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Attention-Deficit/Hyperactivity Disorder and Attention Networks

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Research attempting to elucidate the neuropathophysiology of attention-deficit/hyperactivity disorder (ADHD) has not only shed light on the disorder itself, it has simultaneously provided new insights into the mechanisms of normal cognition and attention. This review will highlight and integrate this bidirectional flow of information. Following a brief overview of ADHD clinical phenomenology, ADHD studies will be placed into a wider historical perspective by providing illustrative examples of how major models of attention have influenced the development of neurocircuitry models of ADHD. The review will then identify major components of neural systems potentially relevant to ADHD, including attention networks, reward/feedback-based processing systems, as well as a 'default mode' resting state network. Further, it will suggest ways in which these systems may interact and be influenced by neuromodulatory factors. Recent ADHD imaging data will be selectively provided to both illustrate the field's current level of knowledge and to show how such data can inform our understanding of normal brain functions. The review will conclude by suggesting possible avenues for future research.
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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric disorder that is characterized by developmentally inappropriate symptoms of inattention, impulsivity, and motor restlessness. With an estimated prevalence of ∼5 to 8% in children, ADHD is among the most common childhood neurobehavioral disorders, and frequently persists into adolescence and adulthood (Biederman and Faraone, 2005; Faraone and Biederman, 2005; Faraone et al, 2006; Mick et al, 2004). Given the established increased morbidity associated with ADHD, including impaired academic, occupational, and social functioning, increased rates of substance abuse, traffic accidents, persistent neuropsychological impairments, and the attendant increased costs to society (Biederman, 2004; Donnelly et al, 2004; Guevara et al, 2001; Secnik et al, 2005; Vos et al,

2005), determining the underlying neural substrate of ADHD is of great import.

Convergent data from various sources, including neuroimaging, neuropsychological, genetics, and neurochemical studies, have generally implicated fronto-striatal network abnormalities as contributing to ADHD (Bush et al, 2005; Durston, 2003; Giedd et al, 2001; Kelly et al, 2007; Schneider et al, 2006; Vaidya and Stollstorff, 2008; Zametkin and Liotta, 1998). Functional imaging studies on ADHD, in particular, have increased almost exponentially over the past decade. As a crude measure, a recent functional imaging review (Bush et al, 2005) included 34 functional imaging studies, whereas a current PubMed search combining the terms 'ADHD and imaging' returned 650 results, with more than 80 papers published in the last year alone.

Given this burgeoning body of research on the neurobiology of ADHD, this review cannot be comprehensive, nor for the most part will it specifically critique individual articles. Instead, it will focus on identifying major themes within the extant ADHD literature. It will then seek to place these issues within a larger framework that shows how cognitive and affective neuroscience influences have helped shape ADHD research, and in turn how ADHD research has

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led to an improved understanding of human brain functions. This dynamic, bidirectional flow of information will be important to future progress on both fronts.

Specifically, the review begins with admittedly reductionistic introductions of the clinical phenomenology and conceptualizations of ADHD, offered to help lay a foundation for subsequent sections on neural systems relevant to ADHD. These are followed by examples of how cognitive neuroscience models of attention have influenced the development of neurocircuitry-based models of ADHD. For example, major components of neural systems potentially relevant to ADHD—such as directed attention networks, a proposed 'default mode' network of the brain, and reward/motivation regions—will be identified. ADHD-related imaging data are then selectively reviewed, highlighting emerging themes and advances. Some structural imaging studies will be mentioned, including morphometric/volumetric magnetic resonance imaging (MRI), cortical thickness analyses, and diffusion tensor imaging (DTI) of white matter connections. Functional studies include mainly positron emission tomography (PET) or functional MRI (fMRI). Neurochemical studies include magnetic resonance spectroscopy (MRS) studies. Brief mention is then made of ways in which these systems can be modulated by neurochemical influences such as dopamine. Finally, the review concludes with some suggested possible directions for future research.

Clinical Features

ADHD is a developmental syndrome whose cardinal signs are inattention, impulsivity, and hyperactivity. ADHD, per DSM-IV-TR (American Psychiatric Association, 2000), currently encompasses multiple forms of the disorder, including an inattentive form, a fairly rare purely hyperactive form, and a combined type that is the most common form and features both inattention and hyperactivity. Inattention, or the inability to direct and maintain selective attention to motivationally relevant tasks, is a key feature of the disorder. Impulsivity refers to acting rashly without apparently thinking of the consequences, such as blurting out answers in class. Hyperactivity refers specifically to excessive motor activity.

Beyond these cardinal signs, many difficult-to-quantify associated signs of ADHD exist. For example, disorganization is frequently cited as one of the main indicators of inattention. However, 'disorganization' can be produced in many different ways. Disorganization can result from poor general motivation or can reflect an impaired ability to value long-range goals over short-term rewards. Even when patients are motivated, disorganization can arise from an inability to plan ahead and order the necessary steps to accomplish the goal. Apparent disorganization could also result from poor working memory skills that impair the ability to maintain goals and/or plans in mind, or it could be produced by an inability to adjust behavior to meet changing contingencies.

To complicate matters further, in addition to diagnostic subtype heterogeneity, there is the oft-observed impression that ADHD patients can show a great deal of intra-individual variation in performance depending on the task and motivational state. ADHD patients may excel at some tasks and may even appear 'hyperfocused' if greatly interested in a task, but in other settings performance may fluctuate rapidly. Moreover, although many ADHD patients have persistent deficits on formal neuropsychological tests, many others show none (Seidman *et al*, 2004a). ADHD patients may be socially adept, or may display decreased frustration tolerance, increased social isolation, and affective instability.

Here especially it is crucial to always bear in mind that ADHD is a *developmental* disorder. This has at least two important ramifications. First, attempts to study ADHD must view ADHD in the context of what is developmentally appropriate and account for age-related changes in the neurobiology of patients at different ages. Stated another way, the neural structures and functional capacity of children, adolescents, and adults vary in both healthy humans and those with ADHD, which complicates intergenerational comparisons. Second, genetically mediated neuronal deficits can lead to secondary functional/psychological impairments that may not necessarily arise directly from primary neural insults. For example, inattention can make it difficult for a child to learn the basic educational skills that lay the foundation for good school performance, which can lead to subsequent anxiety, depression, poor self-esteem, and acting out for attention in a dysfunctional spiral. These affective and behavioral sequelae may have their own effects on neural structures and function that will need to be disentangled from any primary insult. Finally, it should be noted that although diagnostic schemes focus on impairments associated with ADHD, there are arguably likely to be positive aspects of having ADHD—such as increased creativity, novel problem-solving abilities, and possibly greater passion for tasks that interest people with ADHD—that have led to ADHD's persistence over time in humans. Thus, it is difficult to identify which of these processes may be 'core features' of ADHD, and which may emerge as secondary sequelae or comorbidities. However, major points that can be gleaned from this brief clinical overview are (1) that ADHD is diagnostically, developmentally, and neuropsychologically heterogeneous; (2) despite this clinical complexity, it is possible to identify different cognitive, motor, and emotional processes that might, if altered, contribute to ADHD symptomatology; and (3) that testable neural circuitry models can be constructed from these observed clinical features.

Disentangling these issues has important ramifications not only for ADHD but also, in turn, for understanding normal cognition, emotion, and motivation. Myriad dysfunctional processes could potentially contribute to ADHD. These could include abnormalities of neural responses underlying anticipation or planning of actions, target selection, filtering of distracting information, working

memory, response selection and/or inhibition, novelty detection, error signaling, reward evaluation, and feedback-mediated decision-making processes. Thus, research must first identify the neural circuitry that underlies these processes in healthy humans, and then subsequently test the integrity of these pathways in patients with ADHD.

For example, inattention can be produced in a number of ways that can be amenable to testing through functional and structural neuroimaging. Attention dysfunction might result from impaired target selection processes. Alternatively, inadequate filtering ability might allow excessive amounts of distracting information to interfere with the processing of relevant stimuli. Patients with ADHD might be able to select relevant information normally, but motivational deficits or working memory problems might preclude them from being able to maintain focus for long enough periods of time to act on the information. It is possible that central evaluative dysfunction could interfere with the normal ability to link rewards or errors with actions. Such an inability to translate motivational information into appropriate behaviors is likely to be an important part of ADHD, and could explain the observation that patients with ADHD can perform well on interesting tasks, but show inabilities to perform on tasks that are deemed boring or irrelevant. Similarly, impulsivity and/or hyperactivity could be produced by impairments of brain regions that have roles in inhibiting undesired or inappropriate motor behaviors.

In return, each study of ADHD—when viewed as a type of 'natural lesion study'—provides a window on normal cognitive, emotional, motor, and/or motivational brain processes. As dysfunction of many different interacting brain regions could have roles in the pathophysiology of ADHD, studies on ADHD have great relevance to cognitive and affective neuroscience. In these ways, studies on ADHD provide important bidirectional flows of information about multiple brain regions that clarify our understanding of neural function in both clinical and healthy populations.

Conceptualizations of ADHD

Over the past century, the conceptualizations of ADHD have varied, as have the hypothesized explanations for the inattention and disruptive behaviors associated with it. Early accounts of an ADHD-like syndrome (Still, 1902) focused on volitional impairments, attributing the disorder to impaired abilities to inhibit voluntary acts and defects of moral regulation. As reviewed elsewhere (Barkley, 1990; Werry, 1992), based in large part on non-rigorous scientific methods, an ADHD-like syndrome was for a time viewed non-specifically as minimal brain damage. Later, emphasis was placed on the primacy of hyperactivity (Chess, 1960; Denhoff et al, 1957; Laufer and Denhoff, 1957). The work by Douglas (1988)through the 1970s and 1980s then argued for a greater recognition of the role poor-sustained attention and impulse control played, along with reports of preferences for immediate reinforcers, and eventually concluded that the core deficiencies were linked to central impairments of self-regulation.

