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THE NEUROBIOLOGY OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER

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1. ABSTRACT

Attention-deficit hyperactivity disorder is a childhood psychiatric disorder characterized by inattention, impulsivity, and overactivity. Considerable research has focused on the neurobiological substrates of this disorder. Although the specific nature of the brain dysfunction remains elusive, progress has been made and several models of the underlying pathophysiology have been suggested. Research in the fields of neuropsychology, neuroimaging, neurochemistry, and molecular genetics, which points to a multifactorial etiology for the disorder, is reviewed. While several inconsistencies exist across studies, evidence supports dysfunction of fronto-striatal dopaminergic and noradrenergic circuits with resultant executive deficits in cognitive functioning.

2. INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a childhood psychiatric diagnosis, defined according to the presence of symptoms in three domains: inattention, impulsivity, and motor overactivity. Symptoms of inattention include: difficulty maintaining attention and completing tasks, making careless mistakes, not listening, being highly distractible, often losing things, avoiding tasks that require concentration, and being forgetful and disorganized. Behaviors in the realm of hyperactivity and impulsivity are being fidgety and noisy, having difficulty staying seated or waiting in line, being constantly "on the go," interrupting others, and running around excessively. In order to qualify for the diagnosis these symptoms must be present substantially more often than in children of the same age and gender, present across settings (e.g., not only confined to school or home), cause impairment in functioning, and have begun by age seven. The most recent edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) describes three subtypes of the disorder: predominantly inattentive, predominantly hyperactive/ impulsive and a combined type which exhibits features of inattention, impulsivity, and hyperactivity (1). Changes in the conceptualization of ADHD over time are reflected in the revisions of the diagnosis in the DSM. DSM-III considered inattention to be the central feature of the diagnosis and described two subtypes of the disorder based on the presence or absence of hyperactivity in addition to inattention and impulsivity (2). DSM-III-R established a unidimensional framework and did not require a minimum threshold of symptomatology in any of the three behavioral domains (3). The behavioral deficits of ADHD are estimated to be present in 3-5% of all school age children and are believed to arise in early childhood (1).

Often, diagnosis of the disorder persists over development (4), although hyperactivity symptoms tend to diminish with age. Long term follow-up studies indicate that a substantial portion of children with ADHD experience academic/vocational difficulties and as many as 40% may develop antisocial personality disorder, substance abuse and/or criminality during adolescence and adulthood. With regard to the primary symptomatology, long-term outcomes of ADHD include complete remittance of symptomatology, residual ADHD symptoms, or persistence of the full syndrome (5-8).

Using current diagnostic nomenclature, a heterogeneous group of children receive the diagnosis of ADHD. Many of these children qualify for at least one other psychiatric or cognitive diagnosis. Comorbid diagnoses commonly seen in children with ADHD include oppositional defiant disorder and conduct disorder (up to 50% of children), anxiety disorders (25-35%), mood disorders (approximately 15%) and learning disabilities (between 20-30%) (9).

Psychostimulant medications are effective in alleviating the cardinal symptoms of ADHD and are widely

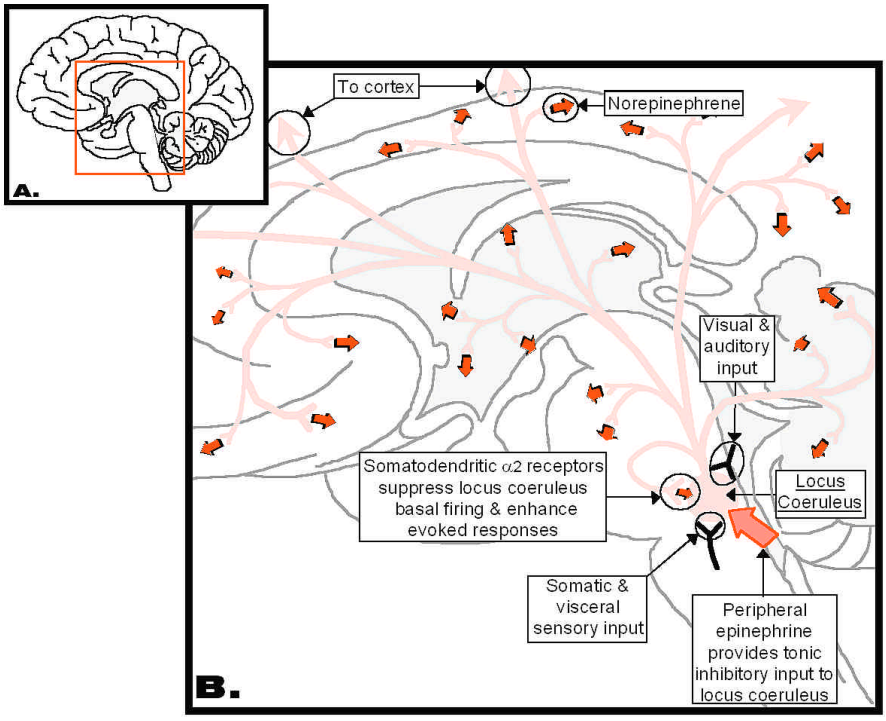

Figure 1. Neurochemical model of attention-deficit hyperactivity disorder (ADHD) proposed by Medford and Potter (1989). A. Mid-sagittal view of the brain with area of detail highlighted. B. Detailed view of the brainstem with the afferents and efferents of the locus coeruleus illustrated.

used to treat the disorder in both children and adults (10). Use of psychostimulant medications dates to 1937, when Bradley first observed that psychostimulants ameliorate certain disruptive behaviors in children (11). Since that time, there has been keen interest in understanding the precise nature of symptoms in children who respond to stimulant medications and also to elucidate the neurobiological basis of ADHD. Despite considerable advances, particularly in recent years, the specific nature of the brain dysfunction in ADHD has remained elusive.

The robust response of children with ADHD to a variety of medications, and in particular to psychostimulants, has strongly indicated a biological etiology (12). Yet, attempts to distinguish children with ADHD from normal or psychiatric controls on measures of cognitive/neuropsychological function (13), neurotransmitter activity (12), genetic factors (13), and, most recently, neuroanatomy (14) have yielded inconsistent results. Nevertheless, findings from studies of neuropsychological, neurochemical, genetic, and neuroanatomical factors have offered glimpses into the nature of the pathophysiology of ADHD. Based on these findings, several investigators have proposed neurobiological/neuropsychological models that attempt to account for the deficits in sustained attention and inhibitory control that are characteristic of children with ADHD (16-19).

