Fundamentals of Attention-Deficit/Hyperactivity Disorder: Circuits and Pathways

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Neuropsychological and imaging studies have shown that attention-deficit/hyperactivity disorder (ADHD) is associated with alterations in prefrontal cortex (PFC) and its connections to striatum and cerebellum. Research in animals, in combination with observations of patients with cortical lesions, has shown that the PFC is critical for the regulation of behavior, attention, and affect using representational knowledge. The PFC is important for sustaining attention over a delay, inhibiting distraction, and dividing attention, while more posterior cortical areas are essential for perception and the allocation of attentional resources. The PFC in the right hemisphere is especially important for behavioral inhibition. Lesions to the PFC produce a profile of distractibility, forgetfulness, impulsivity, poor planning, and locomotor hyperactivity. The PFC is very sensitive to its neurochemical environment, and optimal levels of norepinephrine and dopamine are needed for proper PFC control of behavior and attention. Recent electrophysiologic studies in animals suggest that norepinephrine enhances "signals" through postsynaptic α_{2A}-adrenoceptors in PFC, while dopamine decreases "noise" through modest levels of D_1-receptor stimulation. Blockade of α_2-receptors in the monkey PFC re-creates the symptoms of ADHD, resulting in impaired working memory, increased impulsivity, and locomotor hyperactivity. Genetic alterations in catecholamine pathways may contribute to dysregulation of PFC circuits in this disorder. Stimulant medications may have some of their therapeutic effects by increasing endogenous stimulation of α_{2A}-adrenoceptors and dopamine D_1-receptors in the PFC, optimizing PFC regulation of behavior and attention. *(J Clin Psychiatry 2006;67[suppl 8]:7–12)*

Attention-deficit/hyperactivity disorder (ADHD) is characterized by inattention, impaired behavioral inhibition, and increased motor activity. *Inattention* is a nonprecise term and thus can lead to confusion in diagnosis. For many patients, *inattention* refers to increased distractibility, poor sustained attention, and increased susceptibility to interference, i.e., impaired regulation of attention. However, the term *inattention* can also be applied to symptoms resembling perceptual neglect, i.e., the inability to allocate sufficient attentional resources to stimuli for adequate perception. Recent understanding of the higher cortical circuits underlying attention and behavioral regulation provides important insights to navigate these complexities and helps to elucidate the likely neural bases underlying the symptoms of ADHD. These findings complement those arising from imaging studies of ADHD that have found volumetric differences in prefrontal cortex (PFC), cerebellum, and possibly striatum (reviewed by Giedd et al.[1]). Furthermore, our increasing understanding of catecholamine actions on these circuits provides insight into the mechanism of action of medications used to treat this disorder. These data also help us to understand how genetic changes in catecholamine pathways could result in ADHD symptomatology. This article briefly reviews the anatomy and function of the higher association cortices relevant to ADHD, the connections of these cortical areas to the basal ganglia and cerebellum, and the powerful modulation of these circuits by dopamine and norepinephrine.

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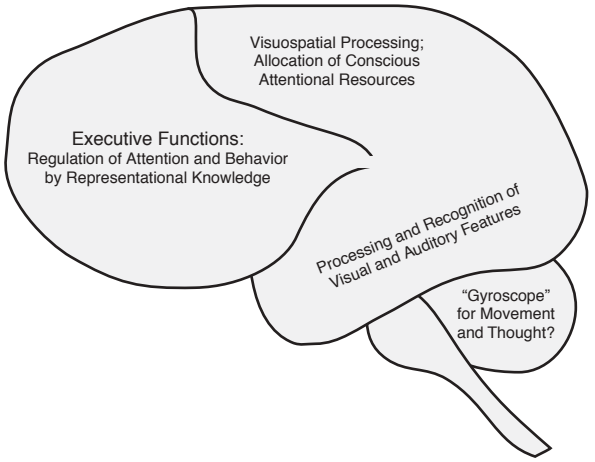
THE FUNCTIONAL CONTRIBUTIONS OF HIGHER ASSOCIATION CORTICES

