The Neurobiology of Attention-Deficit/Hyperactivity Disorder

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We provide a comprehensive review of the neurobiological basis of attention-deficit/hyperactivity disorder. This summary was accomplished by a review of research in three areas: neuroimaging, genetics, and neurochemistry. Additionally, we also discuss a newer conceptualization of the disorder. Although none of the current findings present a unified picture of the pathophysiology of the disorder, the vast array of studies reviewed do highlight CNS abnormalities that, when taken together, present a convincing argument that the cause clearly resides within the realm of developing brain.

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Our review of the neurobiology of attention-deficit/hyperactivity disorder (ADHD) will encompass four major research areas: brain imaging, genetic analysis, neurochemistry, and a newer conceptualization of the core neurologic defect in ADHD. All of these areas contribute to the search to explain the motor hyperactivity, deficits in attention, and impulsivity that characterize ADHD.

BRAIN IMAGING

Brain imaging is one method by which scientists try to view the fundamental neurochemical and neuroanatomical differences in people with ADHD. There are several techniques by which it is possible to view the brain. These studies may be broken down into two types: structural or functional imaging. Computerized tomography (CT) and magnetic resonance imaging (MRI) provide structural images, while single photon emission tomography (SPECT) and positron emission tomography (PET) produce functional images. Functional magnetic resonance imaging (fMRI) combines both types, allowing structural and functional views by measuring blood flow. Of these, CT provides fewer recent insights into the field of ADHD, although, historically, it allowed for the first look at the ADHD brain.

As early as 1978 Bergstrom and Bille[1] as well as Nasrallah and colleagues[2] all used CT imaging. In the first quantitative studies, Shaywitz et al.[3] studied 35 children and adolescents diagnosed with ADHD by DSM-III criteria (29 boys and 6 girls, 4 to 18 years of age; and 27 medical controls, 20 boys and 7 girls). The results showed no significant differences between groups in any of the measurements obtained for biventricular width, widths of the left and right anterior horns of the lateral ventricles, width of the brain plus ventricle, widths of the right and left hemispheres, and two derived measures including an asymmetry index. Interestingly, there were no sex effects found in any of the measurements, and none of the brain measurements significantly correlated with IQ or handedness. The authors did not provide results pertaining to the effects of age. In 1986, Nasrallah et al.[2] published a fatally flawed study of 24 hyperactive male adults (mean age = 23.2 years), including 22 with a history of documented childhood ADHD treated with stimulants. Of particular concern was that 7 of the 24 adults had a history of alcohol abuse, thus severely confounding the interpretation of this study. The hyperactive group showed greater sulcal widening and cerebellar atrophy relative to controls. However, CT studies of alcoholics report an association between alcoholism and cerebellar atrophy.[4]

Functional magnetic resonance imaging, while it has had limited exposure in child and adolescent psychiatry, provides an unparalleled method of mapping brain function and structure. The structural studies for ADHD so far have been of great theoretical interest but as of this writing have failed to find differences between ADHD and normal populations that would allow for diagnostic utility. Given the heterogeneity of this disorder, the long-term search for an application to diagnostic criteria provides a goal for the field of structural imaging not obtainable in the short term. On a more positive note, as summarized in Table 1, of the six completed structural imaging studies[5–10] to date, all have reported some differences between the ADHD brain

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Table 1. Structural MRI Studies in Children and Adolescents

