REVIEW ARTICLE

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Toward a New Understanding of Attention-Deficit Hyperactivity Disorder Pathophysiology

An Important Role for Prefrontal Cortex Dysfunction

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Abstract

Recent advances in neurobiology have aided our understanding of attention-deficit hyperactivity disorder (ADHD). The higher-order association cortices in the temporal and parietal lobes and prefrontal cortex (PFC) interconnect to mediate aspects of attention. The parietal association cortices are important for orienting attentional resources in time/space, while the temporal association cortices analyse visual features critical for identifying objects/places. These posterior cortices are engaged by the salience of a stimulus (its physical characteristics such as movement and colour). Conversely, the PFC is critical for regulating attention based on relevance (i.e. its meaning). The PFC is important for screening distractions, sustaining attention and shifting/dividing attention in a task-appropriate manner. The PFC is critical for regulating behaviour/emotion, especially for inhibiting inappropriate emotions, impulses and habits. The PFC is needed for allocating/planning to achieve goals and organizing behaviour/thought. These regulatory abilities are often referred to as executive functions. In humans, the right hemisphere of the PFC is important for regulating distractions, inappropriate behaviour and emotional responses. Imaging studies of patients with ADHD indicate that these regions are underactive with weakened connections to other parts of the brain.

The PFC regulates attention and behaviour through networks of interconnected pyramidal cells. These networks excite each other to store goals/rules to guide actions and are highly dependent on their neurochemical environment, as small changes in the catecholamines noradrenaline (NA) or dopamine (DA) can have marked effects on PFC function. NA and DA are released in the PFC according to our arousal state; too little (during fatigue or boredom) or too much (during stress) impairs PFC function. Optimal amounts are released when we are alert/interested. The beneficial effects of NA occur at postsynaptic α_{2A}-receptors on the dendritic spines of PFC pyramidal cells. Stimulation of these receptors initiates a series of chemical events inside the cell. These chemical signals lead to the closing of special ion channels, thus strengthening the connectivity of network inputs to the cell. Conversely, the beneficial effects of moderate amounts of DA occur at D_1 receptors, which act by weakening irrelevant inputs to the cells on another set of spines. Genetic linkage studies of ADHD suggest that these catecholamine

pathways may be altered in some families with ADHD, e.g. alterations in the enzyme that synthesizes NA (DA β-hydroxylase) are associated with weakened PFC abilities.

Pharmacological studies in animals indicate catecholamine actions in the PFC are highly relevant to ADHD. Blocking NA α_{2A}-receptors in the PFC with yohimbine produces a profile similar to ADHD: locomotor hyperactivity, impulsivity and poor working memory. Conversely, drugs that enhance α_2-receptor stimulation improve PFC function. Guanfacine directly stimulates postsynaptic α_{2A}-receptors in the PFC and improves functioning, while methylphenidate and atomoxetine increase endogenous NA and DA levels and indirectly improve PFC function via α_{2A}- and D_1 receptor actions. Methylphenidate and atomoxetine have more potent actions in the PFC than in subcortical structures, which may explain why proper administration of stimulant medications does not lead to abuse. Further understanding of the neurobiology of attention and impulse control will allow us to better tailor treatments for specific patient needs.

Over the last two decades there have been significant breakthroughs in our understanding of the neurobiology of attention and impulse control, and how changes in these circuits may contribute to the symptoms of attention-deficit hyperactivity disorder (ADHD). Much of this research has focused on the prefrontal cortex (PFC), a highly evolved region of the brain that regulates attention and behaviour through its widespread connections to sensory and motor cortices, and to subcortical structures such as the basal ganglia and cerebellum. The PFC is especially sensitive to its neurochemical environment, and relatively small changes in catecholamine levels can produce large changes in PFC function. Thus, genetic insults in the pathways mediating catecholamine transmission can impair PFC function whereas medications that optimize catecholamine actions can normalize PFC regulation of attention and behaviour. This article provides a brief review of the cortical circuits mediating attention and impulse control, the dependence of PFC circuits on proper catecholamine transmission, and how these circuits may be altered in ADHD and its treatment.

1. Association Cortices as Substrates of Distinct Aspects of Attention

The term 'attention' loosely refers to a variety of interleaved cortical operations that allow us to process and consciously perceive external and/or internal stimuli. In general, the association cortices in the posterior part of the brain 'pay attention': they analyse what and where stimuli are and respond to stimuli based on their inherent salience (e.g. whether they are brightly coloured, loud, moving, etc.). In contrast, the PFC in the anterior part of the brain regulates attention, inhibiting distractions and sustaining and shifting attention according to stimulus relevance (e.g. paying attention to a boring maths problem because it will be in a test). A brief summary is presented in table I.