A number of cognitive psychology-based causal models have been offered to account for the clinical presentation of ADHD. A landmark paper that helped to transition toward more modern conceptualizations of ADHD by Barkley (1997) posited that the core problem in ADHD lay in dysfunctional behavioral inhibition. The theoretical model linked this dysfunction to impairments of four executive neuropsychological functions, namely working memory, regulation of affect–motivation–arousal, internalized speech, and reconstitution (higher level analysis of behavior). Importantly, although some argue with the conclusion that the inattention of ADHD should be viewed not as a primary symptom, but rather as a secondary manifestation of poor behavioral inhibition and cognitive interference control, this paper also helped drive the field forward by helping to establish testable hypotheses and to integrate the similar conceptualizations of prefrontal cortical functions advocated by Bronowski (1977) and Fuster (1989) into his framework.

Quay (1988) viewed the main problem as an imbalance between behavioral activating and inhibiting systems, arguing that ADHD was caused by underactivity of the behavioral inhibition system. Others (Schachar et al, 2000) have discussed how impulsivity and/or hyperactivity could be produced by impaired inhibition of undesired or inappropriate motor behaviors. Sergeant (2000, 2005) have proposed a cognitive-energetic model that details how the dysfunctional interplay of top-down and bottom-up processes at three levels (computational mechanisms of attention, state factors, and executive functions) could impair the overall efficiency of information processing in ADHD.

Sonuga-Barke and colleagues have pointed out a number of challenges for the exclusive executive function system abnormality frameworks of ADHD, such as that proposed by Barkley, and have instead advocated a dual-pathway conceptualization (Sonuga-Barke, 2003; Sonuga-Barke and Sergeant, 2005; Sonuga-Barke et al, 2008). This dual-pathway account combines meso-cortically mediated executive function deficit concepts with a motivation-based account that implicates dysfunction of reward circuitry. Specifically, impaired delay aversion in some ADHD patients, presumably caused by defects in the meso-limbic modulation of reward-sensitive areas such as the ventral striatum and nucleus accumbens, leads ADHD patients to attempt to escape or avoid delay. Although Sagvolden et al's (2005) dynamic developmental behavioral theory similarly emphasizes the role of delay aversion in its explanation of the hyperactive and combined types of ADHD, Sonuga-Barke's more broad-based model views his proposed dual pathways as complimentary, rather than competing, accounts of multiple subtypes of ADHD (inattentive, hyperactive, and combined). Nigg and Casey's (2005) view of combined-type ADHD extends this type of neuronal modeling by additionally drawing in frontocerebellar

dysfunction to explain timing deficits and frontoamygdalar abnormalities as the substrate of affective problems. The above papers and reviews have discussed some of implications for the various frameworks on our understanding of the pathophysiology of ADHD (Castellanos *et al*, 2008; Coghill *et al*, 2005; Sonuga-Barke *et al*, 2008; Swanson *et al*, 1998; Tannock, 1998). Overall, although parsimonious models are preferred if appropriate, in the case of ADHD it is most likely that broader, more inclusive models akin to those offered by Sonuga-Barke (2005) and Nigg and Casey (2005) will offer a better explanation of the complex and heterogeneous clinical presentations of ADHD subtypes.

Cognitive Neuroscience Influences Relevant to ADHD Research

The field of cognitive neuroscience—with its search for the neurobiological substrates of component brain processes of cognition, attention, working memory, and motor control—has had an enormous effect on the current conceptualizations of ADHD. Although a detailed review comparing and contrasting different cognitive models, such as offered elsewhere (Posner, 2004), is beyond the scope of this paper, a few major influences on ADHD research can be identified.

One of the earliest and most influential cognition-related theories that attempted to explain selective attention was 'selection for action' (Allport, 1980, 1987; Posner and Petersen, 1990). This model sought to connect the modulation of attention and target identification with response selection. Specifically, it posited that attention would be selectively focused on target stimuli that were relevant to a response selection. Selection for action did not, however, *require* that an actual motor response be made, but could refer to an internally represented decision. Norman and Shallice (1986) referred to this form of attention as 'supervisory,' and suggested that it was used whenever processing of non-routine information was required. Furthermore, this form of attention was distinct from simple sensory orienting, and seemed to reflect a high level of cognitive control (Posner and Rothbart, 1998).

The review paper by Posner and Petersen (1990) on the attention system of the brain has been particularly influential. This model proposed that the 'attention system' was composed of three anatomically distinct but interacting network subsystems that influenced lower information processing modules. The three subsystems were those of orienting, detecting, and alerting/vigilance. Orienting referred to sensory processes such as visual foveation of a stimulus, and was proposed to rely on the parietal cortex, superior colliculus, and pulvinar/thalamus. The detection subsystem or 'anterior attention system' consisted of the anterior cingulate cortex (ACC) and lateral prefrontal cortex, and was posited to be responsible for detecting targets that would undergo further information processing. The alerting system, encompassing the noradrenergic locus coeruleus influences on mainly right hemisphere structures,

was responsible for maintaining general vigilance. Early PET studies on attention and vigilance by Pardo *et al* (1990) supported the framework of Posner and Petersen (1990) : performance of a Stroop selective attention task-activated ACC, whereas a vigilance task-activated right lateral prefrontal and parietal cortex did not activate the ACC (Pardo *et al*, 1991). On the basis of, in part, this framework, Corbetta *et al* (1991) concluded that the ACC modulated the lower visual area activity during a divided attention task, and Raichle *et al* (1994) implicated the ACC as supporting novelty processing. Later, Corbetta (1998) and Corbetta *et al* (1998) expanded examination of these systems, identifying roles for frontal and parietal regions in attention. Together, these studies attempted to outline neurally plausible mechanisms for attention that stressed that regulation of subservient brain areas might depend on the degree of cingulo-fronto-parietal (CFP) activation. More recent functional imaging evidence has also supported Posner and Petersen's three-module framework and started to link these brain findings to genetic influences (Fan *et al*, 2003, 2005; Fan and Posner, 2004). Certainly, the selection-for-action influence (Holroyd, 2004), directly or indirectly, was evident in many subsequent papers involving a large variety of motor response selection tasks relevant to ADHD, including modality-specific motor choice (Paus *et al*, 1993), motor control/monitoring, and/or willed action (Badgaiyan and Posner, 1998; Liddle *et al*, 2001; Luu *et al*, 2000; Picard and Strick, 2001; Turken and Swick, 1999), Stroop and Stroop-like tasks (Bush *et al*, 1998; Pardo *et al*, 1990), and tasks involving the over-riding or inhibition of prepotent responses such as go/no-go, stop-signal, or countermanding tasks (Alderson *et al*, 2007; Aron *et al*, 2003; Durston *et al*, 2003a; Ito *et al*, 2003; Kawashima *et al*, 1996). Although lacking in the full, necessary precision desired for a complete mechanistic account of attention, selection for action helped pave the way for studies trying to link brain processes with attention and ADHD.

CFP Attention Network

On the basis of these studies and the wider cognitive neuroscience literature, imaging studies attempting to identify the pathophysiology of ADHD logically searched for abnormalities of brain regions that are normally involved in attention, cognition, executive function, motor control, response inhibition, working memory, and/or reward/motivation. As detailed below, this line of thinking led researchers to gravitate toward studies on the dorsal anterior midcingulate cortex (daMCC), dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and parietal cortex. Although the cingulate cortex nomenclature has been revised as the field has matured, it is noted here that the term 'daMCC' refers to essentially the same region of the cingulate cortex that was referred to previously as the ACC or as the dorsal ACC in many contemporary references (Bush, 2009; Vogt, 2005; Vogt *et al*, 1992). Together, these regions comprise the main
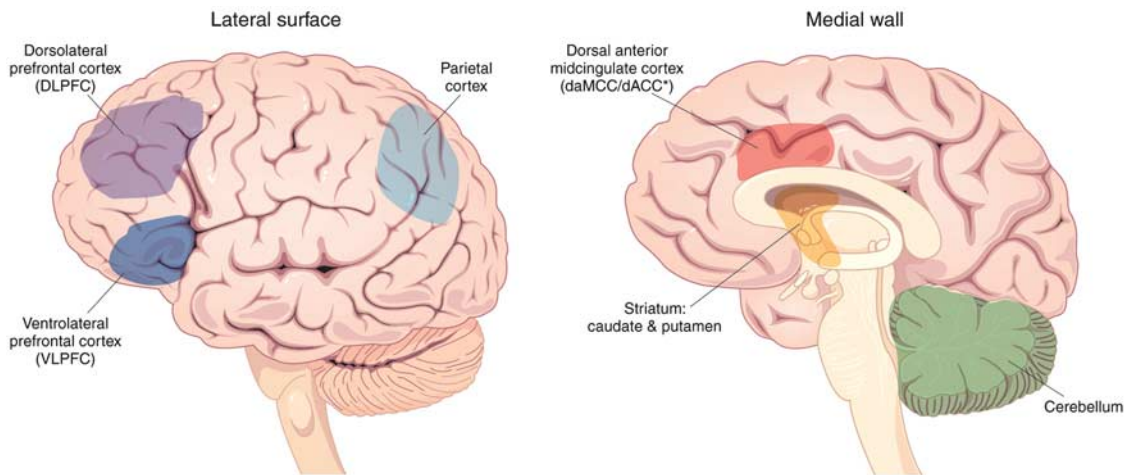
Figure 1. Brain structures implicated in ADHD. Interacting neural regions have been implicated in ADHD. In particular, the dorsal anterior midcingulate cortex (daMCC), dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), parietal cortex, striatum, and cerebellum—all key elements of cognitive/attention networks—have also been found to display functional abnormalities in multiple studies of ADHD.

components of the CFP cognitive–attention network. These areas, along with the striatum, premotor areas, thalamus, and possibly cerebellum, have been identified as nodes within parallel networks of attention and cognition (Alexander *et al*, 1986; Berman and Colby, 2008; Cabeza and Nyberg, 2000; Colby, 1991; Colby and Goldberg, 1999; Duncan and Owen, 2000; Goldman-Rakic, 1988; Mesulam, 1981, 1990, 1999; Morecraft *et al*, 1993; Posner and Petersen, 1990; Posner and Rothbart, 1998) (Figure 1).