Study	ADHD vs Normals	Findings
Hynd et al,[5] 1990	10 vs 10	ADHD: lacks asymmetry in width of cerebral cortex
Hynd et al,[6] 1991	7 vs 10	ADHD: smaller corpus callosum
Giedd et al,[7] 1994	18 vs 18	ADHD: anterior corpus callosum (rostrum and rostral body) smaller
Hynd et al,[8] 1993	11 vs 11	ADHD: abnormal caudate asymmetry
Castellanos et al,[9] 1994	50 vs 48	ADHD: smaller R caudate volume and lack normal caudate asymmetry
Castellanos et al,[10] 1996	57 vs 55	Replicated Castellanos 1994 findings Additionally: Smaller total cerebral volume (4.7%) Smaller right globus palladus, right anterior frontal region, and cerebellum Reversal of normal lateral ventricular asymmetry No decrease in caudate volume Increase in lateral ventricular volumes diminished Did not replicate corpus callosum finding of Hynd 1991 Expected differences in putaminal volume or symmetry were not found

Table 2. PET Brain Glucose Metabolic Studies of ADHD

Study	Age Group	Controls Sex/Age (y)	ADHD Sex/Age (y)	Cortical	Subcortical
Zametkin et al,[13] 1990	Adult	M/28 F/22	M/18 F/7	↓ Global ↓ Premotor cortex ↓ Prefrontal cortex	↓ Right thalamus ↓ Right caudate ↓ Right hippocampus ↓ Cingulate
Zametkin et al,[14] 1993	Adolescents	M/7 F/3	M/7 F/3	↓ Global (girls only) ↓ Left anterior frontal	↓ Left thalamus ↓ Right hippocampus
Ernst et al,[15] 1994	Adolescents	M/14 F/6	M/14 F/5	No global difference No regional difference ↓ Global (girls only)	

and the normal control brain. Not surprising, most of the findings have involved the basal ganglia and basal ganglia asymmetry, and, although the corpus callosum seems to be involved, exactly which portion has yet to be clarified through replication.

Only recently has fMRI been used to study ADHD subjects. This technique holds great promise due to the lack of ionizing radiation and the development of much faster fMRI imaging techniques with the addition of motion correction software. Studies will not require long periods of motionless behavior, which is particularly difficult, even for normal children. This field will see explosive growth in the next few years. First reports[11] from England have revealed abnormalities in ADHD teenagers compared with controls using fMRI techniques measuring brain activation with gradient echo MR images depicting BOLD contrast. Rubia[11] utilized a stop task requiring response inhibitions and a control task. This study is the first fMRI study in ADHD and reports abnormal activation in parietal areas and frontal areas, findings that are partially consistent with earlier PET studies. Given the small sample size, these early fMRI studies clearly will need to be replicated.

Single photon emission tomography has only begun to be more widely used. The use of SPECT in ADHD has yet to gain firm ground or to provide clinical utility in the field of child and adolescent psychiatry, although some proposals[12] for its utility in the diagnosis and management of ADHD have been introduced. SPECT does have some unique benefits that create a unique potential for its contribution to the field of ADHD. SPECT has the potential to measure two different receptor types within the same study. The widespread availability of SPECT cameras and tracers also will be an attractive feature if scientifically based studies ever appear that can demonstrate unequivocally the usefulness in either the diagnosis or the management of this disorder. Although claims have been made that SPECT imaging is clinically useful, to date, careful quantitative clinical research studies have not yet appeared in peer-reviewed journals to support such claims. Given the significant dose of ionizing radiation involved in a SPECT study (considerably more than in PET), the clinician would be wise not to perform SPECT scanning in suspected cases of ADHD for the evaluation or management of this condition.

PET research had recently provided many insights into the field of ADHD (Table 2). Given the greater perceived risk involved in PET studies, due to the radioactive tracer and the corresponding ethical issues, adults have been much more widely studied. In 1990, Zametkin et al.[13] found significant decreases in the brain metabolism of adults using a fluoro-deoxyglucose tracer (FDG). In 1993, Zametkin et al.[14] conducted a similar study on the brain metabolism of adolescents with ADHD. They found some corresponding, significant reductions in the metabolism of

