variety of TPN structures is seen, most prominently in the putamen and daMCC, however the putamen has not seen significant research (Konrad & Eickhoff 2012).

Hypoactivation of the daMCC has been strongly implicated in ADHD pathogenesis, and is a primary component of the TPN. Hypoactivation of the daMCC in conjunction with hyperactivation of DMN structures during cognitive tasks is seen consistently in ADHD subjects in a number of studies (Tomasi & Volkow 2012). Additionally, spontaneous increased DMN activation and reduced daMCC activation is temporally consistent with performance variation in a battery of cognitive tasks. Decreased daMCC-PCC anti-correlation is one of the most prominent DMN correlates in ADHD subjects (Konrad & Eickhoff 2012). The strength of daMCC-PCC anti-correlation has been positively correlated with task performance. In controls, the strength of the anti-correlation between the daMCC and PCC increases with age, however this does not seem to occur in ADHD subjects. Similar findings are seen between the daMCC and MPFC, another prominent DMN structure, though temporal correlation between performance variability has only been seen in working memory tasks. The daMCC-MPFC correlation was
once controversial, but has now been shown to be most prominent in ADHD children, normalizing with age starting during adolescence. Decreased anti-correlation between the daMCC, left MTL, and precuneus has also been seen, but remains the least investigated (Sun et al. 2012).

Abnormalities within the DMN and between the TPN have been firmly established in the pathophysiology of ADHD. However, many studies examining DMN and ADHD have been contradictory, such as when investigating whether DMN itself is deficient, or whether other networks are deficient (Castellanos & Proal 2012; Konrad & Eickhoff 2012). Much remains to be investigated about the role of DMN in ADHD. More generally, there is substantial evidence that connective dysfunction is significant in the etiology of ADHD. For at least some of the localized functional abnormalities associated with ADHD, connective dysfunction has been implicated as the root cause. Considering the distributed nature of cognition, more systems-based approaches in ADHD research would be prudent.

**Pharmacotherapy**

Several fMRI studies have been conducted on the effects of methylphenidate in ADHD subjects. Methylphenidate is the most common ADHD pharmacotherapeutic agent, and is classified as a psychostimulant that acts as a norepinephrine-dopamine reuptake inhibitor, raising levels of both neurotransmitters throughout the brain (Biederman 2005). Methylphenidate has fairly strong

![Figure 4 (Bush 2011): Methylenidate-induced normalization in activation of cortical structures](image)
efficacy in ADHD subjects, with 50-70% displaying significant symptom reduction (Bush 2011). The effects of methylphenidate, in current studies, are most obvious in regions associated with the CFP network. Methylphenidate consistently normalizes activation in the daMCC, DLPFC, VLPFC, parietal cortex, caudate, thalamus, and temporal lobe in a battery of executive-related tasks (Bush 2011). Several studies have concluded methylphenidate’s normalization of functional connectivity—which is seen in a variety of neural networks—as its primary mechanism of action in achieving efficacy, as its normalizing effects seem more prominent in functional connectivity rather than in the activation of individual brain areas (Tomasi & Volkow 2012). Moreover, functional connectivity is most normalized in areas with significant connectivity to the default mode network (DMN) (Sun et al. 2012). Normalized DMN suppression is seen only during high-incentive tasks, but not low-incentive tasks in ADHD subjects using Go/NoGo tasks. When the ADHD subjects were given methylphenidate, normalized DMN suppression was seen regardless of incentive level (Rubia et al. 2009). It is important to note that methylphenidate does not normalize all patterns of activation in the CFP network, for example, methylphenidate does not correct deficits in cingulo-parietal functional connectivity (Konrad & Eickhoff 2012). It is clear that methylphenidate achieves efficacy at least in part by normalizing activation within regions of the CFP network as well as normalizing functional connectivity across the cortex. However it is still unclear as to how methylphenidate’s neurochemical mechanism of action translates to normalization, as not all of its effects correlate with regions with significant catecholaminergic activity (Bush 2011).

**Conclusion**

Dysfunction in localized regions of the CFP network is integral to the pathophysiology of ADHD, manifesting in faulty target detection and inadequate filtering of extraneous information, impaired reward and error feedback, alongside dysfunctional encoding of motivational goals. Behaviorally, this results in inadequate behavioral inhibition, and an impaired ability to pursue
less salient long-term goals versus short-term goals. However, localized dysfunction of the CFP network may only be resultant of dysfunction elsewhere in the brain. Subexecutive deficits in ADHD subjects are characterized by verbal coding deficits that lead to compensatory strategies that recruit—and subsequently overtax—alternate processing mechanisms, including executive functions. Broader-scale network and connective dysfunction has been found consistently in ADHD subjects. Particularly, anomalous functional connectivity with the DMN leads to spontaneous disruptions in cognitive processing: performance variability. Pharmacotherapeutic agents normalize much—but not all—of the anomalous activation found in ADHD subjects, particularly in functional connectivity. Executive dysfunction in ADHD has many neural correlates; however, their relevance, causality, and interrelationships have yet to be determined with certainty. Functional imaging technologies have been instrumental in advancing the understanding of ADHD, and will likely play a key role towards the discovery of fundamental etiologies of the disease.
References


