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PATHOPHYSIOLOGY OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

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Attention-deficit/hyperactivity disorder (ADHD) is a childhood-onset, clinically heterogeneous disorder of inattention, hyperactivity, and impulsivity. Its impact on society is enormous in terms of its financial cost, stress to families, adverse academic and vocational outcomes, and negative effects on self-esteem (1). Children with ADHD are easily recognized in clinics, in schools, and in the home. Their inattention leads to daydreaming, distractibility, and difficulties in sustaining effort on a single task for a prolonged period. Their impulsivity makes them accident prone, creates problems with peers, and disrupts classrooms. Their hyperactivity, often manifest as fidgeting and excessive talking, is poorly tolerated in schools and is frustrating to parents, who can easily lose them in crowds and cannot get them to sleep at a reasonable hour. In their teenage years, symptoms of hyperactivity and impulsivity diminish, but in most cases the symptoms and impairments of ADHD persist. The teen with ADHD is at high risk of low self-esteem, poor peer relationships, conflict with parents, delinquency, smoking, and substance abuse (1).

The validity of diagnosing ADHD in adults has been a source of much controversy (2). Some investigators argue that most cases of ADHD remit by adulthood (3), a view that questions the validity of the diagnosis in adulthood. Others argue that the diagnosis of ADHD in adults is both reliable and valid (2). These investigators point to longitudinal studies of children with ADHD, studies of clinically referred adults, family-genetic studies, and psychopharmacologic studies. Longitudinal studies have found that as many as two thirds of children with ADHD have impairing ADHD symptoms as adults. Studies of clinically referred adults with retrospectively defined childhood-onset ADHD show them to have a pattern of psychosocial disability, psychiatric comorbidity, neuropsychological dysfunction, familial illness, and school failure that resemble the well known features of children with ADHD.

Throughout the life cycle, a key clinical feature observed in patients with ADHD is comorbidity with conduct, depressive, bipolar, and anxiety disorders (4,5). Although spurious comorbidity can result from referral and screening artifacts (5), these artifacts cannot explain the high levels of psychiatric comorbidity observed for ADHD (4). Notably, epidemiologic investigators find comorbidity in unselected general population samples (6,7), a finding that cannot be caused by the biases that inhere in clinical samples. Moreover, as we discuss later, family studies of comorbidity dispute the notion that artifacts cause comorbidity; instead, they assign a causal role to etiologic relationships among disorders.

NEUROPSYCHOPHARMACOLOGY

Pharmacotherapy

Any pathophysiologic theory about ADHD must address the large pharmacotherapy literature about the disorder. The mainline treatments for ADHD are the stimulant medications methylphenidate, pemoline, and dextroamphetamine. These compounds are safe and effective for treating ADHD in children, adolescents, and adults (8,9). In addition, to improving ADHD's core symptoms of inattentiveness, hyperactivity, and impulsivity, stimulants also improve associated behaviors, including on-task behavior, academic performance, and social functioning in the home and at school. In adults, occupational and marital dysfunction tend to improve with stimulant treatment. There is little evidence of a differential response to methylphenidate, pemoline, and dextroamphetamine. The average response rate for each is 70%.

Stimulants enhance social skills at home and in school.

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They also improve maternal-child and sibling interactions. Children with ADHD who are treated with stimulants have increased abilities to perceive peer communications and situational cues and to modulate the intensity of their behavior. They also show improved communication, greater responsiveness, and fewer negative interactions. Neuropsychological studies show that stimulants improve vigilance, cognitive impulsivity, reaction time, short-term memory, and learning of verbal and nonverbal material in children with ADHD.