The above heuristic characterization is admittedly an over-simplified framework that is presented insofar, as it can be useful in helping to integrate new information. Many of the brain 'regions' listed above encompass multiple functional subdivisions and participate in several different information processing calculations. Clearly, a single abnormality of any one region alone does not cause ADHD. The following will provide some representative examples of the logic that drove some ADHD studies to specifically focus on some of these areas. For example, although the CFP network has been central to many studies, a number of studies have focused on the striatum, which not only participates in attention functions but also has crucial roles in motivation/reward processing. This will be followed by the offering of a few examples of complicating factors that preclude straightforward linking of imaging results with defined pathophysiological processes. After this basic foundation is laid, some representative examples of recent advances in ADHD imaging will be highlighted.

Prefrontal cortex. One of the main findings from a pioneering ADHD PET imaging study by Zametkin *et al* (1990) was that of *global* underactivity, with global cerebral glucose metabolism reported as 8.1% lower in ADHD patients than in healthy controls. This study also found that the ADHD group showed regional hypoactivity of attention and motor control areas including the daMCC, superior

prefrontal cortex, and premotor cortex. Most ADHD imaging studies have sought to identify localized brain dysfunction, and the prefrontal cortex was one of the first areas to be studied, because of similarities between patients with ADHD and those with frontal lobe injuries (Barkley, 1997; Barkley *et al*, 1992; Mattes, 1980). Structural imaging studies on ADHD have identified both significantly smaller global cerebral volumes of $\sim$3 to 4% in ADHD, as well as specifically smaller prefrontal volumes in ADHD (Seidman *et al*, 2004b; Valera *et al*, 2007). Some functional investigations extended beyond the frontal lobes, hypothesizing insufficient frontal cortical inhibitory control (Casey *et al*, 1997a, b; Satterfield and Dawson, 1971); a view that drew support from studies on stimulant medications and animal models that have implicated dopaminergic and noradrenergic influences on the prefrontal cortex (Arnsten and Dudley, 2005; Brennan and Arnsten, 2008; Shaywitz *et al*, 1978). Over time, better characterization by cognitive neuroscience of the specific roles that the prefrontal cortex plays within distributed networks of brain regions underlying attention, cognition, and behavioral self-regulation (Cabeza and Nyberg, 2000; Fuster, 1989; Goldman-Rakic, 1988; Posner, 2004; Posner and Petersen, 1990) has led to refined searches for dysfunction in various subdivisions of the prefrontal cortex (Bush *et al*, 2005; Denckla, 1989; Sergeant *et al*, 2002). Specifically, researchers began by focusing on the DLPFC and VLPFC, as these regions are believed to support vigilance, selective and divided attention, attention shifting, planning, executive control, and working memory functions (Duncan and Owen, 2000; Posner and Petersen, 1990). Also, the VLPFC in particular has been associated with behavioral inhibition, as evidenced by its activation using stop-signal tasks (Aron *et al*, 2003; Rubia *et al*, 1999). Together, these findings have made the prefrontal cortex a prime candidate for study by ADHD researchers.

It can be noted that, although the orbitofrontal cortex (OFC) is crucially important to reward processing and motivation, and OFC lesions have been associated with social disinhibition and impulse control problems (Hesslinger *et al*, 2002), OFC has unfortunately remained a relatively understudied prefrontal region. This is likely because of, in part, the generally wider interest in DLPFC functioning, and possibly in part because of the fact that fMRI of OFC is complicated by the well-known high frequency of susceptibility artifacts in this region. OFC thus represents an opportunity area for bidirectional influence, as the need to better understand reward circuitry contributions to ADHD should spur interest in developing refined fMRI methods to image areas such as OFC that are prone to susceptibility artifacts. The use of such methods will help identify potentially dysfunctional reward circuitry in ADHD.

daMCC: cognition/attention and reward. The daMCC, located on the medial surface of the frontal lobe, refers to areas 24c′/32′ in humans. The nomenclature of cingulate subdivisions has evolved over the past few decades (Bush, 2009; Bush *et al*, 2008; Vogt, 2005): for simplicity here, the daMCC is equivalent to the dorsal ACC (Bush and Shin, 2006; Bush *et al*, 2002) and broadly consistent with the older term, the ACC, used by studies above (Alexander *et al*, 1986; Posner and Petersen, 1990). The daMCC maintains strong reciprocal connections with other cognitive/attention and motor regions, including the DLPFC, parietal cortex, premotor cortex, and striatum. Although much attention has been paid to the lateral prefrontal cortex, the most consistent cross-study and cross-modality data identifying a region as dysfunctional in ADHD have been provided for the daMCC (Bush, 2009). The daMCC has 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 through its primary role in feedback-based decision-making. As detailed elsewhere (Bush, 2009; Bush *et al*, 2002; Williams *et al*, 2004), this feedback-based decision-making conceptualization of the daMCC is based on compelling evidence from single-unit studies in monkeys and humans, as well as on human neuroimaging studies. In essence, it states that the daMCC encompasses a local intracortical network comprised of functionally heterogeneous cells. These cells variously anticipate and signal motivationally relevant targets, indicate novelty, encode reward values, signal errors, and influence motor responses. The daMCC's roles in attention and cognition are to integrate goal and feedback-related information from various sources and then to use 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.

Again, the daMCC is but one component of reward circuits that include the striatum, nucleus accumbens, and OFC (Galvan *et al*, 2005; Haber and Brucker, 2009; Schultz *et al*, 2000; Ullsperger and von Cramon, 2003); just as it is a component of CFP cognitive–attention networks. Given this, daMCC dysfunction could directly and/or indirectly lead to all of the cardinal signs of ADHD (inattention, impulsivity, and hyperactivity), and could explain the observation that ADHD subjects can perform well when motivated on some tasks, but may perform poorly when the task is not interesting. As will be discussed below, numerous functional, structural, neurochemical, and pharmacological imaging studies have identified abnormalities of the daMCC in ADHD.

Parietal cortex. The parietal cortex has key roles in attention allocation and encompasses polymodal sensory convergence areas (Corbetta, 1998; Corbetta *et al*, 2000; Culham, 2002; Culham and Kanwisher, 2001). Although the parietal cortex has been the *a priori* focus of relatively few ADHD functional imaging studies, it has been identified as displaying altered function in ADHD. Although this may reflect abnormal input from regions connected to the parietal cortex, some structural (cortical thickness) abnormalities in the parietal cortices of those with ADHD would suggest that the functional abnormalities do have a role in ADHD pathophysiology.

Striatum. Similar to the cingulate and lateral prefrontal cortex, the striatum also has multiple roles relevant to ADHD. The striatum contains key components of separable, parallel-distributed circuits that support executive and motor functions (Alexander *et al*, 1986), reward processing, and decision-making (Haber, 2003; Schultz, 2006). Haber's spiraling circuits model (2003)—which discusses how PDP subsystems can have separate but interacting properties—has particular relevance to ADHD, as it was used as a framework that illustrates dissociable striatal contributions to ADHD. Specifically, Castellanos *et al* (2006) postulate that executive function deficits will be linked with the anterior striatum, DLPFC and daMCC dysfunction, whereas delay aversion symptoms will be tied to dysfunction of motivational/reward areas including the ventral striatum and orbitomedial prefrontal cortex. Pursuit of the answers to these questions represents a true opportunity for bidirectional influences in research, for if these predictions are borne out, then they will not only help determine ADHD pathophysiology but will also shed light on striatal contributions to normal executive functions and reward processing.

As reviewed elsewhere, morphometric MRI studies have frequently reported caudate volumetric abnormalities (Giedd *et al*, 2001; Seidman *et al*, 2005; Valera *et al*, 2007). Over the past decade, numerous studies have focused on the role dopamine may play in both the pathophysiology

of ADHD and the mechanisms of action of medications used to treat ADHD. Owing to technical characteristics of the techniques used to study dopamine, much of this literature has been limited to te striatum. Also, a number of functional imaging studies have identified striatal abnormalities in ADHD. Coupled with the structural and dopaminergic data, and the growing understanding of striatum's role in reward/motivation, these collected fMRI study results will continue to make the striatum a prime target of future imaging studies.

Other regions. Other brain regions, including the cerebellum, superior temporal sulcus, thalamus, and the brain stem reticular activating system, have not been the main focus of many functional imaging studies on ADHD to this point, but this is slowly changing. Reasons vary for the relative neglect of these areas. Regarding the cerebellum, it has only more recently been recognized as contributing to cognitive functions beyond its role in modifying motor output, thus there have been fewer tasks devoted to determining whether and how it is associated with ADHD. The thalamus and the brain stem reticular activating system, which help modulate attention and filter interfering stimuli (Vogt and Gabriel, 1993), can be difficult to image because of susceptibility artifacts and greater pulsatile motion. Future studies will be improved by refined understanding of the specific functions of these brain regions and by continued improvements in imaging techniques that will permit better testing of these regions.

Parallel Distributed Processing

Another example of bidirectional influences is the intertwined cognitive science neural modeling and computer modeling that has occurred in the past half-century. Cognitive neuroscientists were proposing models of cognition and brain functions that emphasized the parallel-distributed processing (PDP) nature of component neurons. These concepts were directly and indirectly drawn from computer neural PDP network models that themselves were inspired by attempts to model biological neural systems (McClelland *et al*, 1986; Rumelhart *et al*, 1986).

Seminal cognitive neuroscience work in this area was contributed by Alexander *et al* (1986), who offered a segregated, basal ganglia-thalamocortical circuitry model supporting functions including motor and oculomotor control, spatial memory, and limbic functions, and by Goldman-Rakic (1988), who laid out PDP model of brain regions supporting cognition. Others have provided PDP models that variously focused on attention (Mesulam, 1990, 1999), orienting and eye movements (Corbetta *et al*, 2002, 2008), parsing of top-down control and reorienting attention subsystems (Fox *et al*, 2006), spatial attention (Colby, 1991; Mesulam, 1981), spatial–motor systems (Colby and Goldberg, 1999), memory (Mesulam, 1990), and computer simulations of attention and effortful processing (Dehaene *et al*, 1998).