Table 3. Basal Ganglia Findings in ADHD PET Studies

Journal	Subjects	Results
Zametkin et al,[13] 1990	Adults: 25 ADHD vs 50 normals	↓Right thalamus (absolute) ↓Right caudate (absolute) ↓Right hippocampus (absolute) ↓Cingulate (absolute)
Zametkin et al,[14] 1993	Teens: 10 ADHD vs 10 normals	↓Left thalamus (normalized) ↓Right hippocampus (normalized)
Ernst et al,[15] 1994	Teens: 20 ADHD vs 19 normals	↓Left thalamus ↓Right hippocampus
Matochik et al,[16] 1993	Adults: methylphenidate N = 13 vs dextroamphetamine N = 14 Acute study	Methylphenidate: no change in basal ganglia Dextroamphetamine: right thalamus ↑7% (normalized), right caudate ↑8% (normalized)
Matochik et al,[17] 1994	Adults: methylphenidate N = 19 vs dextroamphetamine N = 18	Methylphenidate: ↓right putamen Dextroamphetamine: no change in basal ganglia

Table 4. Stimulant Effects on Brain Metabolism

Study	Drug	Adults	Results
Acute administration			
Matochik et al,[16] 1993	Methylphenidate	11 men, 3 women	Minimal inconsistent change
	Dextroamphetamine	9 men, 4 women	
Chronic administration			
Matochik et al,[17] 1994	Methylphenidate	13 men, 6 women	No global/normalized change in FDG
	Dextroamphetamine	8 men, 10 women	Robust behavioral change

those adolescents with ADHD. In 1994, Ernst et al.[15] studied the effect of ADHD and gender on cerebral glucose metabolism. They found that there were greater brain metabolism abnormalities in girls with ADHD than in boys with ADHD. However, this study did not demonstrate differences in cerebral glucose metabolism in boys with ADHD compared with controls. In a subsequent study by Ernst et al., lower brain metabolism in ADHD girls could not be confirmed.[43]

Many of these studies using PET to image cerebral glucose metabolism in ADHD populations (both adult and adolescent) have found a decrease in brain metabolism of the basal ganglia (Table 3). This is of particular interest given the hypothesized implication of the corticostriatal circuits in ADHD.

Additionally, FDG has been utilized to measure the effects of medications typically used to treat ADHD on the metabolism of the brain. Although some regional increases and decreases were demonstrated, particularly in acute dose studies,[16] the chronic studies,[17] in which patients clearly showed clinical improvement, failed to demonstrate changes in cerebral glucose metabolism in adults with ADHD who had been treated chronically with either dextroamphetamine or methylphenidate (Table 4).

The tracer fluoro-dopa (FDOPA) was used more recently, partially due to the inconsistent results when using FDG, to determine the differences in dopaminergic uptake in the brains of adults and adolescents with ADHD versus normals. Early analysis of these studies is highly encouraging.

Another useful brain imaging technique that provides crucial insights into both the pathophysiology of ADHD and the mechanism of action of stimulants has been used by Volkow and collaborators[18,19] at the Brookhaven National Laboratory. In studies comparing the anatomical localization of [^{11}C]methylphenidate and [^{11}C]cocaine, Volkow et al.[18] reported very specific binding of methylphenidate to the striatum, not unlike [^{11}C]cocaine. However, of particular interest was the dramatic difference between the two drugs in their pharmacokinetics of binding to brain structures. Clearance of [^{11}C]methylphenidate was about 90 minutes, much slower than cocaine (20 minutes). Future studies comparing the clearance of the medication from brain structures correlated with behavioral improvements could prove very interesting.

GENETICS

Perhaps the strongest support for a neurobiological basis for ADHD is a multitude of studies supporting the concept that the disorder runs in families. Dating back to the early 1970s, studies of adoption, twins, families, and, most recently, molecular investigations point toward genetics as one mechanism underlying symptoms of ADHD.

Many models for inheritance have been proposed, including single gene, polygenic, and multifactorial models.

Among the earliest models was that of Deutsch et al.,[20] in which a genetic latent structure analysis of dysmorphology was performed. Deutsch and colleagues reported that the autosomal dominant model best fit the data.