Although stimulants are the mainstay of anti-ADHD pharmacotherapy, tricyclic antidepressants (TCAs) also are effective anti-ADHD agents. TCAs include secondary and tertiary amines with a wide range of receptor actions, efficacy, and side effects. Secondary amines are more selective (noradrenergic) with fewer side effects. Most studies of TCAs have found either a moderate or robust response rate of ADHD symptoms (8–10). These studies show anti-ADHD efficacy for imipramine, desipramine, amitriptyline, nortriptyline, and clomipramine. Both short- and long-term studies show that TCAs produce moderate to strong effects on ADHD symptoms. In contrast, neurocognitive symptoms are do not respond well to TCA treatment. Because of rare reports of sudden death among TCA-treated children, these drugs are not a first-line treatment for ADHD and are only used after carefully weighing the risks and benefits of treating or not treating a child who does not respond to other agents.

Other noradrenergic agents help to control ADHD symptoms. Bupropion hydrochloride, which has both dopaminergic and noradrenergic effects, is effective for ADHD in children (11,12)as well as in adults (13). Although they are rarely used because of their potential for hypertensive crisis, several studies suggested that monoamine oxidase inhibitors may be effective in juvenile and adult ADHD (14). The experimental noradrenergic compound tomoxetine showed efficacy in a controlled study of adults with ADHD (15) and in an open study of children with ADHD (16).

In contrast to the beneficial effects of stimulants and TCAs, there is only weak evidence that either α_2-noradrenergic agonists or serotonin reuptake inhibitors effectively combat ADHD (17). A controlled clinical trial showed that transdermal nicotine improved ADHD symptoms and neuropsychological functioning in adults with ADHD (18). Consistent with this finding, a controlled study found the experimental compound ABT-418 to treat adult ADHD effectively (19). ABT-418 is a potent and selective agonist for $\alpha_4\beta_2$-subtype central nervous system neuronal nicotinic receptors.

Catecholamine Hypothesis

As the foregoing review shows, effective medications for ADHD act in noradrenergic and dopaminergic systems. Stimulants block the reuptake of dopamine and norepinephrine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space (20). Solanto suggested that stimulants may also activate presynaptic inhibitory autoreceptors and may lead to reduced dopaminergic and noradrenergic activity (21). The maximal therapeutic effects of stimulants occur during the absorption phase of the kinetic curve, within 2 hours after ingestion. The absorption phase parallels the acute release of neurotransmitters into synaptic clefts, a finding providing support for the hypothesis that alteration of monoaminergic transmission in critical brain regions may be the basis for stimulant action in ADHD (22). A plausible model for the effects of stimulants in ADHD is that, through dopaminergic or noradrenergic pathways, these drugs increase the inhibitory influences of frontal cortical activity on subcortical structures (22).

Human studies of the catecholamine hypothesis of ADHD that focused on catecholamine metabolites and enzymes in serum and cerebrospinal fluid produced conflicting results (23,24). Perhaps the best summary of this literature is that aberrations in no single neurotransmitter system can account for the available data. Of course, because studies of neurotransmitter systems rely on peripheral measures, which may not reflect brain concentrations, we cannot expect such studies to be completely informative. Nevertheless, although such studies do not provide a clear profile of neurotransmitter dysfunction in ADHD, on balance, they are consistent with the idea that catecholaminergic dysregulation plays a role in the origin of at least some cases of ADHD.

The catecholamine hypothesis of ADHD finds further support from animal studies. One approach has been the use of 6-hydroxydopamine to create lesions in dopamine pathways in developing rats. Because these lesions created hyperactivity, they were thought to provide an animal model of ADHD (25). Disruption of catecholaminergic transmission with chronic low-dose *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin, creates an animal model of ADHD in monkeys. In this latter work, MPTP administration to monkeys caused cognitive impairments on tasks thought to require efficient frontal-striatal neural networks. These cognitive impairments mirrored those seen in monkeys with frontal lesions (26,27). Like children with ADHD, MPTP-treated monkeys show attentional deficits and task impersistence. Methylphenidate and the dopamine D2 receptor agonist LY-171555 reversed the behavioral deficits but not the cognitive dysfunction (28, 29).