A recent paper that used sophisticated event-related fMRI and functional connectivity analyses to parse different elements of proposed interacting PDP subnetworks of attention responsible for expectancy, shifting attention, and reorienting (Shulman *et al*, 2009). Specifically, separable attention subnetworks were found to support the maintenance of attention on a target, cued shifts of attention, and reorienting to an unexpected target. Study designs such as this one, or the Attention Network Test (Fan *et al*, 2002), which was designed to identify separate alerting, orienting, and executive attention subnetworks, may help identify specific attention subsystem abnormalities in ADHD. Together with the earlier study of Posner and Petersen (1990), these PDP network papers have combined to identify many of the networked brain regions that have now been implicated in normal attention and motor control, as well as in the pathophysiology of ADHD, such as the daMCC, DLPFC, VLPFC, right temporoparietal junction, striatum, and parietal cortex.

Resting/Default State and Cognition–Emotion–Vigilance Interactions

Recently, studies on 'resting brain' activity have provided complementary information to data produced using cognitive activation paradigms. As will be shown, ADHD theorists have begun to hypothesize and examine how abnormalities of brain systems that normally subserve the resting state and vigilance functions may intrude upon and disrupt attention systems in ADHD (Sonuga-Barke and Castellanos, 2007; Weissman *et al*, 2006). To appreciate how these systems may affect one another requires a brief introduction on cognitive–emotional–vigilance system interactions and recent imaging work on the resting state of the brain.

Cognitive, emotional, and vigilance processes dynamically interact with one another to produce the full range of perceptions, thoughts, feelings, and behaviors observed in humans. For example, external sensory deprivation increases attention to endogenous stimuli (Solomon *et al*, 1961), as does increasing the predictability of external events (Antrobus *et al*, 1966; Pope and Singer, 1976). Conversely, difficult cognitive tasks decrease attention to endogenous stimuli (Antrobus *et al*, 1966; Pope and Singer, 1976; Teasdale *et al*, 1995). A number of studies have now focused on the complex interactions of personality, emotion, cognition, reward, and decision-making (Allman *et al*, 2001; Bechara *et al*, 2000; Bush *et al*, 2000, 2002; Damasio, 2001; Davidson, 2001; Devinsky *et al*, 1995; Gehring and Fencsik, 2001; Gray *et al*, 2002; Mayberg *et al*, 1999; Posner and Raichle, 1998; Simpson *et al*, 2001b; Vogt *et al*, 1992; Whalen *et al*, 1998). Full characterization of these complex relationships will be essential to understanding the pathophysiology of ADHD, but at present there are many unresolved issues.

Functional neuroimaging (fMRI and PET) have provided clues as to how these interactions may occur. Although

most imaging studies have concentrated on activations, or increases in regional cerebral blood flow (rCBF) or fMRI signal during the task of interest as compared with a control task, a few have focused on 'deactivations,' or decreases in rCBF or fMRI signal during the task of interest relative to a control task (Bush *et al*, 2000; Drevets and Raichle, 1998; Gusnard *et al*, 2001; Gusnard and Raichle, 2001; Mayberg *et al*, 1999; Raichle *et al*, 2001; Shulman *et al*, 1997; Simpson *et al*, 2001a, b, 2000; Whalen *et al*, 1998).

Raichle and colleagues (Gusnard and Raichle, 2001; Raichle *et al*, 2001; Simpson *et al*, 2001b) have argued that such decreases provide evidence of a 'default mode' or homeostatic brain state maintained during rest or visual fixation. Paraphrasing Gusnard and Raichle (2001), three separable 'networks' of brain regions support: (1) cognition, or focused, goal-directed behavior; (2) internal state monitoring, involving the regulation of emotions, motivational state and endogenous stimuli; and (3) vigilance for salient external stimuli. Summarizing data from many studies, they noted that compared with a fixation/rest 'default state,' cognitive tasks activate brain regions such as the daMCC, DLPFC, and posterior parietal cortex. Conversely, cognitive tasks deactivate the perigenual ACC, medial PFC, portions of the VLPFC, amygdala, posteromedial areas such as the posterior cingulate cortex (PCC), retrosplenial cortex, and precuneus, and other posterolateral parietal areas near the angular gyrus. This led them to suggest that these latter areas are 'tonically active' during unstructured rest periods to support vigilance of the environment and monitoring of the internal milieu. Suspending activity in brain regions supporting emotion and/or vigilance—such as the perigenual ACC, amygdala, and PCC (Davis and Whalen, 2001; Hayden *et al*, 2009; Rauch *et al*, 2006; Wager *et al*, 2008; Whalen *et al*, 1998)—could improve cognitive task performance by reducing interference from sources unrelated to the task at hand, much as in the same way that during selective attention tasks, gating information from unattended channels improves processing of attended stimuli. However, as these vigilance and internal state regions could help protect against predators and signal important changes in the internal state and/or motivation, they should only be suppressed when necessary, such as when interfering with cognitive task performance. In line with these fMRI and PET results, intracranial single-unit recording work has shown decreased single-neuron activity in the perigenual ACC during a cognitive task in humans (Bush, 2004) and in PCC cells during a cognitive task in monkeys (Hayden *et al*, 2009).

Interestingly, what Raichle and colleagues call 'deactivations' have also been called 'resting state activation' by others (Binder *et al*, 1999; Mazoyer *et al*, 2001). These latter groups view these internal/external monitoring processes as active processes, pointing out that the supposed resting state is not entirely passive, and often includes extraneous thoughts, memories, and emotions. These views are not mutually exclusive, as there are likely multiple processes

contributing to higher fMRI/PET activity during a resting state as compared with that seen during cognitive task performance. Although identifying the specific nature of these reciprocal reactions can be difficult (Buckner *et al*, 2008; Bush *et al*, 2000; Greicius and Menon, 2004; McKiernan *et al*, 2003), elucidating the nature of cognition–emotion–vigilance interactions will be vital to future understanding of ADHD pathophysiology.

Selected ADHD Imaging Data

As stated at the outset, the ADHD imaging literature has grown almost exponentially over the past three decades, and a comprehensive, critical review is beyond the scope of this paper. Such reviews can be found elsewhere (Bush, 2009; Bush *et al*, 2005; Casey *et al*, 2007b; Dickstein *et al*, 2006; Durston, 2003; Giedd *et al*, 2001; Nigg and Casey, 2005; Schneider *et al*, 2006; Seidman *et al*, 2004b, 2005; Spencer *et al*, 2005; Swanson *et al*, 2007; Valera *et al*, 2007). Instead, a selected highlighting of some relevant study will be provided here (1) to give a broad overview of the techniques that are being used to study ADHD, (2) to identify how the emerging data from these studies fits together to inform our current understanding of ADHD neurocircuitry, and (3) to provide a base from which to make suggestions about important trends to follow-up and a number of new possible avenues to explore in the future.

An important point of emphasis must be made at this juncture. Functional imaging techniques can broadly be divided into studies on: (1) pathophysiology, (2) treatment effects, and (3) potential aids in clinical diagnosis. Although functional imaging techniques hold future promise for testing for regional brain dysfunction in neuropsychiatric disorders, the field is not at the point where imaging can be recommended for any clinical purpose besides from ruling out medical/neurological causes from the differential diagnosis of ADHD (Bush, 2008). Functional and structural imaging studies generally use group-averaging and between-group statistical analyses, owing to the usually limited power to detect differences in individuals. Such group-based designs can be useful in studying both pathophysiology and medication effects, but clinical diagnostic decision-making requires the ability to reliably distinguish normal from abnormal, and ADHD from other disorders, at the individual subject level. No technique thus far has been proven and accepted in the peer-reviewed literature as having met this standard. Thus, at this time, besides helping to rule out medical or neurological causes for an ADHD-like presentation, it must be emphasized that no current imaging technique can be recommended for the purpose of aiding with the clinical diagnosis of ADHD.

Structural studies. Structural imaging, particularly morphometric/volumetric MRI, has shed light on our understanding of ADHD. These have generally helped establish that in ADHD, there are widespread abnormalities in the volumes of brain circuitry relevant to attention and

motor control. In addition to relatively consistent findings of decreased total cerebral volume of ~3 to 5% (Castellanos, 2001; Castellanos et al, 1996, 2002; Seidman et al, 2005; Valera et al, 2007), volumetric studies have also found more specific abnormalities within defined regions of the lateral prefrontal cortex, cingulate cortex, striatum, cerebellum, and corpus callosum (Castellanos et al, 1996; Kates et al, 2002; Overmeyer et al, 2001; Semrud-Clikeman et al, 2000).

Smaller cingulate cortical volumes have been reported in adults (Seidman et al, 2006) and children (Semrud-Clikeman et al, 2006) with ADHD. An earlier study of ADHD children, relevant to default mode network studies, showed a reduction in posterior cingulate volume in ADHD (Overmeyer et al, 2001). Together, such studies illustrate the bidirectional flow of information: cognitive and affective neuroscience advances suggested particular regions should be tested, and in turn the ADHD findings provided examples of 'natural lesion' studies on these brain areas.

A number of studies have shown basal ganglia and cerebellar volumetric abnormalities. Globus pallidus has been shown to be smaller (Castellanos et al, 1996). Caudate studies have suggested smaller caudate in ADHD but have been inconsistent. Some have reported decreased volume of caudate in ADHD patients relative to controls (Semrud-Clikeman et al, 2006); Castellanos et al, 2002; Hynd et al, 1993), whereas others found no volume differences (Hill et al, 2003) or larger caudate in ADHD patients (Mataro et al, 1997). Castellanos et al (2002) indicated that initially smaller caudate volumes showed normalization in ADHD males during late adolescence, possibly reflecting the clinical observation that the hyperactivity of ADHD tends to diminish during this time. Prospective studies further examining this possibility, incorporating objective measures of hyperactivity, would be of interest. Multiple studies have reported structural abnormalities of the cerebellum in ADHD patients (Berquin et al, 1998; Castellanos et al, 2002; Mostofsky et al, 1998; Valera et al, 2007; Bledsoe et al, 2009). Overall, although some discrepancies exist, the weight of the evidence indicates that both global and regional volumetric abnormalities occur in ADHD.