A relatively early model (18), shown in figure 1, postulated that noradrenergic (NE) dysfunction in the brainstem nucleus locus coeruleus (LC) produces the deficits in vigilance and sustained attention seen in ADHD. The LC is a large cluster of NE neurons in the dorsal pons that has extensive projections to virtually every level of the neuraxis (20). Research in monkeys has demonstrated that the LC is involved in the selective processing of sensory stimuli, with attended, but not unattended, stimuli evoking large phasic increases in firing (21). The responsiveness of the LC to sensory signals is modulated, in large part, by somatodendritic alpha-2 NE autoreceptors (22). Stimulation of these autoreceptors by the increased NE released from axon collaterals of the LC in response to stimuli suppresses basal firing and enhances evoked responses in the nucleus (23). Further regulation of the LC is provided by a tonic inhibitory input from peripheral epinephrine (18). According to this model, the loss or perturbation of either of these two inputs to the LC causes a hyperreactivity that disrupts stimulus-evoked responding (24), which might produce the deficits in sustained attention characteristic of ADHD (18).

Pliszka *et al.* (19) incorporated findings from cognitive neuroscience into a multi-stage model of ADHD, shown in figure 2, that implicates dysfunction in multiple neurotransmitter systems. Studies in humans indicate that attentional functions are distributed into a posterior attention system, which orients to and engages novel stimuli, and an anterior system that subserves executive functions (25). The posterior attention system, which includes the superior parietal cortex, the superior colliculus, and the pulvinar nucleus, receives dense NE innervation

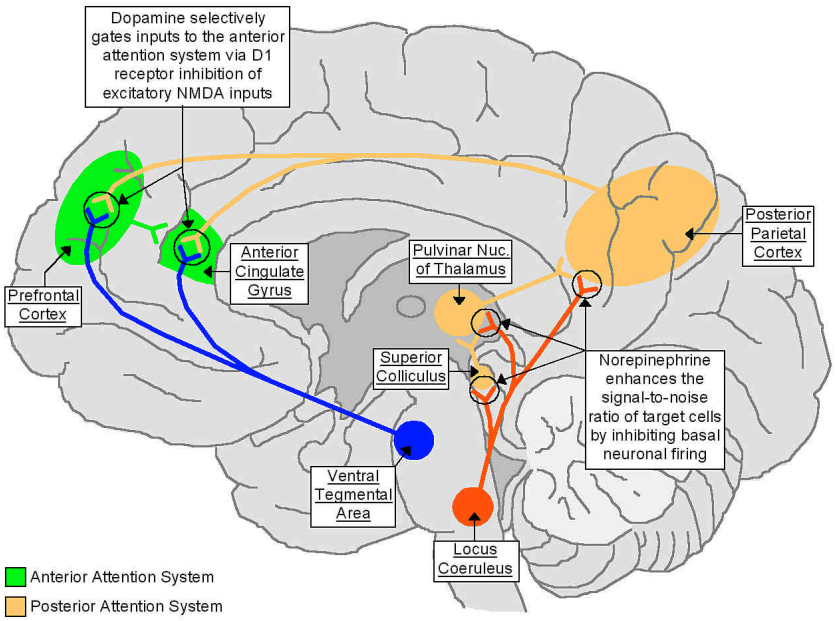

Figure 2. Mid-sagittal view of the brain illustrating Plitzska *et al.* (1996) multi-stage model of attention-deficit hyperactivity disorder (ADHD). *Red lines* indicate noradrenergic pathways and *blue lines* represent dopaminergic pathways.

from the LC (26). NE inhibits the spontaneous discharge of neurons, which enhances the signal-to-noise ratio of target cells and primes the posterior system to orient to and engage novel stimuli (27). Attentional function then shifts to the anterior executive system, which consists of the prefrontal cortex (PFC) and the anterior cingulate gyrus. The responsiveness of the PFC and anterior cingulate to the incoming signals is modulated primarily by dopaminergic (DA) input from the ventral tegmental area in the midbrain (28). Ascending DA fibers stimulate postsynaptic D1 receptors on pyramidal neurons in the PFC and anterior cingulate, which in turn, facilitate excitatory NMDA receptor inputs from the posterior attention system (29). Thus, DA selectively gates excitatory inputs to the PFC and cingulate, thereby reducing irrelevant neuronal activity during the performance of executive functions. According to Pliszka *et al.* (19), inability of NE to prime the posterior attention system could account for the attentional problems seen in children with ADHD, while the loss of DA's ability to gate inputs to the anterior executive system may be linked to the deficit in executive functions characteristic of ADHD.

In contrast to the two previous models, which focus on the role of NE in the regulation of attention, Arnsten *et al.* (16) (see figure 3) proposed that perturbation of NE receptor function in the PFC produces the deficits in inhibitory control characteristic of ADHD. The PFC receives higher-order sensory and mnemonic input from parietal and temporal association cortices (30), and in turn, exerts inhibitory control over motor functions through connections with the caudate nucleus (31). The PFC also inhibits the processing of irrelevant sensory stimuli through reciprocal connections with the association cortices (30), thereby protecting on-going cognitive tasks from interference (32,33). NE input from the LC is critical for these inhibitory functions of the PFC (34). Ascending NE fibers stimulate postsynaptic alpha-2 adrenoceptors on pyramidal cells in the PFC (35), which inhibit spontaneous cell firing, thereby enhancing the signal-to-noise ratio of PFC neurons (36). This alpha-2 adrenoreceptor mechanism primes the PFC to a) process task-relevant stimuli, b) suppress task-irrelevant stimuli, and c) inhibit behavior (16). Arnsten *et al.* (16) argue that diminished brainstem NE activity and release cause a partial denervation of postsynaptic alpha-2 receptors in the PFC, which disrupts the inhibitory control functions of the PFC. In turn, this produces the deficits in behavioral inhibition characteristic of children with ADHD.