The sensory association cortices are situated in the occipital, temporal and parietal lobes in the

Table I. Association cortices and components of visual attention

Association areas	Associated aspect of attention
Temporal + parietal	Orienting based on salience rather than relevance
Inferior temporal cortex	Feature analysis and recognition
Posterior parietal cortex	Analysis of spatial position; perception of movement, orienting in time (left hemisphere) and space (right hemisphere)
Prefrontal cortex (especially right hemisphere)	Regulates attention based on relevance
	Suppresses processing of irrelevant stimuli and enhances processing of relevant stimuli
	Sustains attention on relevant sources, shifts attention to relevant dimensions

posterior part of the brain. These regions have been the focus of intense human imaging and monkey physiology research. Scientists have identified two general streams of visual information processing: a ventral stream that is directed from the primary visual cortex toward the inferior temporal cortex[1] and a dorsal stream that emanates into the parietal association cortices.[1] The ventral stream in the inferior temporal association cortex is responsible for visual-feature analysis and recognition. Lesions to this area cause visual agnosia – the inability to recognize objects or faces. In contrast, the dorsal stream processes visuospatial position and movement, and is important for orienting attention in space (with the right hemisphere in particular) and in time (with the left hemisphere in particular). Lesions to the right parietal association cortex cause contralateral visuospatial neglect,[2] the inability to perceive stimuli in the left hemifield of visual space. The dorsal and ventral pathways interconnect to provide cohesive, conscious perception. Together, the parietal and temporal cortices provide 'bottom-up' attention (i.e. orientation to stimuli based on their salience) [figure 1a].

The sensory association cortices project their information to the PFC, which regulates attention based on relevance (i.e. so-called top-down attention) [figure 1a]. The PFC has extensive projections back to the sensory association cortices to suppress the processing of irrelevant stimuli (distractions)[3] and enhance the processing of nonsalient but meaningful stimuli (e.g. a mathematics book).[4] The PFC is also important for sustaining attention over a delay, for concentration, and for shifting and dividing attention according to task demands (reviewed in Arnsten[5]). The attention operations of the PFC are those most commonly afflicted in ADHD (see below).

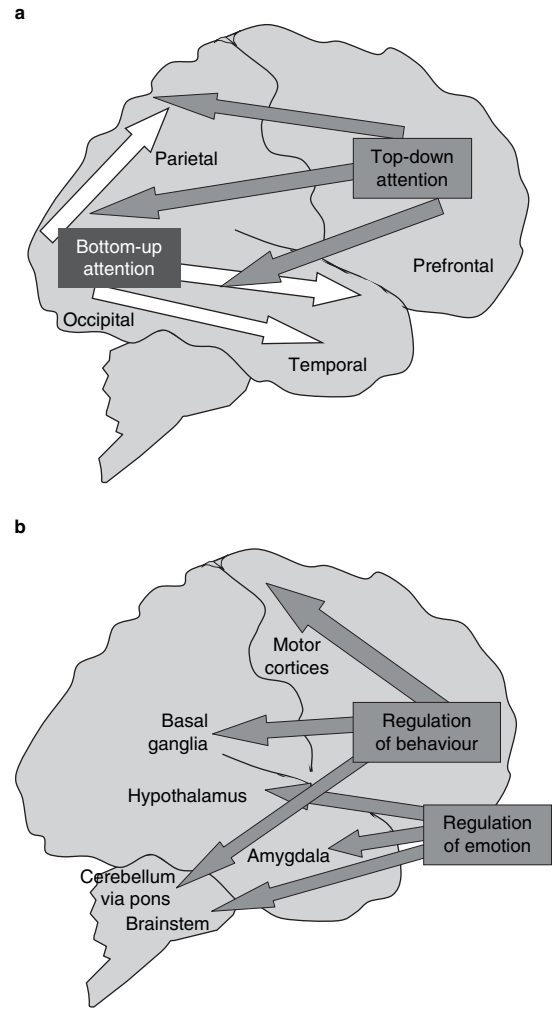

Fig. 1. (**a**) The association cortices mediate different aspects of attention. The posterior sensory cortices mediate 'bottom-up' attention based on the salience of stimulus characteristics (e.g. bold, moving stimuli, as in video games), whereas the prefrontal cortices mediate 'top-down' attention based on stimulus relevance (e.g. focusing on a history book in preparation for a test). (**b**) The prefrontal cortices also regulate behaviour and emotion. The prefrontal cortex has extensive interconnections with the motor cortices and subcortical structures such as the caudate and cerebellum to regulate behaviour, and with the amygdala, hypothalamus, nucleus accumbens and brainstem to regulate emotion.