Cortical (gray matter) thickness studies. Cortical thickness quantification through high-resolution MRI structural scans has been recently applied to the study on ADHD. Children with ADHD had significant global thinning of the cortex, most prominently in the medial and superior prefrontal and precentral regions (Shaw et al, 2006). These data in children were generally consistent with the findings Makris et al (2007) that showed selective cortical thinning of the CFP attention networks in adults with ADHD. Importantly, vis-à-vis the growing interest in possible contributions of the altered default mode network to ADHD pathophysiology, this study also reported cortical thinning of the PCC. However, cortical thickness results have not always been consonant. Wolosin et al (2009), although finding that children with ADHD displayed expected overall decreases of total cerebral and cortical volumes, and a significant

decrease in cortical folding bilaterally, did not detect significant differences in cortical thickness between ADHD and healthy children.

The Shaw/NIMH group also reported delay in cortical thickness maturation in ADHD (Shaw et al, 2007a). These delays in ADHD were most prominent in the lateral prefrontal cortex, especially the superior and DLPFC regions. In a separate study combining cortical thickness and genetics, Shaw et al (2007b) reported that possession of the dopamine D4 receptor (DRD4) 7-repeat allele in healthy children and ADHD was associated with significant cortical thinning of multiple regions including the OFC, inferior prefrontal cortex, and posterior parietal cortex. These brain regions were generally thinner in ADHD patients than in controls, although the matter is complex as ADHD patients with the 7-repeat allele fared better clinically, suggesting further study is required.

Connection abnormalities: corpus callosum and DTI. The corpus callosum connects the two cerebral hemispheres, and callosal abnormalities might therefore affect interhemispheric communication in ADHD. Callosal volumetric reductions could reflect fewer axons and/or decreased axonal myelination, but could also secondarily indicate fewer cortical neurons within the regions connected by these fibers. Abnormalities of corpus callosum volume and morphometry have been reported many times in ADHD. There is some evidence indicating regional specificity, with anterior abnormalities including the genu (Hynd et al, 1991) and the rostral regions (Baumgardner et al, 1996; Giedd et al, 1994), suggesting abnormal prefrontal and premotor connections, as well as posterior abnormalities of the splenium (Hill et al, 2003; Hynd et al, 1991) and isthmus (Lyoo et al, 1996), suggesting parietal and temporal lobe connection problems. However, the area is not without controversy. Although meta-analysis by Valera et al (2007) reported reduced splenium volumes in children and adolescents with ADHD, a subsequent meta-analysis that agreed with Valera's main finding suggested that gender may have played a role, with smaller splenium in females with ADHD and smaller rostral body in boys with ADHD (Hutchinson et al, 2008). Together, these results indicate that callosal abnormalities exist in ADHD, but gender, age, and other factors need further study.

DTI, a relatively new MRI technique that permits assessment of the integrity of white matter tract connections, has recently been applied to studying ADHD. Fractional anisotropy (FA), an indicator of the non-random diffusion of water within axons, has been the most often used DTI measurement parameter. Ashtari et al (2005) reported children with ADHD had decreased FA in the premotor cortex, striatum, cerebellum, and left parieto-occipital areas. Casey et al (2007a) used fMRI maps from a go/no-go task to identify portions of the VLPFC and striatum involved in suppressing an inappropriate action in parent–child dyads with and without ADHD. They reported FA in the right prefrontal fiber tracts was correlated with

both functional activity in the inferior frontal gyrus and caudate nucleus and with performance of a go/no-go task in parent–child dyads with ADHD. Further, prefrontal fiber tract measures were associated between ADHD parents and their children, suggesting disruption of frontostriatal connections has a role in ADHD. Makris *et al* (2008) showed that abnormalities of the cingulum bundle and superior longitudinal fascicle II—connection pathways that subserve attention and executive functions—are evident in adults with ADHD. Lower corticospinal tract and superior longitudinal fasciculus FA (Hamilton *et al*, 2008) similarly suggested disruption of motor and attention networks in ADHD children, whereas the study by Silk *et al* (2008) indicated that fronto-striatal and fronto-parietal circuitry abnormalities exist in children with ADHD. Finally, pediatric samples showed decreased FA in the anterior corona radiata and abnormalities across multiple white matter tracts in ADHD, including the cingulum bundle, the superior and inferior longitudinal fasciculi, and internal capsule (Pavuluri *et al*, 2009). Together, the data argue that white matter abnormalities are associated with ADHD. However, more advanced methodology will be needed to determine whether these observed abnormalities are becuase of primary problems with the connecting tracts themselves, are secondary to pathology in the regions that the white matter tracts connect, or whether they reflect some combination of effects.

Functional Studies: PET and fMRI

Radioactivity-based techniques. Single-photon emission computed tomography (SPECT) and photon emission tomography (PET) are functional imaging studies that provide indirect measures of neuronal activity. Both SPECT and PET have generally been supplanted by fMRI for functional studies, as fMRI offers superior spatial and temporal resolution, and SPECT and PET's use of radio-pharmaceuticals makes it ethically difficult to justify their use in healthy volunteers, especially children (Castellanos, 2002). However, both SPECT and PET still have important uses that other non-invasive techniques do not offer, such as neurotransmitter receptor characterization, measurement of dopamine transporter (DAT) levels, and quantification of extracellular dopamine (Madras *et al*, 2006; Spencer *et al*, 2006, 2005; Volkow *et al*, 2005, 2007). Early SPECT studies suggested striatal/basal ganglia abnormalities (Lou *et al*, 1984, 1990, 1989), despite some methodological issues (Castellanos, 2002). Another SPECT study showed that methylphenidate (MPH) increased rCBF in the DLPFC, caudate, and thalamus in previously treatment-naive children and adolescents with ADHD (Kim *et al*, 2002).

Zametkin *et al* (1990) were the first to publish a large-scale, well-designed functional imaging study of ADHD. This PET study used [18F]fluoro-2-deoxy-D-glucose to measure cerebral glucose metabolism in 75 adult subjects (25 treatment-naive ADHD and 50 controls). They found that global cerebral glucose metabolism was 8.1% lower in the ADHD group and that even after normalization for these global decreases regional metabolism remained lower in the daMCC, premotor, and somatosensory areas. These findings are consistent with the structural data discussed above that indicate cerebral volume is lower in ADHD patients than in healthy controls. Fronto-temporal abnormalities during a working memory task in ADHD were found in another PET study (Schweitzer *et al*, 2000). Ernst *et al* (2003), employing a gambling task, provided data implicating the daMCC and VLPFC in ADHD and highlighting the need to further examine cognitive, emotional, and motivational interactions in its pathophysiology.

fMRI. fMRI, the newest of the major functional imaging methods, presents a number of advantages over both SPECT and PET for functional neurocircuitry studies. fMRI is non-invasive and does not require ionizing radiation. Thus, subjects can be scanned repeatedly, facilitating longitudinal, developmental, and pharmacoimaging studies. This ability to repeatedly scan the same subject multiple times enables 'functional dissections,' in which different tasks can be used to interrogate neural circuits. fMRI has superior spatial and temporal resolution, and tasks can be performed in either a blocked format or an event-related manner, which allows greater flexibility in task design. Newer arterial spin labeling (ASL) techniques can characterize brain activity during 'resting states' and other methods can identify functional connections between brain regions. Higher field strength magnets, coupled with specialized cognitive activation tasks, are able to produce brain maps in individual subjects, which have enabled characterization of drug effects in single subjects and analyses of intersubject variability (Bush *et al*, 2008). For these reasons, fMRI has become the dominant functional imaging modality used by psychiatric imaging researchers as well as cognitive and affective neuroscientists.

Regionally, the most consistent theme that has emerged has been the repeated finding of daMCC dysfunction. The daMCC normally has key roles in attention, cognition, motor control/response selection, motivation, error detection, and feedback-based decision-making (Bush, 2009; Bush *et al*, 2000, 2002; Vogt *et al*, 1992). Numerous fMRI, PET, and event-related potential (ERP) studies have reported daMCC hypofuction in ADHD, using various tasks and techniques (Bush *et al*, 1999; Durston *et al*, 2007, 2003a; Konrad *et al*, 2006; Liotti *et al*, 2005; Pliszka *et al*, 2006; Rubia *et al*, 1999; Smith *et al*, 2008; Tamm *et al*, 2004; Zametkin *et al*, 1990; Zang *et al*, 2005). Moreover, a meta-analysis of neuroimaging studies by Dickstein *et al* (2006) found the daMCC among a short list of brain regions that were hypoactive in ADHD patients relative to healthy controls. Recently, Bush *et al* (2008) used fMRI to show that 6 weeks of MPH significantly increased daMCC activation, as compared with placebo, in adults with ADHD. Similarly, an ERP study reported that stimulant treatment increased ACC activity (Pliszka *et al*, 2007). Clearly, the accumulated evidence from these fMRI, PET, and ERP studies, when

combined with the cortical thickness and volumetric data reviewed above, provide a compelling argument that daMCC dysfunction contributes to ADHD.

Key confirmatory evidence indicating wider CFP neurocircuitry dysfunction in ADHD was provided by a voxel-based meta-analysis of 16 ADHD imaging studies by Dickstein et al (2006). The use of an activation likelihood estimate meta-analytic method (Lancaster et al, 2005) allowed a relatively unbiased overview of ADHD imaging findings. ADHD was found to be associated with significant hypoactivity of the daMCC, DLPFC, VLPFC, superior parietal cortex, caudate, and thalamus. Moreover, limiting the focus to studies on response inhibition tasks, as suggested by the study of Aron and Poldrack (2005) and Durston et al (2003a), identified a more limited set of regions, including the VLPFC, daMCC, parietal cortex, caudate, and precentral gyrus, but notably not the DLPFC. These data help resolve some surprising apparent inconsistencies observed with respect to lateral frontal cortical areas (DLPFC and VLPFC) in previous separate imaging studies. Thus, it appears that dysfunction of the DLPFC and VLPFC (Aron et al, 2003; Bush et al, 2005; Durston, 2003; Kobel et al, 2008; Pliszka et al, 2006; Schneider et al, 2006; Smith et al, 2008; Vaidya and Stollstorff, 2008) have important and separable roles in ADHD.