Noting that the current clinical view of ADHD (i.e., hyperactivity-impulsivity and inattention) can not account for the many cognitive deficits associated with the disorder, Barkley (17) presented a model which postulates that the various deficits associated with ADHD emanate from a central impairment in behavioral inhibition. Whereas laboratory measures have failed to identify an actual deficit in attention in children with ADHD (37), considerable research has supported a deficit in response inhibition in these children (38). According to the model presented by Barkley (17), in addition to producing the impulsive and hyperactive behavior of children with ADHD, this inhibitory deficit causes ancillary impairments in four executive functions that require inhibition for their effective performance. These secondary impairments in a) working memory, b) self-regulation of affect/motivation/ arousal, c) internalization of speech (e.g., rule-governed behavior, reflection), and d) reconstitution (e.g., synthesis

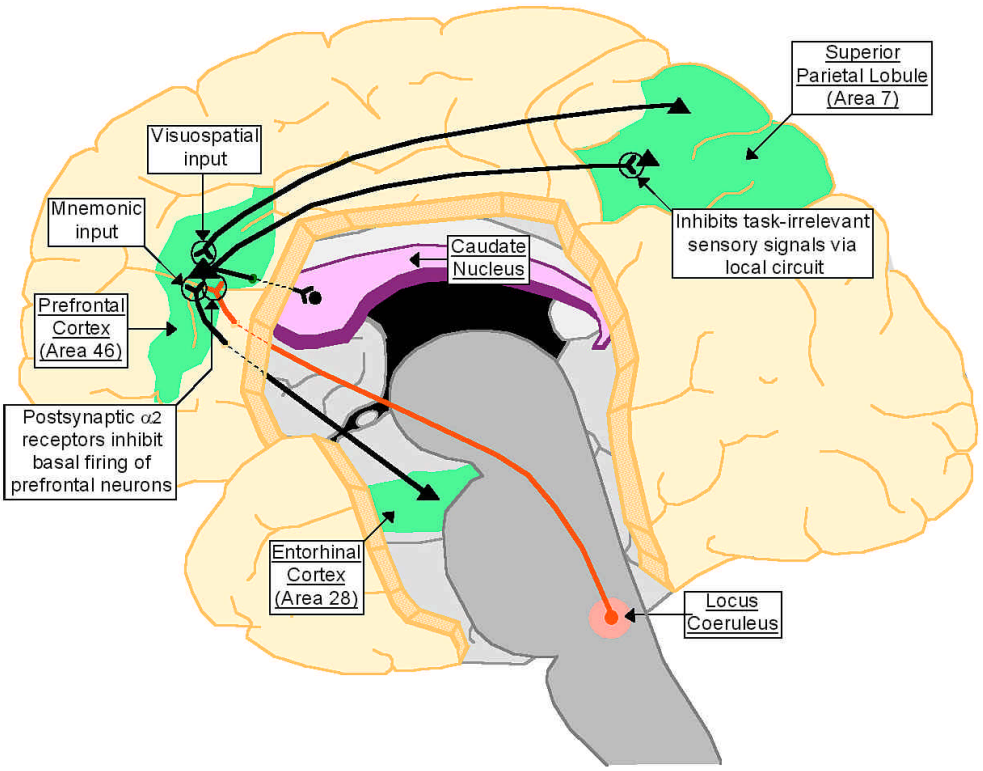

Figure 3. Neuroanatomical and functional model of attention-deficit hyperactivity disorder developed by Arnsten *et al.* (1996). Lateral view of the brain with a section of the cortex removed. *Red lines* represent noradrenergic pathways and *black lines* indicate cortical pathways mediated primarily by excitatory amino acids.

of behavior, verbal fluency) yield the many cognitive and behavioral deficits associated with ADHD. Importantly, since these four neuropsychological capacities serve to regulate motor functions via internal representations and self-directed action, impairments in these abilities contribute to the impulsive and disorganized behavior seen in children with ADHD. Moreover, this reduced control of behavior via internal representations creates the appearance of poor sustained attention. According to Barkley (17), the deficits in response inhibition and the four related executive functions are associated with abnormalities of the PFC and its connections with the striatum.

While these four neuropsychological models of ADHD differ considerably, there are several similarities between them. Notably, three of the models involve pathophysiology of neural circuitry in the PFC. Furthermore, three models focus on perturbations of brainstem catecholaminergic systems in the pathophysiology of ADHD. Finally, three of the models stress the primacy of deficits in response inhibition and other executive functions in ADHD. This paper will review the neuropsychological, neuroimaging, neurochemical, and molecular genetics literature focusing on the neurobiological substrates of ADHD. Within each of these four domains, attempts will be made to examine the extent to which findings support the various hypothesized models of neurobiological dysfunction in ADHD. Areas where findings diverge will also be discussed, with consideration given to implications regarding validation of the disorder.

3. NEUROPSYCHOLOGICAL FUNCTION

Numerous studies have examined the cognitive/neuropsychological deficits seen in children with ADHD. Impaired information processing in children with ADHD was initially believed to be associated with an inability to attend appropriately during social and academic tasks (39). Support for an attentional deficit in children with ADHD principally derives from their poor performance, relative to normal controls, on attention-demanding laboratory tasks, such as a continuous performance test (CPT). When comparing the performance of children with and without ADHD on CPTs, children with ADHD have consistently displayed slower reaction times, greater within subject variability, and more omission and commission errors (40-45). However, mean differences in overall performance on the CPT between children with and without ADHD can be due to deficits in a variety of different processes (46). Importantly, the majority of studies that have examined the degree of performance decrement over time do not reliably show a difference between ADHD children and normal controls (47-49), suggesting that the attentional dysfunction in ADHD is not specific to sustained attention. This finding is at variance with descriptive characteristics of children with the disorder. Furthermore, most studies reviewed by van der Meere (37) have not demonstrated deficits in orientation, sustained,

focussed, or divided attention, nor in the encoding, memory search or decision stages of processing in ADHD children. Taken together, these findings suggest that there is no single type of attention dysfunction which is characteristic of ADHD.

More recently, investigators have suggested that the cognitive correlates of ADHD are principally accounted for by deficits in executive function (17). Executive function was defined by Luria (50) as those functions that are involved in the planning, regulation, and verification of an action. Some of the cognitive abilities included in this domain are self-regulation, set maintenance, response organization and cognitive flexibility. These functions are believed to be mediated by the PFC. Behavioral similarities between children with ADHD and adults with damage to the PFC support the hypothesis that prefrontal functioning may be a contributing etiological factor in ADHD (51, 52). However, despite the fact that numerous authors have hypothesized dysfunction of the PFC as a neurobiological substrate of ADHD, studies comparing the performance of children with and without ADHD on neuropsychological tests which assess executive functioning have yielded inconsistent results**.** Of note, discrepant results were found across studies that employed the same measures of executive function (for review of 22 studies, see 13).

Research comparing the performance of children with ADHD to normal controls on neuropsychological measures of executive function continues to exhibit the pattern of mixed results described by Barkley *et al.* in 1992 (13). Three recent studies found that children with ADHD exhibited impaired performance on some, but not all, measures of executive function relative to normal controls (53-55). Increasing attempts are being made by investigators to compare the performance of ADHD children and psychiatric or cognitively-impaired control groups on executive tasks to ascertain whether deficits in executive function are: a) inherent to ADHD, b) characteristic of a disorder which is commonly seen comorbid with ADHD, or c) found only in a circumscribed group of children with ADHD.