The association cortices make distinct contributions to our attentional experience (summarized in Figure 1): the higher-order sensory cortices, such as the inferior temporal cortex, process sensory features and can focus resources on a particular detail, e.g., the color red; the posterior parietal association cortex allocates attentional resources, allowing us to orient attention in time and space; and the PFC regulates attention, inhibiting processing of irrelevant stimuli, sustaining attention over long delays, and dividing and coordinating attention. These cortical areas are intricately interconnected,[2] creating both feedforward and feedback

Figure 1. Brain Regions Involved in the Regulation of Attention in the Primate Brain as Shown on the Lateral Surface[a]



[a]The basal ganglia circuits are not evident from this view. The basal ganglia are thought to contribute to the automatic planning, selection, initiation, and execution of complex movements and thoughts.

loops[3] that work together to provide a unified attentional experience. The PFC plays a similar role in regulating movement, inhibiting inappropriate behavioral responses. The following is a brief review of these cortical systems.

Inferior Temporal Cortex

The inferior temporal cortex is specialized for processing visual features, determining "what" things are based on their color and shape. (In contrast, the superior temporal cortex processes auditory information, performing both featural and spatial analysis. This work has proceeded more recently[4] and thus will not be discussed in this review). Processing of a visual stimulus by inferior temporal neurons can be either diminished or enhanced, depending upon sensory conditions and internal directions (reviewed in Desimone[5] and Kastner et al.[6]). The activity of these neurons is captured by salient stimuli (e.g., high contrasts), but repeated experience with the same visual stimulus leads to decreased responding.[5] This decrease may account for the boredom of repetition, e.g., in a school setting. Processing of visual stimuli is also diminished by interference from nearby stimuli in the same visual field. Both of these suppressive effects result from intrinsic properties of inferior temporal neurons and can be prevented by inputs from the PFC or parietal association cortex. These "top-down" projections thus allow for directed selective attention of visual feature processing.

Posterior Parietal Association Cortex

The parietal association cortex plays a critical role in "paying attention."[7] This cortex is specialized for analyzing movement and spatial relationships, for analyzing quantity and constructing spatial maps, and for orienting attention in time and space.[8] Lesions to the right posterior parietal association cortex can result in contralateral neglect: the loss of perception for the left side of visual space. This cortex is therefore critical to conscious attention. Recordings from parietal neurons in monkeys are consistent with a role in the allocation of attention, including the covert movement of attention.[9] Neurons in area 7a also appear to create world-referenced maps of visual space,[10] and they project this information to the PFC, which uses this information to guide behavior during spatial working memory tasks.

Prefrontal Cortex

The PFC has particular relevance to ADHD, as imaging studies indicate that ADHD patients often have smaller PFC volume, particularly on the right side.[11–13] The PFC uses representational knowledge, i.e., working memory, to guide overt responses (movement) as well as covert responses (attention), allowing us to inhibit inappropriate behaviors and to gate the processing of irrelevant stimuli (reviewed in references 14–17). Patients with PFC lesions are easily distracted, have poor concentration and organization, are more vulnerable to disruption from proactive interference, and can be impulsive, especially when the lesions involve the right hemisphere.[18] PFC lesions impair the ability to sustain attention, particularly over a delay, and reduce the ability to gate sensory input.[19] PFC lesions impair divided and focused attention, and these attentional deficits have been associated with lesions in the left, superior PFC.[15] PFC lesions similarly impair attentional function in monkeys and rats, rendering animals more vulnerable to distraction or other types of interference and impairing attentional regulation on set-shifting tasks.[20,21]

Electrophysiologic studies in monkeys have shown that PFC neurons are able to hold modality-specific information "on-line" over a delay and use this information to guide behavior in the absence of environmental information. Importantly, PFC neurons can maintain delay-related firing in the presence of distracting stimuli, protecting performance from interference.[22] Delay-related firing also underlies behavioral inhibition, i.e., the ability to suppress a prepotent response.[23] Therefore, the cellular basis of many executive functions can be studied in monkeys performing higher cognitive tasks.