2. The Prefrontal Cortex Regulates Behaviour and Emotion as Well as Attention

In addition to regulating attention, the PFC also regulates behaviour and emotion (figure 1b). Taken together, these abilities are often referred to as 'executive functions', functions that are essential for organizing and planning for the future. The PFC is functionally specialized by region. The dorsal and lateral portions of the PFC regulate attention and motor responses via connections with the sensory and motor cortices,

the basal ganglia and the cerebellum.[6,7] In contrast, the ventral and medial portions regulate emotion through extensive projections with the amygdala, hypothalamus, nucleus accumbens and brainstem nuclei that mediate the arousal response.[8]

The right inferior PFC is especially important for the regulation of behavioural responses.[9] Functional human imaging studies have shown that this region is active when subjects successfully inhibit or stop movements, while transmagnetic stimulation of this area can weaken the ability to stop an ongoing movement.[10,11] Lesions to this region of the PFC in monkeys induce hyperactivity and impulsivity.[12] Imaging studies have often shown that the right inferior PFC is underactive in patients with ADHD.[13,14]

The ventral (orbital) and medial portions of the PFC regulate emotion and are needed for appropriate social behaviour. Lesions to the right ventral PFC are associated with syndromes of disinhibited emotion, such as those observed in mania.[15] Dysfunction of these pathways may be involved with the oppositional symptoms that are often comorbid with ADHD.[16]

Pyramidal cells of the PFC form higher-order networks that process and transmit goals and other relevant information that regulate attention, behaviour and emotion. These networks use glutamate as their neurotransmitter and are able to excite each other to maintain firing even in the absence of environmental stimulation.[17] These PFC networks are highly sensitive to their neurochemical state, and thus are especially susceptible to genetic and environmental insults. PFC networks make their connections on the dendritic spines of PFC pyramidal cells. These dendritic spines bear noradrenaline (NA) α_{2A}-receptors[18] or dopamine (DA) D_1 receptors,[19] and receive NA and DA input from arousal systems in the brainstem.

3. The Critical Role of Noradrenaline and Dopamine in Prefrontal Cortex Function

The catecholamines NA and DA are so critical to PFC function that depleting them is as detrimental as removing the cortex itself.[20] The stimulation of postsynaptic α_{2A}-receptors by NA enhances PFC function by strengthening appropriate network connections and allowing networks to maintain their firing for long periods (increasing 'signals'). In contrast, the stimulation of D_1 receptors by DA exerts its beneficial effects by weakening inappropriate connections (decreasing 'noise') [reviewed in Arnsten[21]].

3.1 Noradrenaline

Moderate levels of NA release (e.g. when we are alert and interested) engage α_2-receptors, which have a high affinity for NA. There are three subtypes of α_2-receptors: A, B and C. The A subtype is concentrated in the PFC. α_{2A}-Receptor stimulation improves PFC regulation of attention, behaviour and emotion by strengthening network connections between neurons with shared inputs.[18] Conversely, blockade of α_2-receptors in monkey PFC with yohimbine induces a profile similar to that of ADHD: inducing locomotor hyperactivity and impulsivity, and impairing working memory.[22-25]

In contrast to the beneficial effects of moderate NA release, high levels of NA release engage lower-affinity α_1- and β-receptors, which impair PFC function. Very high levels of NA release can occur during exposure to stress (including chronic stress), and with excessive stimulant doses.[26,27] High levels of NA release during stress impair PFC function through the engagement of α_1-receptors, which suppress PFC cell firing.[28] NA can also have detrimental actions through the stimulation of β_1-receptors.[29]

3.2 Dopamine

Dopamine is also essential to PFC function.[20] Most research has focused on the D_1 family of receptors, as these are most abundant in the PFC.[30] As with NA, either too little or too much DA D_1 receptor stimulation impairs PFC function (figure 2). Moderate levels of D_1 receptor stimulation improve PFC working memory functions by suppressing inputs to the cell that are irrelevant to current demands.[31] However, excessive levels of D_1 receptor stimulation, which occurs during stress or an excessive dose of