Caudate functional abnormalities were found in the above meta-analysis, just as they have been fairly consistently found with individual fMRI studies, especially when using response inhibition tasks, such as go/no-go or stop-signal tasks (Durston et al, 2003b; Epstein et al, 2007; Rubia et al, 1999; Vaidya et al, 1998). Vance et al (2007) also recently reported lower right caudate in ADHD during a mental rotation task. Lower resting putamen blood flow was reported in ADHD (Teicher et al, 2000) by a study that used T2 relaxometry, which is an indirect MRI measure of steady-state regional blood flow that pre-dates the more recent use of ASL techniques. Together, these data fit with the structural imaging findings, previous SPECT/PET studies, and the reports of DAT abnormalities found in the striatum discussed below.

The parietal cortex, although long known to have important roles in attention and spatial processing, has only more recently been the focus of ADHD imaging studies. Tamm et al (2006) reported ADHD subjects performing a visual oddball task showed significantly less activation of parietal cortical areas, including the superior parietal gyrus and multiple areas of inferior parietal lobe, along with the lower precuneus and thalamus activation. Vance et al (2007) reported that ADHD subjects performing a spatial working memory-dependent mental rotation task displayed significantly less inferior parietal lobe activation, in addition to lower parieto-occipital and caudate activation. In another study, children with ADHD showed less activation than controls in multiple areas of the parietal cortex, DLPFC, and putamen. A lack of a difference in the daMCC in this study may have been attributable higher error rates in the ADHD group, as errors activate the

daMCC (Cao et al, 2008). Parietal hypofunction has also been observed in ADHD in tasks of mental rotation/spatial processing (Silk et al, 2005), task switching (Smith et al, 2006) and sequential finger tapping (Mostofsky et al, 2006). Although it is clear that hypofunctioning parietal cortical subdivisions have roles in ADHD pathophysiology, the challenges ahead will be in specifically pinpointing how the various areas contribute to create the observed symptoms.

The cerebellum has increasingly gained recognition as part of disordered circuitry that underlies ADHD. As Schneider et al (2006) discuss, imaging studies have helped show that cerebellum has multiple complex roles beyond its traditional primary role in motor coordination. The study by Schmahmann has been particularly illuminating (Schmahmann and Caplan, 2006; Schmahmann and Sherman, 1998; Schmahmann et al, 2007), and a recent neuroimaging meta-analysis identified cerebellar contributions to various processes, including motor, somatosensory, language, verbal working memory, spatial processing, executive functions, and affective processing (Stoodley and Schmahmann, 2009). Substantial evidence of structural abnormalities of the cerebellum in ADHD has been presented above. In addition, a number of fMRI studies have identified functional abnormalities of the cerebellum in ADHD. Although more of the studies have reported decreased cerebellar activation in ADHD during task performance (Durston et al, 2007; Valera et al, 2005; Zang et al, 2005) or at rest (Anderson et al, 2002; Kim et al, 2002), others have reported increased activation in ADHD (Rubia et al, 2009; Schulz et al, 2004). It is anticipated that improved understanding of cerebellar contributions to various cognitive and affective functions, along with increasingly focused studies on cerebellum's potential role in ADHD, will help to shed light on this controversy.

Although abnormalities of the CFP cognitive/attention network, striatum, and cerebellum have figured most prominently in functional imaging studies on ADHD, other brain regions have been implicated by fMRI. Thalamic abnormalities have been found during active tasks (Dickstein et al, 2006; Tamm et al, 2006) and at rest (Zhu et al, 2008), and occipital cortex abnormalities have been identified (Dickstein et al, 2006; Valera et al, 2005). Differences in the temporal cortex between groups with ADHD and healthy controls have been noted during active tasks (Rubia et al, 2009; Smith et al, 2006; Vaidya et al, 2005). Contralateral motor cortex hypoactivity during motor sequencing has been reported (Mostofsky et al, 2006). Midbrain dysfunction in ADHD, as hypothesized by Castellanos (1997), and as reported by Ernst et al (1998) using a PET measure of dopa decarboxylase activity, can unfortunately be technically challenging to assess with fMRI due to the pulsatile motion of brainstem (Guimaraes et al, 1998) and possible differences in blood flow regulation in this area (Hart et al, 2006). However, given its potential role in ADHD pathophysiology, it is hoped that more prospective studies on midbrain will be performed, perhaps using

advanced techniques such as cardiac-gated fMRI (Guimaraes *et al*, 1998).

Functional pharmacoimaging studies. Functional pharmacoimaging, by showing the ways in which drugs act on different brain regions, not only directly adds to the understanding of the mechanisms of drug effects but also indirectly helps to identify alterations in the neural circuitry that may underlie ADHD. An emerging literature of functional pharmacoimaging studies now suggests that the generally observed hypoactivation of the CFP cognitive/attention network and the striatum in ADHD is counteracted by the medications used to treat ADHD. For the sake of discussion, this section will highlight the fronto-striatal effects using techniques other than dopaminergic-specific imaging studies, which will be discussed separately below.

Although a series of early PET studies on acute and chronic stimulant medication effects in ADHD (Ernst *et al*, 1994; Matochik *et al*, 1994, 1993) could not identify consistent brain responses, they laid the groundwork for subsequent studies on medication effects. Vaidya *et al* (1998), in an fMRI study of the effects of MPH on children performing go/no-go tasks, showed not only that fronto-striatal activity differed between ADHD and healthy controls but also that the groups' responses to MPH differed. MPH increased prefrontal activation to an equal extent in both groups on one task, but on the other go/no-go task MPH increased striatal activation in the ADHD group while reducing striatal activation in healthy controls.

Studies using various techniques followed. A steady-state MRI-based method (T2 relaxometry) showed that in children with ADHD, MPH significantly changed blood flow to the putamen (Teicher *et al*, 2000) and cerebellar vermis (Anderson *et al*, 2002). SPECT studies, despite some limitations, also made contributions. One reported MPH increased rCBF in the DLPFC, caudate, and thalamus bilaterally in previously treatment-naive children and adolescents with ADHD (Kim *et al*, 2001). Another study showed medication withdrawal had measurable brain effects, highlighting the need to better define drug washout periods for both pharmacoimaging and pathophysiology studies (Langleben *et al*, 2002). A resting state PET study with scans performed 3 weeks apart found the off-MPH condition was associated with relatively higher rCBF in the precentral gyri, caudate, and claustrum; whereas MPH increased rCBF in the cerebellar vermis (Schweitzer *et al*, 2003).

An fMRI study using a divided attention task reported that unmedicated subjects with ADHD recruited the left ventral basal ganglia less than did healthy controls, and MPH increased activation in this region (Shafritz *et al*, 2004). An acute MPH medication fMRI study showed MPH consistently (i.e., in both children and adults) produced increased activation of the caudate and cerebellum, along with inconsistent changes in other brain regions (Epstein *et al*, 2007). Pliszka *et al* (2007) using ERPs found that stimulant treatment increases ACC activity in ADHD.

Subsets of children from a long-term (1 year) fMRI study of ADHD found data suggestive of long-term MPH-induced changes in the insula, putamen, and cingulate cortex (Konrad *et al*, 2007).

A recent study by Bush *et al* (2008) used fMRI in conjunction with a specialized cognitive task, the Multi-Source Interference Task (MSIT) (Bush and Shin, 2006), to determine whether an MPH preparation 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 × scan interaction and *t*-test confirmation of higher activation in the daMCC at 6 weeks in the MPH group, as compared with the placebo group. Moreover, use of the MSIT permitted single-subject daMCC volume-of-interest analyses that confirmed the group-averaged findings and suggested that daMCC activity might be related to clinical response. Beyond daMCC, 6 weeks of MPH also increased activation of many structures implicated in ADHD pathophysiology, including the DLPFC, VLPFC, parietal cortex, caudate, thalamus, and temporal lobe. These findings indicate that MPH may act, in part, by normalizing the daMCC and CFP hypofunction in ADHD. These data dovetail well with those from a recent MRS study that found decreased choline and increased *N*-acetyl-aspartate (NAA) levels in the daMCC after treatment of ADHD with 5–6 weeks of MPH, indicating that biochemical changes occur in the daMCC with longer term MPH treatment (Kronenberg *et al*, 2008).

Non-stimulant medications for ADHD are just starting to be studied with fMRI in humans. Building on clinical and animal work, a recent contribution was made by Chamberlain *et al* (2009). Using fMRI, they showed that atomoxetine, a selective noradrenaline reuptake inhibitor used to treat ADHD, increased both inhibitory control on a stop-signal task and right VLPFC activation in healthy male adults. Given established VLPFC hypofunction in ADHD, it will be interesting to see in future studies if ADHD subjects respond to atomoxetine with a predicted VLPFC activation increase, and how ADHD brain responses to atomoxetine compare with responses to stimulants. Also, these data provide an excellent example of how ADHD research can also shed light on normal brain circuitry, as they provide a better understanding of response inhibition processes in healthy humans.

Resting state studies. Although the majority of functional imaging studies have concentrated on using various cognitive activation paradigms to specifically target different elements of the neural circuits subserving cognition, attention, and motor functions, growing interest has been noted in the use of techniques that focus on subjects' resting brain activity. Such resting studies are important as one of the main problems in ADHD may lie in dysfunction of brain regions that, as discussed above, support a proposed 'default network'. Specifically, it may be the case that an abnormally high default mode network activity may interfere with CFP attention network activity.