Large family studies with 140 ADHD probands and 368 first-degree relatives were consistent with a model of highly penetrant autosomal dominant gene transmission.[21] An important point from this study was that female members of the family seemed to be linked to an increased familial risk of the disorder. Additionally, if a parent had ADHD, the risk was 6.6 times greater for sisters and 1.5 times greater for brothers. The authors rejected the hypothesis of a more severe genetic disorder in girls. Their model speculated that a proportion of male cases were caused by environmental rather than genetic factors.

Adoption Studies

Dating as far back as 1973, the earliest attempts at using adoption data have supported a genetic basis for ADHD. Morrison and Stewart[22] reported that 7.5% of the biological parents of adopted-away hyperactive children were themselves hyperactive as compared to 2.1% in the adopting parents. A somewhat different methodology[23] reported a higher frequency of ADHD in the biological parents as opposed to the adoptive parents of ADHD children.

Twin Studies

Perhaps the strongest evidence to date for the heritability of ADHD is the large series of studies done in twins and siblings. Sibling studies reported that full sibling pairs have a concordance rate of 50%, while half siblings have only a 9% concordance rate.[24] Additionally Goodman and Stevenson[25] found a 51% concordance rate for hyperactivity in 39 pairs of monozygotic twins compared with 33% in dizygotic twins. More recent data for the Colorado Reading Project[26] suggest that ADHD follows the pattern of either a single dominant gene or a single major gene. Finally, more recent family studies report a higher risk for ADHD in siblings of ADHD probands (20.8%) than in siblings of normal probands (5.6%).[27]

Molecular Studies

Three recent reports have brought the investigation of ADHD into the molecular age. In 1993, Hauser et al.[28] reported an association between a mutation in the human thyroid receptor-β (hTRβ) gene on chromosome 3 and ADHD. The mutant gene results in peripheral resistance to the action of thyroid hormone causing the rare thyroid condition known as generalized resistance to thyroid hormone (GRTH), an autosomal dominant condition. In this study, 42% of adults and 70% of minors positive for GRTH were diagnosed with ADHD. Although GRTH is an exceedingly rare condition unlikely to be associated with routine cases of ADHD, GRTH serves as an interesting model for a genetic pathway to symptoms of ADHD.

In an attempt to ascertain whether ADHD individuals have an increase in thyroid hormone abnormalities, Weiss et al.[29] reported that no cases of GRTH were found but a prevalence rate of 5.4% of ADHD subjects with some thyroid abnormality was noted, higher than that expected by chance alone.

In Cook and colleagues' 1995 paper[30] on the association of attention deficit disorder and the dopamine transporter gene, the authors cite two lines of evidence that do not support the Hauser finding.[28] First, they cite that GRTH is extremely rare in ADHD individuals.[29] Although this is certainly a true observation that was never claimed by Hauser, the study they cite in no way disputes the association between GRTH and ADHD if one looks only at GRTH individuals, a very different proposition than looking at ADHD populations. Cook et al. then cite Weiss and associates' 1994 paper[31] as evidence that low intelligence, but not ADHD, is associated with GRTH by a mutation in the R316H allele in the thyroid hormone receptor or the β gene. However, Cook and coauthors[30] fail to report that the Weiss paper[31] involved only one kindred with 16 family members. This hardly constitutes the contention that "subsequent studies have not supported genetic linkage of ADHD and GRTH."[30]

In the same study, Cook et al.[30] reported an association of attention deficit disorder and the dopamine transporter gene. The major drawback of association studies is that affected individuals are compared with controls who may be selected from different populations with different allele frequencies. To avoid this type of problem, known as population stratification, Cook and associates used the haplotype-based haplotype relative risk (HHRR) method to test for association between a variable nucleotide random repeat (VNTR) polymorphism at the dopamine transporter locus (DAT1) and DSM-III-R-diagnosed ADHD (N = 49) and undifferentiated ADHD (N = 8).