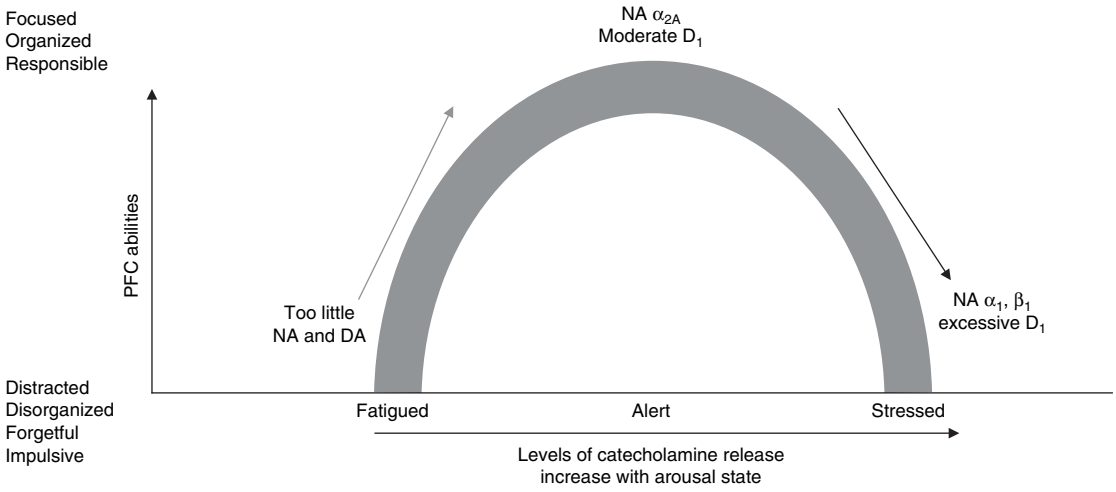

Fig. 2. The prefrontal cortex (PFC) is very sensitive to its neurochemical environment. The catecholamines are released in the PFC according to an arousal state, based on the relevance of the stimuli occurring in the environment. Either too little or too much catecholamine release impairs PFC function. Moderate levels of noradrenaline (NA) engage postsynaptic α_{2A}-receptors to improve PFC function, while high levels engage α_1 and β, which impair PFC function. Animal studies suggest that therapeutic doses of stimulants improve PFC function by increasing endogenous NA and dopamine (DA) stimulation of α_{2A} and D_1 receptors, respectively.

stimulant medication, impairs PFC function by weakening too many network connections and suppressing all neuronal firing.[31]

DA also has important effects on PFC function via DA D_2 and D_4 receptors, the latter of which is particularly relevant to ADHD. D_2 receptor stimulation in PFC modulates a response-related firing of PFC neurons,[32] while D_4 receptor stimulation may be particularly important for the suppression of γ-aminobutyric acid (GABA)-containing inhibitory neurons.[33] Thus, inadequate D_4 receptor actions, as can occur with the genetic variations in this receptor, may lead to excessive inhibition of PFC network firing. However, these receptors have not been studied as well as D_1 receptors.

4. The Prefrontal Cortex, Catecholamines and Attention-Deficit Hyperactivity Disorder

The symptoms of ADHD are similar to those caused by lesions to the right PFC, and imaging studies have indeed shown reduced size and functional activity of the right PFC in patients with ADHD.[13,34-38] The white matter tracks emanating from the PFC are also more disorganised in patients with ADHD, consistent with weaker prefrontal connectivity.[39,40] Other brain regions connected to the PFC, notably the caudate and cerebellum, also have been reported to be smaller in some studies of children with ADHD.[41] There is also evidence of slower prefrontal maturation,[42] although ADHD is often a lifelong disorder.[43,44]

ADHD is highly heritable but complex, where multiple genes each contribute a small risk to ADHD symptomatology.[45] Many linkage studies report alterations in the genes encoding for molecules involved in catecholamine signalling: the DA D_1 and D_5 receptors, the DA and NA transporters, the D_4 receptor, the α_{2A}-receptor and DA β-hydroxylase, the enzyme needed for the synthesis of NA.[45,46] There are also associations with the catabolic enzyme monoamine oxidase and some serotonergic genes. Recent studies have begun to relate genotype to symptomatology. For example, genetic variation in the gene encoding for DA β-hydroxylase is related to deficits in executive function and the ability to sustain attention.[47,48] These studies suggest that weaker NA production may impair the PFC

circuits mediating the regulation of attention and behaviour.