Several investigators used the spontaneously hypertensive rat (SHR) as an animal model of ADHD because of the animal's locomotor hyperactivity and impaired discriminative performance. Studies using the SHR have implicated dopaminergic and noradrenergic systems. For example, the dopamine D2 receptor agonist, quinpirole, caused significantly greater inhibition of dopamine release from caudate-putamen but not from nucleus accumbens or prefrontal cortex slices in SHR compared with control mice (30). In another study, dopamine release secondary to electrical stimulation was significantly lower in caudate-putamen and prefrontal cortex slices of SHR compared with control mice. These findings were attributed to increased autoreceptor-mediated inhibition of dopamine release in caudate-putamen slices but not in the prefrontal cortex. Another study showed that the altered presynaptic regulation of dopamine in SHR led to the down-regulation of the dopamine system (31). The authors hypothesized that this may have occurred early in development as a compensatory response to abnormally high dopamine concentrations.

Other SHR studies implicated an interaction between the noradrenergic and dopaminergic system in the nucleus accumbens, but they ruled out the idea that a dysfunctional locus ceruleus and A2 nucleus impairs dopaminergic transmission in the nucleus accumbens through α_2-adrenoceptor–mediated inhibition of dopamine release (32). Papa et al. used molecular imaging techniques to assess the neural substrates of ADHD-like behaviors in the SHR rat (33). Their data showed the corticostriatopallidal system to mediate these behaviors. King et al. showed that exposure to excess androgen levels early in development led to decreased catecholamine innervation in frontal cortex and enhanced expression of ADHD-like behaviors (34). Carey et al. used quantitative receptor autoradiography and computer-assisted image analysis to show a higher density of low-affinity D1 and D5 dopamine receptors in the caudate-putamen, the nucleus accumbens, and the olfactory tubercle of SHR (35). Stimulant treatment normalized these receptors by decreasing the number of binding sites and increasing affinity to the control level.

In contrast to the large body of evidence implicating dopaminergic and noradrenergic systems in ADHD, evidence implicating serotonergic systems is mixed. Although the tertiary amines (imipramine and amitriptyline) are more selective for the serotonin transporter than the norepinephrine transporter (36), the secondary amines (desipramine, nortriptyline, and protriptyline) are more selective for the norepinephrine transporter (36). Moreover, measures of serotonin metabolism appear minimally related to the clinical efficacy of the stimulants (22), a finding consistent with the lack of efficacy of serotonergic drugs for treating ADHD. This suggests that the anti-ADHD efficacy of the TCAs stems from their actions on catecholamine reuptake, particularly that of norepinephrine.

Despite these equivocal findings, work by Gainetdinov et al. suggests that we cannot rule out a role for serotonergic systems in the pathophysiology of ADHD (37). These authors studied knockout mice lacking the gene encoding the dopamine transporter (DAT). These mice have elevated dopaminergic tone, are hyperactive, and show decreased locomotion in response to stimulants. Gainetdinov et al. showed that the effects of stimulants were mediated by serotonergic neurotransmission (37).

The anti-ADHD efficacy of nicotine and ABT-418 suggests that nicotinic dysregulation may also play a role in the pathophysiology of ADHD. Patients with ADHD are more likely to smoke and have an earlier age of onset of smoking than persons who do not have ADHD (38–40). In addition, maternal smoking during pregnancy appears to increase the risk of ADHD in the children (41), and *in utero* exposure to nicotine in animals confers a heightened risk of an ADHD-like syndrome in the newborn (42,43). That nicotine dysregulation could play an important role in the pathophysiology of ADHD is not surprising considering that nicotinic activation enhances dopaminergic neurotransmission (44,45).

BRAIN ABNORMALITIES

Satterfield and Dawson were among the first to propose that ADHD symptoms were caused by frontolimbic dysfunction (46). These investigators suggested that weak frontal cortical inhibitory control over limbic functions could lead to ADHD. A review of the neurologic literature showing similarities in disinhibited behavior between adult patients with frontal lobe damage and children with ADHD provided further evidence that the frontal lobes could be involved in the pathophysiology of the disorder (47). Two sources of data have tested the frontolimbic hypothesis of ADHD: neuropsychological studies and neuroimaging studies.