CORTICAL PROJECTIONS TO BASAL GANGLIA AND CEREBELLUM

The association cortices project down to both the basal ganglia and cerebellum in a series of parallel, closed-loop circuits.[24] The PFC and parietal and temporal association cortices all project to the caudate nucleus as part of the "cognitive circuit" through the basal ganglia, which in turn projects back to the PFC and premotor cortices. Simi-

larly, the PFC and parietal association cortices project to the cerebellum by way of the pontine nuclei, and the cerebellum in turn projects back to the association cortices by way of dentate projections to thalamus. Although the basal ganglia and cerebellum have long been known to be important for the regulation of movement, their role in higher cognitive function is just beginning to be researched. If these structures influence cognition in a manner similar to their influences on movement, the basal ganglia may be important for the planning, selection, initiation, and execution of thoughts, while the cerebellum may serve as a "biological gyroscope," correcting cognitive function on a faster timescale. Recent data suggest that the cerebellar circuits may influence basal ganglia circuits via projections through the intralaminar thalamic nuclei (P. Strick, Ph.D.; electronic communication; August 2005). Parts of the cerebellum have been found to be consistently smaller in children with ADHD.[25]

Interestingly, the basal ganglia are powerfully modulated by dopamine, while the cerebellum is heavily innervated by norepinephrine. Dopamine promotes thalamocortical stimulation of movement and thought via D_1-receptor activation of the direct pathways and D_2 inhibition of the indirect pathways in basal ganglia (for example, see Steiner and Gerfen[26]). Norepinephrine modulates cerebellar processing through β-receptor mechanisms that activate cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) intracellular signaling (for example, see Cartford et al.[27]). Therefore, genetic alterations that affect catecholamine actions may alter basal ganglia and cerebellar function. In addition to these dense subcortical projections, both dopamine and norepinephrine innervate the association cortices in primates,[28,29] and this will be the focus of the current review.

MODULATION OF CORTICAL CIRCUITS

There are multiple arousal systems that project to the cortical mantle. Although the present article focuses on dopamine and norepinephrine, the reader should remember that many more molecules perform related functions, e.g., acetylcholine, serotonin, and orexin. Research on the modulatory influences of dopamine and norepinephrine on parietal and temporal cortical function is limited, although existing research suggests that norepinephrine may enhance "signal/noise" processing in these areas via the actions of β- and α_1-adrenoceptors and impair the cognitive operations of these brain regions via α_2-adrenoceptors.[30–32] There has been a much greater tradition of studying catecholamine influences on PFC, given the landmark findings of Brozoski et al.,[33] who showed that catecholamine depletion in PFC is as destructive as ablation of the tissue itself. The following is a brief summary of this field (for more detailed reviews, see Arnsten and Robbins[34] and Arnsten and Li[35]).

Dopamine

Dopamine acts at both the D_1 (D_1 and D_5) and D_2 (D_2, D_3, and D_4) receptor families. It should be noted that norepinephrine has very high affinity for D_4-receptors[36] and thus should really be considered a catecholamine receptor rather than a dopamine receptor. Currently, there are no pharmacologic agents that distinguish D_1- from D_5-receptors; thus, these receptors are discussed as 1 entity. Finally, as there is little information on D_3-receptor actions in PFC at this time, this receptor is not reviewed.

D_1-receptor actions. The PFC is rich in D_1-receptors, with a bilaminar distribution found in both upper and lower layers.[37] The D_1 subtype is especially focused on spines, while the D_5 subtype is found more commonly on shafts of pyramidal neurons.[38] Stimulation of this family of receptors in the PFC produces an inverted "U"-shaped dose-response influence on the working memory and attention regulation processes of the PFC.[39,40] While modest levels of D_1-receptor stimulation are essential to PFC function, high levels of dopamine release, e.g., during exposure to stress, impair working memory. Therefore, high doses of D_1-agonist impair working memory performance. This inverted U has been observed in mice,[41] rats,[42] monkeys,[43] and humans.[44] A similar inverted "U" has been described at the cellular level (S. Vijayraghavan, B.S.; M. Wang, Ph.D.; S. G. Birnbaum, Ph.D., et al.; manuscript submitted), where moderate levels of D_1-receptor stimulation suppress neuronal processing of irrelevant information (i.e., reduce "noise"), sharpening tuning and rendering PFC firing more selective. In contrast, high levels of D_1-receptor stimulation reduce the relevant signals as well as noise, thus producing a nonspecific inhibition of cell firing. These effects most likely occur through cAMP/PKA intracellular signaling (S. Vijayraghavan, B.S.; M. Wang, Ph.D.; S. G. Birnbaum, Ph.D., et al.; manuscript submitted).