Several of these investigations have asked whether the presence of reading disabilities (RD), which co-occur relatively frequently among children with ADHD (20-30%, 56), accounts for some of the above findings. These studies focus on whether ADHD children with and without RD may represent distinct groups that differ in neuropsychological function. One of the early studies to investigate the behavioral and cognitive differences between subgroups of ADHD children with and without RD found that those without RD were more impulsive and had higher rates of conduct disorder, compared to the comorbid group who displayed poorer performance on measures of attentional, language and memory functions (57). Further research has shown that children with comorbid ADHD + RD differ from children who exhibit RD only in terms of their functioning in several domains related to executive function, e.g.: visuomotor integration and planning (58, 59), delayed recall of nonverbal material (60), and attention (61).

The differential neuropsychological functioning of ADHD children with and without RD has led some investigators to hypothesize that ADHD children who also have RD are similar to children with RD only and that the presence of ADHD in this group represents an epiphenomenon of their RD. In support of this hypothesis, McGee *et al.* (60) reported that children with comorbid RD + ADHD differ from those with pure ADHD, but not those with RD only, on measures of verbal and non-verbal neuropsychological functions. Furthermore, Pennington *et al.* (62) reported a double dissociation such that children with comorbid ADHD + RD performed poorly on measures of phonological processing, but demonstrated intact executive functions. In contrast, a group of ADHD children without RD exhibited the opposite pattern, i.e., deficits in executive function but not in phonological processing. Similarly, Hall *et al.* (63) found impairment on an executive function task in a group of pure ADHD children, that was not exhibited by ADHD children with comorbid RD, or by children with RD only.

On the other hand, a study conducted by Purvis and Tannock (64), comparing the three groups (ADHD with and without RD, and RD only) on measures of language function, did not support the findings of the Pennington and McGee groups. The RD group displayed aberrant expressive and receptive language, while the ADHD subjects without RD displayed organizational difficulties. However, the co-morbid group displayed difficulties in both organizational and language processing. The latter findings suggest that ADHD + RD does represent a true comorbidity, with characteristics of both disorders. Most recently, Lazar and Frank (65) found that the performance of learning disabled children with and without ADHD on executive function tasks did not differ from each other, while both groups performed worse than the ADHD only group. These findings also differ from those of Pennington *et al.* (62) and McGee (60) and suggest that executive function deficits are not exclusive to ADHD. It is noteworthy that the learning disabled group in the study of Lazar and Frank (65) included children with math, reading and/or spelling disabilities, whereas most of the other studies focused exclusively on children with RDs.

Additional efforts to understand the nature of the neurocognitive dysfunction seen in children with ADHD have concentrated on the array of psychiatric comorbidities commonly seen in ADHD. Research comparing the performance of children with ADHD to children with other psychiatric conditions supports the hypothesis that executive dysfunction is a deficit intrinsic to ADHD and not to disorders that are frequently comorbid with ADHD. Koziol *et al.* (66) compared a group of boys with ADHD to a psychiatric control group of depressed children on a measure of verbal fluency and reported that the children with ADHD performed poorer than the psychiatric control group. Additionally, Wiers *et al.* (67) tested executive functioning in children with ADHD as compared to a group of sons of multi-generational alcoholics. Executive dysfunction was only detected in the children with ADHD.

Final support for the existence of executive dysfunction in some children with ADHD is offered by a pharmacological treatment study. Kempton *et al.* (68) found that children with ADHD who were successfully treated with stimulant medication were not impaired on measures of executive function, whereas children with ADHD who were unmedicated exhibited deficient performance on these tasks. This suggests that the efficacy of stimulant medications in the treatment of ADHD may be partially mediated by their ability to rectify the executive dysfunction seen in the disorder.

Taken together, neuropsychological research reviewed above presents partial evidence for the models of Arnsten *et al.* (16), Pliszka *et al.* (19), and Barkley (17) but does not preferentially support any of their hypotheses. Converging data across studies presents strong evidence for a PFC-mediated contribution to the pathophysiology of ADHD, with characteristic deficits in executive function. However, the precise nature of the executive deficits, and their specificity to ADHD, has only partially been resolved.

4. NEUROIMAGING

The increasing application of brain imaging techniques to developmental research has produced the first direct evidence of brain dysfunction in ADHD. Studies using computed tomography (CT; 69-72), and more recently magnetic resonance imaging (MRI; 73-85), found significant, albeit small, differences in brain structure that may be unique to ADHD. In addition, differences in brain metabolism and task-related changes in brain activity between children with and without ADHD have been demonstrated using single photon emission tomography (SPECT; 86-90), positron emission tomography (PET; 91), and functional magnetic resonance imaging (fMRI; 92-94). Taken together, and consistent with neuropsychological findings, the preponderance of data point to dysfunction of prefrontal-striatal neural networks in ADHD.

Structural abnormalities of the brain were first examined in children with ADHD using CT scans. Two early studies reported an increased prevalence of nonspecific abnormalities (e.g., cerebral atrophy and asymmetry) in heterogeneous samples of children with developmental disorders, some of whom had ADHD (69,70). Furthermore, CT scans of young men treated for hyperactivity and followed from childhood revealed a significantly greater frequency of cerebral atrophy than matched controls (71). In contrast, a well-controlled CT study found no evidence of abnormalities in children with ADHD (72), which suggests that the atrophy reported by the first three studies might have been associated with some factor other than ADHD.

The development of MRI for use with human subjects has led to a plethora of new research on brain morphology in children with ADHD. The greater spatial resolution of MRI as compared to CT makes it sensitive to subtle structural anomalies, which has allowed researchers to identify a number of brain regions that may be abnormal in ADHD. However, many of the reports in the literature come from studies in the same samples, and hence can not be viewed as independent. Research has primarily come from: 1) Johns Hopkins (73,74,84); 2) NIMH (75-77, 80); 3) Filipek, Semrud-Clikeman, and collaborators (79,85); and 4) Hynd and collaborators (81-83).

Consistent with clinical research implicating PFC dysfunction in ADHD (17), three studies reported significantly smaller area in the right PFC of ADHD children relative to normal controls (78,79,81). In contrast, no difference was found in the left PFC. The fact that reduced area in the right PFC was found in three samples of ADHD children which varied widely with regard to age, gender, comorbidity, and medication status suggests this region may be central to ADHD. Notably, this result was not found in a comparison group of dyslexic children who did not have ADHD (81). Reduced white matter volume in the posterior parietal-occipital regions was also found in ADHD boys relative to age- and IQ-matched controls (79), which is noteworthy given the reciprocal connections between the PFC and the posterior parietal cortex (95).