The Cook study utilized trios of family members including 24 mother-child diads, 4 father-child diads, and 27 mother and father and child triads. The finding that certain stimulants, which so dramatically ameliorate the symptoms of ADHD, bind to and inhibit the dopamine transporter (see Volkow above) led the investigators to study DAT1 as a primary candidate gene.

Cook et al. reported that there was a significant association between the 480-base pair DAT1 allele and ADHD. Notably, in a subsequent report, Lahoste et al.[32] did not confirm this finding. Other shortcomings of the study included the fact that many of the comparisons included only one parent and thus information about the other parent's allele was not available. Also the allele status of unaffected siblings would have made a much more convincing case. Finally, this study did not examine the gene directly and, as the authors suggest, the association may have been with some sort of ADHD susceptibility gene close to but not the dopamine transporter gene itself.

NEUROCHEMISTRY

The study of brain neurochemistry has made modest advances in the field, although newer techniques have replaced earlier methods looking at peripheral markers.

In a review article in 1987, Zametkin and Rapoport[33] discussed the history of the study of medications used to treat ADHD. They concluded that no basis had been found to believe that one single neurotransmitter abnormality is responsible for the symptoms of ADHD. Additionally, they felt that the most informative areas to study in the future would be stimulant response and brain imaging of neurophysiology.

Rogeness et al.[34] reviewed the three main neurotransmitters that may influence behavior problems in children: dopamine, norepinephrine, and serotonin. They feel that ADHD is best understood by the interaction of multiple neurotransmitters. They suggest that the balance between the norepinephrine and the dopamine systems is critical, rather than the variations within the individual systems. Additionally, the authors state that the development of the individual systems from infancy to adulthood is influential on behavior, as this process affects the relative activity of the systems based on neuronal maturation. Based upon these points, it becomes important to measure multiple neurotransmitter systems at once and to confine patient groups within a study to a narrow age range in order to measure similar neurotransmitter activity.

Oades[35] reviewed the role that catecholaminergic activity plays in symptoms of ADHD. He reviewed the effect of abnormalities of dopamine function on behavior, resulting in problems like hyperactivity, inattention, tics, dyskinesia, and self-mutilation. These effects can be seen in disorders characterized by some of these symptoms, such as Tourette's syndrome and Lesch-Nyhan disease. Additionally, Oades discussed the potential role of estrogen in the development of hyperactivity, given the ability of estrogen to act as a dopamine receptor agonist. He felt that this proposed role of estrogen was in agreement with variations in our understanding of the brain metabolism of ADHD, as well as with variations in ADHD with gender.

Mefford and Potter[36] hypothesized that an imbalance in tonic epinephrine formation, which would disrupt the normal inhibition of locus ceruleus neurons, results in inattention, distractibility, sleeping difficulties, and some cognitive deficits. They suggest that this may be the underlying influence in ADHD.

Voeller[37] examined neurologic models of attention, inattention, and arousal in order to better understand ADHD. She suggests that the inappropriate motor activity resulting from right hemisphere lesions might have some application in the understanding of ADHD.

McCracken[38] theorized that in order for a drug to be an effective treatment in ADHD two events must happen: (1) an increase in dopaminergic release, and (2) an increase in the adrenergic inhibition in the locus ceruleus.

Shenker[39] examined the mechanism of action of drugs on catecholamine receptors in the treatment of ADHD. Although the explanations behind the pharmacologic treatments of ADHD are not clear, he believes that catecholamine may play a key role in the process of understanding.

Mercugliano,[40] in the most recent and comprehensive review, examined previous studies of drug action in patients with ADHD. She reviewed the research to show that ADHD may be a consequence of frontal-striatal dysfunction, explaining why the most apparently efficacious drugs are those that increase the transmission of dopamine and norepinephrine.