Human experiments also note an inverted "U," with the more D_1-like compounds being most effective in improving working memory.[45] Interestingly, genetic studies in humans indicate similar results.[44] Some people have a substitution (methionine for valine) in the enzyme catechol *O*-methyltransferase that breaks down dopamine and norepinephrine. The methionine substitution results in weaker enzyme activity and thus more dopamine. Under basal conditions, subjects with this substitution have better working memory and more efficient PFC activation than those with the native enzyme. However, following amphetamine and/or stress exposure, those with the methionine substitutions become markedly impaired (presumably due to excessive dopamine stimulation), while those with the native enzyme improve (presumably due to more optimal dopamine levels).[44]

D_2-receptor actions. There has been far less research on the influence of D_2-receptor stimulation on PFC function. D_2-receptors are concentrated on neurons in layer 5

(the output layer that projects to striatum) and overall show lower levels of binding than the D_1-receptor family.[37] Initial studies showed that blockade of D_2-receptors in the PFC of monkeys performing a working memory task had no effect on performance.[46] However, there was no room for improvement in this task, and studies in rats suggest that excessive D_2-receptor stimulation impairs working memory abilities.[47] Recent electrophysiologic studies have shown that D_2-receptor stimulation increases the response-related firing of PFC neurons in monkeys performing a working memory task,[48] consistent with the localization of these receptors on cells projecting to areas guiding movement. The response-related firing may be a form of corollary discharge, informing the brain that a response has taken place. Given the potential role of impaired corollary discharge in hallucinations, and the role of D_2 blockade in antipsychotic efficacy, these findings may have special relevance to schizophrenia.

D_4-receptor actions. D_4-receptors are concentrated on γ-aminobutyric acid (GABA)-ergic interneurons[49] and appear to inhibit GABA transmission via G_i-mediated reduction of cAMP signaling.[50] Weaker D_4-receptor actions thus lead to excessive GABA transmission and suppression of pyramidal cell firing (Wang et al.[50] and M. Wang, Ph.D.; A.F.T.A.; manuscript in preparation). ADHD is associated with the increased incidence of the 7-repeat polymorphism of the D_4-receptor, which weakens D_4-receptor efficacy.[51,52] Therefore, the basic physiology in animals would suggest that subjects with this polymorphism would have insufficient D_4 inhibition of GABA and thus insufficient PFC pyramidal cell firing. Stimulant medication may increase endogenous dopamine (and norepinephrine) stimulation of D_4-receptors, thus normalizing GABAergic inhibition. However, there is also some evidence from basic physiologic studies indicating that D_4-receptors can inhibit pyramidal cells,[50] so the actions of these receptors are not entirely straightforward.

Norepinephrine

Norepinephrine acts at α_1- and α_2-adrenoceptors and β_1-, β_2-, and β_3-adrenoceptors. Research to date indicates that it has distinct actions at these receptors, improving PFC function through actions at α_{2A}-receptors and impairing working memory through actions at α_1- and β_1-receptors.

α_{2A}-Adrenoceptor actions. Norepinephrine improves PFC function through actions at postsynaptic[53,54] α_{2A}-receptors[55] at both the cognitive and cellular levels (reviewed in Arnsten and Li[35]). The α_{2A}-agonist guanfacine improves working memory, attention regulation, behavioral inhibition, and/or planning in rodents,[55,56] monkeys,[57–60] and humans.[61] These enhancing effects are most likely mediated through G_i-mediated suppression of cAMP intracellular signaling.[62] Electrophysiologic studies have shown that α_2-receptor stimulation increases delay-related firing,[63] the cellular measure of working memory and behavioral inhibition (see Prefrontal Cortex). This increase is especially observed for the preferred spatial direction, indicating that α_{2A}-receptor stimulation increases "signals" in PFC (M. Wang, Ph.D.; A.F.T.A.; manuscript in preparation). Conversely, blocking α_2-receptors in monkey PFC with yohimbine markedly reduces delay-related cell firing[63] and impairs working memory[64] as well as impulse control.[65] Yohimbine infusions into PFC have also been shown to induce locomotor hyperactivity.[66] Therefore, insufficient α_2-receptor stimulation in monkey PFC can re-create the profile of ADHD. In this regard, it is of interest that ADHD has been associated with genetic alterations in dopamine β-hydroxylase (DBH), the enzyme that synthesizes norepinephrine. It is possible that weaker DBH would lead to insufficient endogenous stimulation of α_{2A}-receptors in PFC, resulting in a profile similar to that of yohimbine-treated monkeys. Stimulant or α_{2A}-agonist medications might correct this condition. Guanfacine is currently used for treating ADHD,[67–69] especially in patients who cannot take stimulants, e.g., those with tics or risk of drug abuse.