Volumetric studies using MRI have also found evidence of altered basal ganglia morphology in ADHD. Three of four studies that measured the basal ganglia in children with ADHD found reduced volume in the caudate nucleus relative to matched controls, with two of those studies reporting reduced volume in the left caudate (79,83) and the third reporting a smaller right caudate (77,78). These three studies also reported a loss, or reversal, of the normal asymmetry of the caudate nucleus in ADHD subjects. The significance of these findings is not known given disagreement over the normal pattern of asymmetry (96,97). In contrast to the findings in children, adolescents with ADHD were found to have a larger right caudate area as compared to controls (98). While seemingly discrepant, the findings in children and adolescents with ADHD may be reconciled by data indicating a lack of normal age-related reductions in caudate volume in ADHD (78, 98). One possible interpretation is that children with ADHD, who initially have smaller caudate relative to healthy peers, may not undergo normal developmental processes (e.g., synaptic pruning) and may subsequently have larger caudate area in adolescence. Alternatively, given the cross-sectional nature of the studies, the difference between the findings in children and adolescents may reflect cohort effects.

Additional regions of the basal ganglia were implicated in the pathophysiology of ADHD by two studies that examined the putamen and the globus pallidus. Both studies found reduced volume in the globus pallidus in children with ADHD compared to healthy children, with one reporting a smaller right pallidum (78) and the other reporting a smaller left pallidum (73). However, neither study reported differences in volume or symmetry measures of the putamen (73,78).

The finding of structural abnormalities in the PFC and basal ganglia of children with ADHD has led several researchers to search for similar morphological anomalies in the corpus callosum. Five of the six studies that examined corpus callosum morphology using MRI reported smaller area in children with ADHD compared to

normal controls (74,80,82,99,85). However, these studies largely found different callosal regions to be smaller in ADHD, with reductions alternatively reported in anterior genu (82), rostral (80), and rostral body (74,80) regions, as well as in posterior splenial regions (82,85). A fifth study also found smaller isthmus and splenial regions of the posterior corpus callosum in children with ADHD (99). However, the high frequency of dyslexia in the latter sample makes the results more difficult to interpret, since dyslexia is also associated with changes in posterior callosal regions (100, 101). Given that none of these studies found a change in the shape of the corpus callosum in children with ADHD, it is unlikely that the smaller callosal size in ADHD results from a gross morphological anomaly. Rather, research indicates that reduced callosal area reflects fewer fibers traversing the corpus callosum (102). While the majority of evidence points to an association between ADHD and reduced interhemispheric connections, the discrepancy among the studies obfuscates the exact nature of this relationship. Regional differences in fiber composition in the corpus callosum (102) suggest that lesions in different callosal segments will have varying functional consequences. Thus, the genu and splenial callosal regions are composed primarily of lightly myelinated, thin fibers that connect the prefrontal and posterior association cortices, respectively, while the body of the callosum consists of heavily myelinated, large-diameter fibers that link primary and secondary sensorimotor areas (102). Reduced fibers in the former regions is consistent with the findings of smaller prefrontal area (78, 79, 81) and reduced posterior parietal white matter (79) in children with ADHD, while the findings of smaller callosal body regions raises some interesting issues regarding the involvement of sensorimotor areas in ADHD.

Several studies have also used MRI to examine brain regions not traditionally considered to be part of the frontal-striatal system in ADHD. Measures of the temporal lobe, insula, hippocampus, amygdala, and central grey nuclei did not differ between children with ADHD and normal controls (78,79). However, two studies reported that the posterior vermis of the cerebellum was significantly smaller in children with ADHD (75, 84), with reductions in the inferior posterior lobe (lobules VIII-X), but not in the superior posterior lobe. While the significance of this finding is not entirely clear, recent neuroanatomical evidence indicates that cerebellar output nuclei project via the thalamus to the PFC, and premotor and primary motor cortices (103). Thus, the neural circuits arising in the cerebellum are in a position to influence the function of the PFC, and one of its primary terminal areas (i.e., premotor cortex).

Notwithstanding the differences between the above studies, the findings of morphological brain imaging studies reveal a pattern of structural abnormalities in prefrontal-striatal neural networks in ADHD. While these studies provide some insights into the brain structures that may be involved in ADHD, structural abnormalities do not necessarily imply functional impairments. Functional brain imaging studies are required to correlate morphological anomalies with functional deficits. Therefore, recent attention has centered on functional neuroimaging techniques that allow researchers to examine the working brain in vivo.

A series of studies using xenon-133 and SPECT to measure cerebral blood flow in small, heterogeneous samples of ADHD children with and without comorbid learning disabilities (87-89) consistently found striatal hypoperfusion in both groups of ADHD children compared to controls. In contrast, posterior cortical regions were hyperperfused in children with ADHD only. Abnormal cerebral blood flow in these areas was reversed by methylphenidate, which increased perfusion in the striatum and decreased perfusion in primary motor and sensory cortices (87,88). Reduced cerebral perfusion was also found in the PFC during a concentration task in a large sample of children and adolescents with ADHD compared to normal subjects (86). Recently, a small study using I-123 SPECT found greater uptake asymmetry with less activity in the left frontal and parietal regions compared to psychiatric controls (90). While these findings seem to indicate that structural anomalies in the PFC and striatum may have functional significance in ADHD, several methodological concerns (e.g., small samples, wide age range, medication effects, and inclusion of subjects with mental retardation) highlight the need for replication.

Studies of functional brain abnormalities in ADHD using [^{18}F] flurodeoxyglucose and PET to measure cerebral glucose metabolism have yielded inconsistent results. Adults with childhood-onset hyperactivity who were also parents of children with ADHD had global reductions in glucose metabolism that were most prominent in the premotor and superior PFC, but were also detected in the striatum, thalamus, hippocampus, and cingulate regions (91). However, it must be noted that the gender effect in this study was larger than the effect of ADHD, thus making interpretation of findings more difficult. Subsequent studies of adolescents with ADHD and matched controls found no significant differences in glucose metabolism in frontal, thalamic, and hippocampal regions (104,105). While post-hoc analyses in these studies revealed reduced glucose metabolism in females, but not males, with ADHD (104,105), this finding was not replicated in a second study of adolescent females (106). Studies of stimulant effects on glucose metabolism in adults with ADHD have also produced conflicting results. Whereas acute administration of methylphenidate and dextroamphetamine produced distinct regional patterns of both increases and decreases in glucose utilization (107), these patterns did not correspond to the areas of altered metabolism found in adults with ADHD. In contrast, chronic treatment with either stimulant had no effect on global or regional glucose metabolism (108).