BARKLEY'S NEW CONCEPTUALIZATION

Despite the research that has been conducted so far, the neural underpinning of ADHD has yet to be elucidated. There have been many theories attempting to explain the symptoms over the years, resulting in a progression of names for the disorder (ADD with or without hyperactivity, hyperactive child syndrome minimal brain dysfunction).

Russell Barkley[41] has recently presented a new unified theory of ADHD, impaired delayed responding. This theory proposes that the symptoms described by ADHD are most accurately explained by an impairment in response inhibition, which results in difficulty self-regulating response to stimuli. This impairment causes the symptoms seen in ADHD, such as hyperactivity, inattention, distractibility, and impulsivity. Barkley further postulates that this delayed responding is mediated by underfunctioning of the orbital frontal cortex and subsequent connections to the limbic system. The result is a hyperresponsivity to stimuli producing hyperactivity primarily and, secondarily, inattentiveness.

Barkley contends that impaired delayed responding is able to provide a unified explanation of every aspect of life affected by ADHD based upon the theory of Jacob Bronowski.[42] Bronowski theorized that the unique ability of man to delay response to a stimulus may be explained by four axes: separation of affect, prolongation, internalization, and reconstitution. These axes allow man to better utilize the complexity of his brain and to respond to each stimulus in the most effective fashion, rather than by automatic, instinctual habit.

Separation of affect is the interim between the acquisition of a stimulus and the subsequent response that allows for the separation of the emotional content of the stimulus from the factual content. This allows man to react in a more impartial manner, based upon the wisest response rather than the most passionate response. In this separation, the brain begins to utilize multiple centers to process the situation.

Prolongation is the use of the delay between stimulus and reaction to compare the incoming information to similar memories and to use the imagination to consider future, hypothetical situations. Barkley likened this axis to the term *working memory* that exists among today's psychological terminologies.

Internalization of language is the learned separation of response into inner and outer language. The inner language is created through three developmental stages: "pliance" or the external control by others over an individual's behavior through language; internal control over behavior by quiet or silent speech to one's self; and problem-solving or the conception of new rules to self-govern behavior. This final stage involves the use of memories and imagined situations to develop new solutions. It is the subsequent step after prolongation. Across development, the ability to problem-solve becomes more sophisticated, allowing for a greater ability to deal with new and difficult situations. These inner considerations are then translated into the practical instructions of the outer language.

Reconstitution is made up of two processes that are enabled by the structure of the internalization of language. The first process is the dissection of the stimulus into parts that may be considered separately to understand it more completely. The second process is the reassembly of these parts into a whole that can be adjusted to provide a new view or conceptualization of the situation. It is this reconstitution that provides people with the capacity to develop new concepts and solutions that may only be tangentially related to the initial input.

These four concepts create a hierarchical response system that enables people to fine tune their behavior. Barkley asserts that it is this system that is impaired in children and adults with ADHD, preventing them from delaying their responses until they have considered the situation fully.

Barkley feels that drug intervention may be effective in temporarily relieving the symptoms of ADHD due to the resulting activation of the motor inhibitory system of the orbital-frontal–limbic axis and the inferred subsequent increase in delayed responding. However, he feels that there is no permanent remedy for this disorder at present and believes that ADHD should be viewed as a developmentally handicapping condition. He proposes that his theory will shed some light on the field of ADHD and provide a clearer avenue to understand old treatments and to explore new ones.

SUMMARY

Little doubt exists that there has been explosive growth in the knowledge gained from clinical research in the field of attention-deficit/hyperactivity disorder. Although biological measures to identify children with the disorder have remained elusive, the tools, be they genetic markers, measurements of brain structure, or physiology, are at hand. The coming decades will clarify the multiple routes leading to the disruptive behaviors of children with ADHD.

Drug names: dextroamphetamine (Dexedrine and others), methylphenidate (Ritalin).

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