Neuroreceptor imaging also supports weakened catecholamine transmission in adults with ADHD. The vast majority of this work has focused on DA mechanisms in the striatum, as there are currently no good tracers with which to image NA or DA levels in the cortex. There have been mixed results with studies of the DA transporter in the striatum, possibly reflecting genetic heterogeneity in the DA transporter gene. A recent imaging study has assessed DA release in the striatum and found evidence of decreased DA release in adult patients with ADHD.[49] It is likely that this reflects global reductions in DA release throughout the brain, as earlier research has suggested reduced catecholamine levels in the PFC as well,[50] and it is DA depletion in the PFC, not the striatum, that induces hyperactivity.

5. Treatments for Attention-Deficit Hyperactivity Disorder Enhance Catecholamine Actions in the Prefrontal Cortex

All currently approved pharmacotherapies for ADHD – stimulant and nonstimulant – potentiate catecholamine transmission in the PFC. Stimulant therapies, such as methylphenidate and amphetamine salts, block the transporters for both DA and NA. It is important to note that stimulants do not have paradoxical effects in individuals with ADHD; they improve PFC functions in normal individuals as well as those with ADHD.[51] In rats, as in humans, lower, therapeutic doses of stimulants reduce locomotor activity and improve PFC cognitive function.[27,52] These doses also preferentially increase catecholamine release in the PFC compared with subcortical regions, which may explain why, when used correctly, they actually protect against drug abuse.[27]

Although methylphenidate is often referred to as a DA drug, lower, beneficial doses of stimulants actually have a greater effect on NA release than on DA release in the PFC in rats.[27] In rats, the cognitive benefits are mediated by the increase of endogenous stimulation of both NA α_2- and DA D_1 receptors.[52] The nonstimulant atomoxetine also acts via NA- and DA-related mechanisms in the PFC. It selectively blocks the NA transporter, which is responsible for clearing both DA and NA in the PFC.[53] The cognitive adverse effects of high-dose stimulant medications may involve excessive catecholamine actions in PFC. Very high doses of stimulants may reduce creativity and induce mental inflexibility by undue narrowing of network inputs and large reductions in PFC firing.

The α_2-agonists clonidine[54] and guanfacine[55] mimic NA actions in the PFC through the stimulation of α_{2A}-receptors on PFC neurons. Clonidine has high affinity for all three subtypes of α_2-receptors (A, B and C), as well as for imidazoline I1 receptors,[56,57] which mediate many of the hypotensive effects of clonidine in the brainstem.[58] The sedative effects are probably mediated via all three subtypes, including potent actions at presynaptic receptors and actions in the thalamus.[59] Guanfacine acts more preferentially at postsynaptic NA α_{2A}-receptors, strengthening PFC network connectivity.[18] Animal studies have shown that guanfacine improves a variety of PFC functions, including working memory, response inhibition, attention regulation and conditional motor responding.[60-66] Electrophysiological studies have demonstrated that guanfacine enhances prefrontal network activity.[18] Guanfacine is currently given to patients with ADHD who cannot take stimulant medications because of tics, aggressive impulses or drug abuse liability. In these patients, guanfacine has been shown to improve ratings on both the Inattention and Hyperactivity-Impulsivity scales, which is consistent with its widespread beneficial effects on many PFC functions.[67-69]

6. Conclusion

The temporal, parietal and prefrontal association cortices mediate different aspects of attention. The right hemisphere of the PFC is especially important for 'top-down' attentional processes and for impulse control, which are often impaired in ADHD. The catecholamines NA and DA have powerful influences on PFC

function, and proper levels are required for optimal PFC function. A growing body of evidence indicates weakened PFC circuits among patients with ADHD. Genetic studies are also finding links with altered catecholamine transmission in some families (e.g. alterations in the synthetic enzyme for NA are associated with weaker PFC function). Treatments for ADHD enhance catecholamine actions in PFC and improve PFC functions in animals and humans. Although previous work has focused on stimulant actions on DA transmission in the striatum, recent data indicate that therapeutic doses have even more powerful effects in the PFC, where they increase levels of NA as well as DA. A deeper understanding of the neurobiology of attention and impulse control and their relationship to genetic and environmental insults will allow us to better match treatments with the individual needs of patients.

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