Recent studies using the fMRI technique, which measures localized brain activation during performance of cognitive tasks, have already yielded preliminary evidence regarding the neuronal basis of poor attentional and inhibitory control mechanisms in ADHD. One study using two versions of a response inhibition task (i.e., the Go-No-Go task) alternately found enhanced frontal activation and

reduced striatal activation on these tasks in children with ADHD (94). Methylphenidate increased activation in frontal and striatal areas on both tasks in ADHD children. In contrast, adolescents with ADHD were found to have significantly reduced activation in the right mesial frontal cortex, right inferior PFC, and left caudate during a similar response inhibition task (93). The difference in PFC activation between children and adolescents with ADHD may be accounted for by a normal age-related decrease in PFC activation (76). A more recent study using fMRI in adults with ADHD found reduced activation in the anterior cingulate cortex during a cognitive interference task (i.e. the Counting Stroop task) that required the inhibition of prepotent responses and the selection of competing responses (92). While the exact role of the anterior cingulate is still uncertain, it is known to have reciprocal connections with both the PFC and parietal cortex (109), and becomes active during tasks that require inhibitory control or divided attention (110).

The findings of morphological and functional brain imaging studies of ADHD identify subtle anomalies and dysfunction in several brain regions previously postulated to be involved in the pathophysiology of ADHD (16,17,18). However, closer inspection of the findings reveals some discrepancies. For example, while there is convergence of evidence regarding involvement of the PFC in ADHD, there was disagreement over the precise callosal region that was smaller in ADHD. In addition, while there is general agreement that the basal ganglia are involved, results differ regarding the pattern of asymmetry and volumetric reductions in the caudate nucleus and globus pallidus. In part, these inconsistencies may be due to differences in imaging methods (e.g., scanning parameters) between the studies. However, the considerable differences among the samples with regard to age, gender, and comorbidity suggests that the discrepancies also likely reflect the heterogeneous nature of ADHD. Nonetheless, imaging studies do reveal a pattern of abnormalities in the PFC and the basal ganglia that are likely to play a central role in ADHD.

5. NEUROCHEMISTRY

The neurotransmitter systems most commonly implicated in the pathophysiology of ADHD are the catecholamines: DA and NE. Strong support for a catecholaminergic etiology of ADHD arises from a variety of clinical and pre-clinical data from pharmacological treatment studies. Virtually all medications that are effective in the treatment of ADHD affect catecholamine transmission and medications that do not interact with catecholaminergic transmission are rarely effective in the treatment of ADHD (12). Therefore, this review will focus on studies that assess NE and DA function in children with ADHD.

Studies employing peripheral measures to assess catecholaminergic function in ADHD are plentiful, but highly inconsistent in their findings. Studies which examined levels of urinary 3-methoxy 4-hydroxyphenylglycol (MHPG), a metabolite of NE, in children with ADHD and normal controls found either no differences (111, 112), decreased levels in the ADHD subjects (113-117), or increased levels in the ADHD subjects (118-119). Although the majority of studies which examine peripheral markers of NE function assess MHPG levels, Hanna *et al.* (120) examined urinary excretion of another NE metabolite, 3,4-dihydroxyphenylglycol (DOPEG), and found that ADHD children excreted lower levels of DOPEG than normal controls.

Another method of obtaining a peripheral index of catecholaminergic function is the measurement of substances in plasma. Castellanos *et al.* (121, 122) reported that both plasma and urine HVA and MHPG did not correlate with behavioral measures of hyperactivity or aggression, or predict response to stimulant medications. Similarly, Halperin *et al.* (123) failed to find an association between plasma HVA and MHPG and behavioral indices. Oades *et al.* (119) found slightly elevated levels of plasma NE and epinephrine in children with ADHD relative to normal controls. In an effort to secure a measure of active neurotransmitter systems, plasma levels of hormones or neurotransmitter metabolites were obtained after administration of a pharmacological agent. Children with ADHD were found to have an enhanced increase in plasma growth hormone levels following administration of the alpha adrenergic agonist clonidine, relative to a non-ADHD patient group (124). Similarly, the plasma levels of DA, NE and their metabolites were measured following the administration of the monoamine oxidase inhibitor type B, selegiline, in adults with ADHD. DA indices were found to be associated with self-ratings of ADHD symptom severity, while NE indices were associated with performance on a CPT (125).

Shekim *et al.* (126) attempted to predict medication response in ADHD children by examining platelet binding characteristics of children with ADHD and normal controls. Children with ADHD tended to have lower levels of platelet alpha-2 adrenergic receptor binding. Administration of dextroamphetamine did not effect the level of platelet binding; however, medication non-responders showed the lowest level of platelet binding, relative to responders and normal controls. These findings led authors to hypothesize that normal alpha-2 adrenergic activity is present in those ADHD children who respond well to dextroamphetamine. In contrast, non-responders exhibit aberrant NE activity, possibly secondary to their having fewer alpha-2 adrenergic receptors, which, when present in sufficient numbers, regulate the release of NE through a negative feedback mechanism.

Given the invasive nature of research that measures central neurotransmitter functioning, relatively few studies have obtained central measures of catecholaminergic functioning in children with ADHD. Two early studies which used less well-refined diagnostic criteria reported conflicting results. Shetty and Chase (127) found no significant differences between “hyperactive” children and normal controls in cerebrospinal fluid (CSF) levels of the DA metabolite homovanillic acid (HVA).

However, Shaywitz *et al.* (128) found lower CSF levels of HVA in children with "minimal brain dysfunction."

More recently, Kruesi *et al.* (129) failed to find differences in CSF levels of HVA or MHPG in a group of children with disruptive behavior disorders, many of whom had ADHD, as compared to a group of children with obsessive compulsive disorder. These authors also reported that CSF HVA was not correlated with behavioral measures of impulsivity or aggression in children with disruptive behaviors, while CSF MHPG was inversely correlated with behavioral measures of aggression. In contrast to these findings, Castellanos *et al.* (121) found that CSF HVA was positively correlated with several measures of hyperactivity and CSF MHPG was positively correlated with several measures of aggressive and disruptive behavior. The finding of a positive correlation between CSF HVA and hyperactivity was replicated by Castellanos *et al.* (122).

The discrepant findings across studies which assess central catecholaminergic function may be partially explained by sampling differences. The research conducted by Shaywitz *et al.* (128) and Shetty and Chase (1257 utilized early diagnostic criteria which generated patient groups that likely would differ from those identified using more recent diagnostic criteria. Early diagnostic schema focussed on the presence of hyperkinesis, a construct that has become secondary in the more operationally defined current diagnostic system**.** Furthermore, the sample used by Kruesi *et al.* (129) was recruited for the presence of aggression and was considerably more aggressive than the other samples which only included children with ADHD.