One resting state PET study showed that MPH increased rCBF in the cerebellar vermis and was associated with decreased rCBF in the precentral gyri, caudate, and claustrum (Schweitzer *et al*, 2003), whereas another reported MPH potentiates dopaminergic activity in the striatum of adolescents with ADHD (Rosa-Neto *et al*, 2005). A series of resting state MRI studies has also provided insights into functional connectivity among brain regions, primarily fronto-cingulate-cerebellar circuits (Tian *et al*, 2006; Zang *et al*, 2006; Zhu *et al*, 2005). Later, resting state discriminative analysis indicated dysfunction of the daMCC, lateral prefrontal cortex, thalamus, and lateral parietal cortex in ADHD (Zhu *et al*, 2008), whereas Tian *et al* (2008) used resting state MRI to show that ADHD patients exhibited higher resting state activity in the lower-level sensory cortex, concluding that this was related to inattention. Interestingly, Castellanos *et al* (2008) identified reduced functional connectivity between the daMCC and default network structures (precuneus and PCC) and altered connectivity within default network itself (VMPFC, precuneus, and PCC)—findings that were essentially confirmed by the same group using a different network homogeneity model (Uddin *et al*, 2008). Work in this vein has been based on hypothesized interruption of attention network activity by altered default network activity (Weissman *et al*, 2006), which in ADHD has been thought to lead to greater variability in ADHD performance (Sonuga-Barke and Castellanos, 2007). ASL techniques, which can provide absolute measures of rCBF during rest (Aguirre *et al*, 2005; Detre and Wang, 2002; Kim *et al*, 2006; Wang *et al*, 2005) should help better define the pathophysiology of ADHD and other psychiatric disorders (Broyd *et al*, 2009).

Dopaminergic studies. Although this review focuses on neurocircuitry, it is illustrative to mention how work on dopaminergic modulatory functions can be integrated with neurocircuitry models. Imaging has increasingly been used to characterize the modulatory effects that different neurotransmitters may have on the brain circuits underlying ADHD. Dopamine has been of prime interest, given our although limited understanding of how it may increase neuronal signal-to-noise characteristics and its established roles in reward signaling. The interested reader can find reviews of the intricacies and debates surrounding dopaminergic imaging methods (Spencer *et al*, 2005; Swanson *et al*, 2007), as well as the roles various neurotransmitters may play in the pathophysiology of ADHD (Arnsten, 2001, 2006; Brennan and Arnsten, 2008) (Figure 2).

Dopamine has been a particular focus of ADHD research because in healthy humans it has roles on attention, cognition, and reward processes (Brennan and Arnsten, 2008; Schultz, 1998, 2006; Solanto, 2002). Dopamine can have both short-term phasic (milliseconds to seconds) and long-term tonic (minutes to hours) modulatory influences on CFP attention networks, meso-limbic circuitry, and fronto-cerebellar circuits. Dopaminergic modulation can increase the neuronal signal-to-noise ratio both by boosting
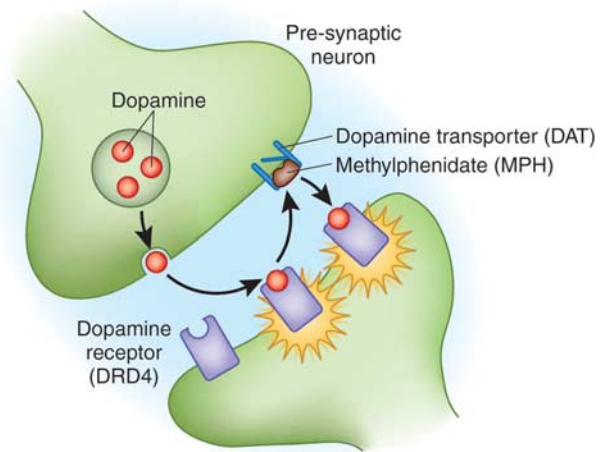

Figure 2. Dopamine synapse. Dopaminergic neurons release dopamine into the synapse, where it signals to post-synaptic neurons through specific receptors (illustrated here is the DRD4 receptor). Dopamine is then taken back into the presynaptic neuron through the dopamine transporter (DAT). Stimulants such as methylphenidate have been shown to block DAT, thus making more dopamine available in the extracellular space.

signal and by dampening background noise (Volkow *et al*, 2005). 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 (Brennan and Arnsten, 2008).

Pioneering PET work by Volkow and colleagues has showed the specific activity of MPH's *d*-enantiomer in the basal ganglia (Ding *et al*, 1997), that oral MPH blocks the DAT with a time course matching behavioral effects (Volkow *et al*, 1998), and that MPH increases extracellular dopamine in the striatum (Volkow *et al*, 2001). Spencer *et al* (2006) have subsequently provided confirmatory PET data illustrating how striatal effects of MPH match behavioral effects using immediate and extended release formulations of MPH. Recent study in ADHD adults has also shown depressed dopamine activity in the caudate, and possibly some default network regions (amygdala/hippocampus) were associated with inattention (Volkow *et al*, 2007). Jucaite *et al* (2005) reported altered midbrain dopaminergic function in adolescents with ADHD, dovetailing well with previous midbrain dopamine abnormalities reported by Ernst *et al* (1999). Recent results have suggested neurotransmitter specificity, in that dopaminergic but not serotonergic transmitter reuptake was reduced in adults with ADHD (Hesse *et al*, 2009).

A related but contentious line of investigation involves the quantification of striatal DAT. As mentioned above, DAT is primarily responsible for presynaptic reuptake of dopamine, and it has been shown that MPH blocks DAT and increases extracellular dopamine (Spencer *et al*, 2005; Swanson *et al*, 2007; Volkow *et al*, 2002, 2005, 2007). Although initial reports found large (up to 70%) increases in striatal DAT in ADHD (Dougherty *et al*, 1999; Krause

et al, 2000), subsequent reports using different ligands and techniques have found lesser effect sizes, and in some cases, even lower DAT in ADHD (Volkow et al, 2007). Such discrepancies, which may be attributable to differences of ligands or imaging techniques used (Spencer et al, 2005; Volkow et al, 2007), will need to be resolved before firm conclusions about dopamine's role in ADHD can be made. Given this, in vivo imaging of dopaminergic function and modulation of the attention and reward networks would be lines of inquiry to follow.

Lastly, although these approaches have provided new information on possible mechanisms of stimulant medications used to treat ADHD at the synaptic and inter-cortical network levels, this should not be taken to suggest that dopamine is the only neurotransmitter relevant to ADHD. Instead, these recent advances should be seen as but the first waves of pharmacoimaging studies that will identify the ways that dopamine and other neurotransmitters (norepinephrine, acetylcholine, serotonin, glutamine and GABA) might modulate neurocircuitry implicated in causing ADHD.

Future Research Directions

Progress has been made in increasing our understanding of the neural circuitry of attention, cognition, and reward, as well as in applying that knowledge to elucidating both the pathophysiology of ADHD and the mechanisms by which treatments for ADHD work. The sections above have traced how observations of clinical phenomenology have been combined with cognitive neuroscience advances in the formulation of various models of ADHD. It has been shown that identifiable parallel distributed networks support different neural processes relevant to ADHD. For example, the CFP cognitive–attention network interacts with the striatum, premotor cortex, cerebellum, superior temporal sulcus, thalamus, and the brain stem reticular activating system to support cognitive–motor processing. Motivational information is encoded by reward regions including the striatum, daMCC, nucleus accumbens, and OFC. In healthy humans, these systems interact with one another and with default mode network regions (perigenual ACC, medial PFC, portions of VLPFC, amygdala, and PCC), which activate tonically during unstructured rest periods to support vigilance and internal state monitoring. Functional, structural, biochemical, and connectionist imaging data have varying degrees of illustrated abnormalities of brain regions within these functional systems, and pharmacoimaging has begun to identify precise ways in which medications used to treat ADHD exert their effects.

Still there is much unresolved. Outstanding neuroscientific questions include (1) what functions the individual CFP network regions and striatum perform during cognitive and reward processing, (2) how they interact with one another, and (3) how they might exert top-down control over lower processing modules. Dosenbach et al (2008, 2007) suggest that both separable fronto-parietal and cingulo-opercular

subnetworks may modulate downstream processing activity, but that transient activity of the fronto-parietal network reflects trial-by-trial adjustments, whereas sustained activity of cingulo-opercular regions throughout trials may indicate that it is more responsible for set maintenance. Previous study has suggested that the DLPFC exerts top-down control early, whereas the cingulate cortex monitors performance (MacDonald et al, 2000). Dosenbach et al (2007) suggests that parallel 'hybrid' control systems are possible, which would be most consistent with the available data, although the exact mechanisms by which CFP networks act remain to be determined.

ADHD research is dependent on cognitive neuroscience to provide more specific answers as to the mechanisms of these processes, but as has been shown it can also push such basic research in certain directions. In turn, ADHD studies can enrich understanding of these processes and network interactions by providing sophisticated natural lesion studies. As ADHD is a heterogeneous, multi-factorial disorder (e.g., cognitive/attention system dysfunction in some, reward/motivation abnormalities in others, and perhaps intrusive default mode activity in others), opportunities for bidirectional influences between disciplines abound. These final sections will highlight some of the expected trends to follow and offer some suggestions for possible new avenues of research.

Resting state studies. Resting functional connectivity studies have recently formed a major trend in ADHD research and can provide valuable new information. Greater efforts to directly link such connectivity data with fMRI attention task and DTI connectivity data will be helpful. More importantly, the use of ASL techniques (Aguirre et al, 2005; Detre and Wang, 2002), which can provide absolute, as opposed to relative, measures of resting state brain activity, will be crucial to defining the relationships between cognitive, vigilance, and emotional circuits. Such ASL studies would provide uniquely important data not available from typical fMRI data sets nor resting state connectivity studies. Specifically, ASL studies would allow testing of the hypothesis that abnormally high default network activity interferes with normal CFP attention network activity in ADHD—a hypothesis suggested and supported by the study of Weissman et al (2006) and Sonuga-Barke and Castellanos (2007).