α_1-Adrenoceptor actions. In contrast to α_2-receptor mechanisms, high levels of norepinephrine release (e.g., during stress) impair PFC function through actions at α_1-receptors coupled to protein kinase C (PKC) intracellular signaling.[70] Thus, agonists such as phenylephrine (similar to pseudoephedrine) impair working memory when infused into the PFC in rats[71] and monkeys.[59] Similar effects are observed at the cellular level, where α_1-receptor stimulation suppresses delay-related neuronal firing.[70] Conversely, α_1-antagonists such as urapidil and prazosin protect PFC cognitive abilities, preventing stress-induced PFC impairment.[72,73] The PKC inhibitor chelerythrine also protects PFC function at the behavioral and cellular levels.[70] On the basis of this research in animals, prazosin is being successfully used to treat patients with posttraumatic stress disorder.[74] Interestingly, most effective antipsychotic medications, including the "atypical" neuroleptics, have potent α_1-blocking properties, and overactivity of the PKC signaling pathway has been associated with mania[75] and possibly schizophrenia.[76] These mechanisms may be particularly relevant in children who have symptoms resembling ADHD that worsen with stimulant treatment and who are found to have childhood bipolar disorder.[77]

β_1-Adrenoceptor actions. Recent studies suggest that stimulation of β_1-adrenoceptors impairs PFC function.[78] Therefore, systemic or local application of the β_1-antagonist betaxolol improved working memory in rats and monkeys. However, this treatment appeared to be associated with serious pancreatic side effects and thus may not be appropriate for human use.

Summary

The PFC appears to thrive under conditions of moderate catecholamine release, when norepinephrine α_{2A}-receptor

stimulation increases "signals" and optimal dopamine D_1-receptor stimulation decreases "noise." In contrast, PFC working memory functions are impaired under conditions of high catecholamine release that engage α_1- and β-receptors and excessive D_1-receptor stimulation. These neurochemical needs are opposite to those of posterior cortical and subcortical structures.[79] Therefore, catecholamines may act as a chemical switch, turning on PFC during normal waking and turning it off during drowsiness or stress. In contrast, high levels of catecholamines may turn on more primitive brain structures such as the amygdala for more automatic control of behavior under conditions of danger.[80]

RELEVANCE TO ADHD MEDICATIONS

Drugs such as amphetamine and methylphenidate act to enhance the release and/or inhibit the reuptake of both dopamine and norepinephrine. Methylphenidate can improve PFC working memory function and enhance the efficiency of PFC activation in healthy adult humans[81,82] as well as in patients with ADHD.[83] Recent studies in rats show that low oral doses of methylphenidate that produce plasma drug levels similar to therapeutic doses in humans[84] also improve PFC function.[85] These enhancing effects in rodents depend on dopamine D_1- and norepinephrine α_2-receptor stimulation.[85] It is likely that both dopamine and norepinephrine actions contribute to the therapeutic effects of stimulants in patients with ADHD. In contrast, excessive doses of stimulant medication may produce cognitive inflexibility through α_1-, β-, and high D_1-receptor stimulation.

In summary, catecholamines have powerful influences on the brain circuits that appear altered in ADHD. Medications that optimize catecholamine transmission may normalize the function of these circuits and ameliorate ADHD symptomatology.

Drug names: amphetamine (Adderall and others), betaxolol (Kerlone and others), guanfacine (Tenex and others), methylphenidate (Ritalin, Concerta, and others), prazosin (Minipress and others), pseudoephedrine (Sudafed, Efidac, and others).

Disclosure of off-label usage: The author has determined that, to the best of her knowledge, guanfacine is not approved by the U.S. Food and Drug Administration for the treatment of attention-deficit/hyperactivity disorder, and prazosin is not approved for the treatment of posttraumatic stress disorder.

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