The remarkable consistency of response to stimulant medications amongst children with ADHD has led several groups to examine the relationship of DA function to response to stimulant medications. Shetty and Chase (127) found that a decrease in CSF HVA levels after treatment with dextroamphetamine correlated significantly with clinical improvement ratings. In a sample of adults with ADHD, Reimherr *et al.* (130) determined that methylphenidate responders had lower CSF HVA than non-responders. Using a regression model, Castellanos *et al.* (122) reported that after baseline symptom severity, CSF HVA level was the best predictor of response to either methylphenidate or dextroamphetamine. In contrast to Reimherr's report, however, Castellanos *et al.* (122) showed that relatively higher levels of HVA were predictive of enhanced response to stimulant medication, while lower levels of HVA were associated with worsening of symptoms on some measures. It is noteworthy that Reimherr's research was conducted with adult subjects, while the other two groups of researchers worked with children. Although the direction of the relationship between measures of central DA and response to medication is unclear, the work of Shetty and Chase (127), Reimherr *et al.* (130) and Castellanos *et al.* (122) suggests a mediating role of DA in the efficacy of stimulant medication treatment for people with ADHD.

Some investigators have attempted to reconcile the discrepancies across neurochemical studies by considering the possible modulating effects of psychiatric or cognitive comorbidities. Pliszka *et al.* (131) compared levels of urinary NE, epinephrine, and their respective metabolites, normetanephrine and metanephrine; in ADHD children with and without anxiety and normal controls. ADHD children excreted more normetanephrine than normal controls and less epinephrine than those with ADHD + anxiety. These findings were interpreted to suggest that children with ADHD have higher tonic activity of the NE system, while children in the comorbid group have higher adrenergic activity than the pure ADHD group. Pliszka *et al.* (19) argue that these findings, considered in context of the majority of neurochemical studies of ADHD, suggest multi-system dysfunction of NE, DA and epinephrine in children with ADHD. In attempting to reconcile these findings, they posit that NE dysregulation may be responsible for disruption of the cortical posterior attention system, DA dysfunction may lead to impairment in frontally mediated executive functions, and adrenergic imbalances may undermine the physiological functioning necessary to respond appropriately to environmental stimuli.

Nevertheless, other studies indicate that NE dysfunction is not consistently present in children with ADHD. Halperin *et al.* (123) compared plasma levels of MHPG in ADHD children with and without RD. The children in the comorbid group exhibited higher plasma MHPG than the pure ADHD group. Furthermore, MHPG correlated negatively with measures of academic achievement, but was not associated with behavioral ratings. These findings were replicated in an independent sample of children (132). Pilot data comparing the growth hormone (GH) response to administration of the alpha-2 adrenergic agonist guanfacine in ADHD children with and without RD support these findings (133). Following guanfacine administration, the change in plasma levels of GH was significantly higher in the ADHD children without RD relative to the comorbid group. Halperin's group hypothesized that separate ADHD subgroups exist with regard to NE function, such that ADHD children with RD are not characterized by dysfunction of the NE pathways which regulate executive function in the PFC. Rather, cognitive dysfunction in children with ADHD + RD may be attributed to abnormalities in posterior temporal/parietal function. Conversely, children with pure ADHD do show evidence of dysregulation of NE mechanisms which are consistent with abnormalities of PFC function and executive dysfunction observed in this population. The findings in the non-RD group are consistent with the model put forth by Arnsten and colleagues (16) which suggests that decreased NE turnover is responsible for the executive dysfunction seen in that subgroup of children with ADHD.

Although the body of neurochemical research in ADHD reveals many inconsistencies, taken as a whole, this work does show evidence of dysfunction in multiple neurotransmitter systems in ADHD. Inconsistency of findings may relate to the use of peripheral measures of neurotransmitters, whose relationship to central neurotransmitter functioning is questionable (134). Alternatively, given the heterogeneity of children with

ADHD, perhaps it is not reasonable to expect a uniform deficiency in one neurotransmitter system to be found across the varied presentations of the disorder. Nevertheless, research with more homogeneous subgroups of children with ADHD as exemplified in the work of Pliszka *et al.* (131) and Halperin *et al.* (123, 132, 133) seems to provide the most consistent findings.

6. MOLECULAR GENETICS

Support for a genetic contribution to the multifactorial etiology of ADHD has been gleaned from several lines of research: 1) family studies, which demonstrate increased prevalence of the disorder in relatives of probands with ADHD, compared to relatives of normal and psychiatric controls (135-137); 2) twin studies, which are consistent with a moderate to high rate of heritability of attentional dysfunction (138) and 3) adoptive studies which have shown elevated levels of attentional dysfunction in the biological parents of ADHD probands, relative to the lower levels in their adoptive parents (139). Research aimed at delineating the genetic component of ADHD has focused on DA, especially the DA transporter gene and the gene for the DA D4 receptor (for review see 140). Emphasis has been placed on DA because structures, such as the striatum, which are rich in DA innervation, have been implicated in imaging studies of ADHD.

One of the earliest studies to investigate genetic contributions in ADHD found an association between the DA D2 receptor gene and ADHD after comparing the genetic makeup of children with ADHD and a normal control group (133). Yet, the use of two subject groups from different populations, with allele frequencies that varied by definition, confounded this research. An additional study by Comings and colleagues (142) examined the polymorphisms of three DA genes: D2 receptor, beta hydroxylase, and the transporter, in children with Tourette's syndrome, their relatives, and a group of normal controls. The degree of loading for each gene correlated significantly with various behavioral comorbidities in the subjects, one of which was ADHD. However, it is unclear whether this finding would stand in a group of ADHD subjects without Tourette's syndrome. These results, while of interest, have not been replicated.

More recent work has focused on the DA transporter and D4 receptor genes. The rationale for focusing on the DA transporter gene is that medications that have been shown to inhibit the DA transporter (e.g., methylphenidate, amphetamine, pemoline and bupropion) are efficacious in the treatment of ADHD. To avoid the effects of population stratification, Cook *et al.* (143) utilized the haplotype-based haplotype relative risk method to investigate polymorphisms on the DA transporter gene in familial trios of biological parents and the affected offspring. An association between polymorphism at the DA transporter site and ADHD was found. One limitation in this study was that 24 fathers and four mothers were missing from the analysis. However, these results have been replicated (144).

Other groups have directed their investigations towards the DA D4 receptor gene because of its functional relevance to ADHD. Variability in this gene has been found to be associated with novelty seeking behavior, a behavior that is implicated in ADHD. Two studies conducted by Swanson and colleagues (145, 146) found an association between polymorphisms in this gene and ADHD. In their first study, children with ADHD were found to have a higher frequency of the 7-fold repeat form of the DA D4 receptor gene as compared to normal controls matched for ethnicity (which partially accounts for the population stratification issue mentioned earlier). This polymorphic variation in the gene encoding for the DA D4 receptor has been shown to mediate a blunted intracellular response to dopamine (145). A second study by this group (146) replicated the finding and then extended it by using a family based approach similar to that of Cook *et al.* (143). Faraone *et al.* (147) also replicated the finding of an association between polymorphisms in the DA D4 receptor gene and ADHD in a sample of adults with ADHD.