Need for different tasks and different foci. Replicating results using known and validated tasks is needed, but it will be equally if not more important to develop new tasks to make further headway in identifying the neurobiology of ADHD. As detailed above, established executive function and response inhibition tasks, including the Stroop and Stroop-like tasks, Flanker, go/no-go, and stop-signal tasks, and the MSIT have shed light on ADHD pathophysiology and treatment effects. However, newer and better tasks and techniques that focus attention on different brain regions are needed.

For example, the use of existing tasks has revealed much about cingulo-fronto-striatal abnormalities, but other brain regions have been comparatively understudied. Parietal cortex is a prime example. Although it plays roles in attention and cognition and has therefore been implicated by a few studies, more spatial working memory task variants and other new paradigms specifically targeting parietal subregions should be used to test the integrity of parietal cortical areas in ADHD. Similarly, tasks can and should be developed that specifically test functioning of the OFC, cerebellum, midbrain, and thalamus. In related manner, motivational issues and their intersection with reward systems circuitry—including the striatum, nucleus accumbens, OFC, and daMCC—have theoretical and observed underpinnings that can be tied to known dopaminergic dysfunction in ADHD and must be fleshed out through new approaches. Interactions of emotional systems with attention/executive systems will be another important line of research.

It would be helpful if new tasks were designed that specifically focused on cognitive processes that have heretofore been underserved, such as vigilance or target detection functions. For example, continuous performance tasks have been used with limited success, but are inadequate to fully characterize vigilance and target detection. Pardo et al (1991) used a visual fixation dimming task that could be modified to study vigilance in ADHD. Alternatively, event-related fMRI might be used to characterize brain activity between widely spaced response trials that might capture neuronal lapses of attention or vigilance in a manner not confounded by motor responses. Such a task would support hypothesized attention impairments caused by inappropriate intrusion of default network activity, as proposed by Sonuga-Barke and Castellanos (2007).

More studies seeking to understand possible impairments of error processing in ADHD and individual performance differences would also be useful. These could consist of studies that explore the effects of variable performance on imaging data, both on mean differences between groups and on trial-to-trial variability within individual runs for a subject (Castellanos et al, 2005; Sonuga-Barke and Castellanos, 2007). Regardless of the task used, errors are intimately related to performance, and as discussed previously (Bush et al, 2005), error detection systems in the brain can have a profound impact on brain imaging results. Thus, error system signaling must be studied more prospectively and accounted for independent of task or data analysis techniques.

Variability analyses. Along with new foci of study must come novel study designs and statistical approaches. For example, traditional statistical comparisons emphasize looking for differences in means between groups while taking into account variability. Although mean differences are important, fMRI or ASL signal variability within subjects could be tested (perhaps by modified voxel-wise

Levene's tests for equality of variance between groups) and may turn out to be of great relevance to ADHD. Statistical comparisons of the 'noise' elements, which could be directly attributable to decreased dopamine levels that normally serve to dampen background neuronal firing noise, could additionally help evaluate apparent hypoactivation of ADHD groups (Bush et al, 1999). Future studies should therefore consider not only reporting statistical differences but also report means and variance of fMRI signal for subject samples through variability difference maps. Note that the noise comparisons may be in some cases related to previously hypothesized and observed findings on intra-individual variability due to lapses in attention (Castellanos et al, 2008; Sonuga-Barke and Castellanos, 2007), as neuronal noise characteristics may be independent of performance and may or may not vary within a scan.

Variability may manifest in other ways. Anatomic variability of brain structures makes region definition complex. Further complicating this fact is the suggestion from a recent study that ADHD brains may show greater degrees of anatomic variability than those of healthy controls (Bush et al, 2008). Such anatomic variability will need to be quantified and accounted for. Dopaminergic tests are also in some cases dependent on a cognitive state, and even 'resting' studies on DAT may be confounded, as controversy exists surrounding the definition of whether or not the healthy brain has a 'default resting state' or how to determine what mental activities are taking places when a subject is 'resting' (Raichle et al, 2001; Sonuga-Barke and Castellanos, 2007).

Multimodal imaging and technique refinement. The combined use of multiple techniques to study the same subject samples can reduce anatomical variability. It will also produce enriched data sets that will benefit from incorporating the relative strengths of some techniques while offsetting the weaknesses of the others. For example, fMRI has excellent spatial and fair temporal resolution, whereas ERPs (Barry et al, 2003; Liotti et al, 2005; Pliszka, 2007; Tannock, 1998) and magnetoencephalography (MEG) possess millisecond temporal resolution but relatively poor spatial resolution. Combined fMRI and electroencephalography (EEG) can also be used for cognitive or affective tasks (Menon and Crottaz-Herbette, 2005). It is anticipated that ADHD studies will increasingly combine fMRI with ERPs (Crottaz-Herbette and Menon, 2006), MEG, or EEG.

Other ways to improve such multi-level integration would be to combine fMRI with PET dopaminergic imaging techniques (Schott et al, 2008), connectivity techniques (such as DTI or other resting state connectivity techniques), or possibly with MRS measures of biochemical markers. For example, MRS has been used with some success to identify biochemical abnormalities in ADHD (Bush et al, 2005; Carrey et al, 2003; Courvoisie et al, 2004; Jin et al, 2001; Kronenberg et al, 2008; MacMaster et al, 2003; Perlov et al, 2007, 2008; Sun et al, 2005; Yeo et al, 2003), but has been limited because of previous requirements that restricted

measurements to one or two *a priori* anatomical sites per study. More recently, although, chemical shift imaging techniques have been developed that can simultaneously measure the same MRS metabolites across whole brain, all within ∼15 to 20 min. Similar improvements will be likely for other existing techniques. DTI can be improved to better assess anatomical connections through greater resolution of crossing fiber tracts. Better dopaminergic imaging would permit more sensitive and reproducible DAT findings, and could include enhanced dopamine release study methods that would allow addressing of tonic versus phasic release issues (Duzel *et al*, 2009; Goldstein *et al*, 2009). Improved PET receptor characterization studies would permit *in vivo* dopamine receptor identification, which could synergistically improve functional and connectivity studies by refining our understanding of neuromodulatory effects. Better measures of other neurotransmitters, including noradrenergic, cholinergic, serotonergic, glutamatergic, and GABAergic systems, will similarly aid ADHD research. Although such technological improvements will occur with time, current efforts may be improved simply using batteries of tasks to study already well-characterized patient samples. Individual studies on single tasks, such as cognitive interference, target detection, vigilance, response inhibition, or working memory tasks, are certainly useful. However, such approaches only test a specific cognitive domain, and will not provide a comprehensive assessment of ADHD patients. Batteries of imaging tests can interrogate different aspects of neural circuits while simultaneously cutting down on anatomical variability and study costs.

Genetic studies. Genetic influences on the neural circuitry of attention need to be explored further. Work has already been published that begins to link genotype and/or familial linkage with structural findings in ADHD (Casey *et al*, 2007a; Monuteaux *et al*, 2008; Shaw *et al*, 2007b) and to cognitive/executive function in healthy humans (Fan *et al*, 2003). Koten *et al* (2009) recently reported data from healthy twins that are very relevant to ADHD, as they showed how specific genetic factors could affect fMRI activation patterns within the brain regions of the CFP cognitive/attention network. Thus, genetic studies, as discussed recently (Durston, 2008; Greene *et al*, 2008; Rapoport and Shaw 2008), should be encouraged.

Clinical, translational and developmental issues. Many other factors will need to be addressed before fully characterizing the neurobiology of ADHD. The neural substrate of clinical subtypes will have to be determined, as ADHD is heterogeneous and likely to be associated with multiple causations. Some patients may have dopaminergic, noradrenergic, serotonergic, or cholinergic abnormalities, whereas others may show prominent genetic-based structural abnormalities. Still others may have disordered cortico-cortical connections. Moreover, each of these groups may have a different imaging profile. A related accounting must be made for phenomenological sub-types of ADHD, as it is likely that inattentive, hyperactive, and combined sub-types have distinct neuroimaging features.

Imaging findings must be viewed from a refined developmental perspective, requiring more longitudinal structural, functional, and biochemical studies to be performed. Previous examples of structural studies generating hypotheses have been offered, such as normalization of caudate volumes in adolescence (Castellanos *et al*, 2002) potentially being responsible for the lack of hyperactivity in adults. Previous developmental study on the maturation of attention/CFP networks (Casey *et al*, 2005; Fair *et al*, 2007), reward circuitry (Galvan *et al*, 2006), and resting state networks (Fair *et al*, 2008) will also help inform ADHD studies. Follow-up studies are needed to determine the neural basis for why ADHD does or does not persist into adulthood in different cases.

Pharmacoimaging. Imaging has begun to characterize stimulant effects, but more studies are need to follow-up on these preliminary findings and to compare the mechanisms of action of different treatments. Beyond simply studying drugs although, it will be important to also identify the neural effects of alternative treatments such as cognitive-behavioral therapy, meditation, and yoga—all of which can affect the cognitive and emotional brain circuitry in powerful ways. Large-scale databases of imaging data, including cross-cultural studies, would also be helpful additions to the literature. Potential confounds, such as anxiety, substance abuse, effects of other medications, caffeine, IQ, brain laterality effects, and motivational status, will need to be accounted for, and ADHD must be differentiated from other disorders that display attention dysfunction, such as schizophrenia or depression. Such studies will undoubtedly have bidirectional beneficial effects.

Imaging studies face a number of challenges. Owing to their relatively high expense, sample sizes have tended to be small. Such underpowering renders them particularly susceptible to both type I and type II errors, which may also account for a number of the inconsistencies among studies. These limitations and many others have been reviewed at length elsewhere (Bush *et al*, 2005; Castellanos, 2002), and many other hurdles must still be overcome before functional imaging can be clinically useful (Bush, 2008). Collectively although, functional, structural, and biochemical neuroimaging techniques have begun fulfilling their promise as tools for defining both the neural circuitry of attention and the neurobiology of ADHD.

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DISCLOSURE

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