Nevertheless, research conducted by other groups examining the DA D4 receptor gene in ADHD has revealed inconsistent results. Smalley *et al.* (148) found support for an association between the polymorphism in the gene for the DA D4 receptor and ADHD using a transmission disequilibrium test, but then found no evidence of increased identity by descent sharing among affected sibling pairs. Furthermore, Castellanos *et al.* (149) found that the frequency of the DA D4 receptor polymorphism did not vary across groups when comparing subjects with severe ADHD and normal controls who were matched for gender and ethnicity.

Mixed findings in genetic research may, in part, be due to the variability of diagnostic subtypes, as well as the range of symptom severity, across samples. Rowe *et al.* (150) found that children with either ADHD, combined type, or ADHD, primarily inattentive type had a higher frequency of the 7-repeat allele on the DA D4 receptor gene than normal controls. Furthermore, subjects with more high-risk alleles than their siblings also displayed more inattentive symptoms than their siblings did. Notably, however, this relationship did not hold for hyperactive/impulsive symptoms. The same group used a similar approach to analyze the association between ADHD and the high-risk allele for the DA transporter gene. Within family analysis confirmed and extended the findings of Cook *et al.* (143), showing an association between ADHD and the DA transporter gene, especially in ADHD, combined type. Sibling analysis revealed that those children who had greater frequency of the high-risk allele on the DA transporter gene showed more hyperactive/impulsive and inattentive symptoms than their siblings showed. However, between family association analyses revealed that levels of hyperactive/impulsive symptoms, and not inattentive symptoms, were related to the number of DA transporter gene high-risk alleles (151). Thus, the work conducted by this group suggests that the relationship between ADHD and DA genetic markers may vary with the degree of symptom severity and the subtypes of ADHD being studied.

7. PERSPECTIVE

The PFC and the basal ganglia play prominent roles in a complex neural system that serves to regulate motor function and behavior via working memory (152). The PFC receives higher-order sensory and mnemonic input from association cortices (30), and in turn, exerts inhibitory control over motor functions through connections with the caudate nucleus (31). The caudate nucleus projects to the globus pallidus, which in turn provides feedback to the PFC and premotor cortex via thalamic nuclei (103). Consequently, the findings of smaller PFC and caudate size in children with ADHD suggest the presence of fewer corticostriatal fibers linking these two regions. Furthermore, the smaller anterior callosal regions and reduced pallidal volume in ADHD imply less interhemispheric connectivity in the PFC, as well as diminished pallidal feedback to the cortex, respectively. More tellingly, recent studies have provided preliminary evidence linking functional abnormalities in the basal ganglia, the PFC, and the related anterior cingulate with the deficits in executive functions frequently observed in ADHD. While these findings are still somewhat inconsistent, if confirmed, they would provide strong support for models of ADHD that propose a central role for deficits in executive function and PFC functioning (16,17,19).

Consistent with some theories of ADHD (16,19), morphological anomalies have also been found in posterior brain regions that provide input to the prefrontal-striatal neural networks (75,79,84). The finding of reduced white matter volume in the posterior parietal cortex and in corresponding regions of the posterior corpus callosum in children with ADHD indicates the presence of fewer fibers in this sensory association cortex. The posterior parietal cortex is specialized to process visuospatial information, and provides the PFC with higher-order sensory input through reciprocal projections (152). In turn, the PFC inhibits the processing of irrelevant stimuli in the posterior parietal cortex (32), thereby protecting ongoing cognitive tasks from interference. Reduced fibers in posterior parietal regions raise the possibility that perturbations of this system may be related to the deficits in vigilance and attention seen in ADHD, as suggested by Arnsten *et al.* (16) and Pliszka *et al.* (19).

The finding of reduced area in regions of the corpus callosum in children with ADHD is consistent with several cognitive theories that stress the role of interhemispheric interaction in attentional processing (153, 154). In general, these theories posit that the corpus callosum is involved in the distribution of attentional processes across the hemispheres, thereby permitting the brain to perform different operations in the two hemispheres in parallel (153-155). Thus, the finding of reduced callosal fibers in children with ADHD suggests that disturbances in the interhemispheric transfer of information may be involved in the attentional deficits seen in ADHD. Interestingly, reduced callosal area has been tentatively associated with an increase in brain asymmetries in corresponding brain regions, as well as with an increase in hemispheric lateralization (156).

The inferior posterior lobe of the cerebellar vermis was also found to be smaller in children with ADHD, although the significance of this finding is not entirely clear. However, the cerebellum does project to the PFC via the thalamus (103) and has recently been found to be involved in both motor (157) and non-motor cognitive tasks (158).

Both the PFC and the posterior parietal cortex receive stimulation of postsynaptic alpha-2 adrenoreceptors via ascending NE projections from the LC. Furthermore, stimulation of postsynaptic alpha-2 adrenoreceptors on DA terminals in the PFC modulates DA activity in this brain area and improves PFC function (159). The implication of frontal-striatal pathways, which are rich in DA circuitry, in imaging studies and the evidence for DA gene polymorphisms further highlight the involvement of DA function in the pathophysiology of ADHD. Dysfunction of postsynaptic alpha-2 adrenoreceptors in the posterior parietal cortex and the loss of NE to prime the posterior parietal cortex may produce the disruption of the selective processing of sensory stimuli necessary to orient to and engage novel stimuli (19). Similarly, dysfunction of these receptors disrupts the functioning of the PFC and may produce the executive deficits characteristic of children with ADHD (16).

The heterogeneity in ADHD and the interactive nature of brain function across regions and neurotransmitter systems begs the inference that the disorder has a multifactorial etiology. While the neuropsychological, neurochemical, genetic, and neuroanatomical literature partially support the models of ADHD suggested by Arnsten *et al.* (16), Pliszka *et al.* (19), and Barkley (17), the inconsistencies in the research do not allow unqualified support of a unitary model of ADHD. A most promising direction for future research in the neural substrates of ADHD appears to be in the continued efforts to find meaningful subgroups of children with the disorder who yield more uniform neurobiological profiles. Increased attention to the behavioral and cognitive variations among children with ADHD may illuminate parallels between subtle clinical characteristics and variations in neurobiological assessments. Alternatively, research strategies which attempt to describe the phenotypes associated with the various neuropsychological profiles observed in children that we now call ADHD may lead to identification of more specific diagnostic groupings.

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