Neuropsychological Studies

Neuropsychological tests indirectly assess brain functioning by assessing features of human perception, cognition, or behavior that have been clinically or experimentally linked to specific brain functions (48). Although limited in their ability to localize brain dysfunction, these tests have several advantages. Many of these tests have been standardized on large populations, thus making it straightforward to define deviant performance. Because of the extensive use of these tests in brain-damaged populations, performance on many of these tests can lead to hypotheses, albeit weak, about the locus of brain dysfunction. Being noninvasive and inexpensive, neuropsychological tests are frequently used to generate hypotheses about brain dysfunction.

Given that inattention is a one of the defining clinical features of ADHD, many neuropsychological studies of the disorder have assessed the attention of children with ADHD. The most commonly used measure of attention is the *continuous performance test,* which requires subjects to sustain their attention to subtle sensory signals, to avoid being distracted by irrelevant stimuli, and to maintain alertness for the duration of the session. Most of these studies find children with ADHD to be impaired on this measure (1).

Children with ADHD also perform poorly on tasks requiring inhibition of motor responses, organization of cognitive information, planning, complex problem solving, and the learning and recall of verbal material (49). Examples of tests that measure these functions are the Stroop Test, the Wisconsin Card Sorting Test, the Rey-Osterrieth Test, the Freedom from Distractibility factor from Wechsler's Tests of Intelligence, and the California Verbal Learning Test.

Some studies suggest that the impairments found in children with ADHD cannot be accounted for by psychiatric comorbidity (50). Moreover, having a family history of ADHD may predict a greater degree of neuropsychological impairment. This latter finding suggests that familial ADHD and neuropsychological impairment identify a more biologically based type of ADHD. In contrast, nonfamilial cases of ADHD with lesser neuropsychological impairments may have other etiologic factors. Children with ADHD do not appear to be impaired on simple motor speed, verbal fluency, or visual spatial accuracy, findings that suggest that observed neuropsychological impairments are caused by specific, not generalized, deficits (51).

Notably, neuropsychological studies have consistently found adults with ADHD to be impaired on measures of vigilance using the continuous performance test (52,53). These studies have also shown adults with ADHD to be impaired in other functions known to affect children with ADHD. These include the following: perceptual-motor speed as assessed by the digit symbol/coding tests (54,55); working memory as assessed by digit span tests (53,56); verbal learning, especially semantic clustering (52,56); and response inhibition as assessed by the Stroop Color-Word Test (57,58). Because neuropsychological tests are free of the potential biases of self-reported symptoms, the finding that the neurocognitive profiles of adults with ADHD are similar to those of children with ADHD suggests that the diagnosis of ADHD is valid as applied in adulthood.

Our description of neuropsychological dysfunction in ADHD describes trends that have emerged in the research literature, not findings that have been consistently replicated. Although there are inconsistencies among studies, it is notable that the pattern of deficits that has emerged is similar to what has been found among adults with frontal lobe damage. Thus, the neuropsychological data tend to support the hypothesis that the frontal cortex or regions projecting to the frontal cortex are dysfunctional in at least some children with ADHD.

Because neuropsychological tests provide indirect measures of brain function, we must be cautious in using them to make inferences about the locus of brain impairment in ADHD. Yet because many of these tests have been standardized on normative populations and administered extensively to brain-damaged populations, observed deficits tests can stimulate hypotheses about the role of specific brain regions in the pathophysiology of ADHD.

With this considerations in mind, we view the pattern of neuropsychological impairment in children with ADHD as consistent with Satterfield and Dawson's (46) idea that symptoms of ADHD derive from abnormalities of prefrontal cortex or its neural connections to subcortical structures. This inference derives from the clinical and behavioral features that have been linked to regions of the prefrontal cortex (59). Notably, orbital frontal lesions predict social disinhibition and impulsivity, and dorsolateral lesions affect organizational abilities, planning, working memory, and attention. Studies of children with ADHD find impairment in all these neuropsychological domains. Thus, the neuropsychological test data—along with the clinical features of the disorder—implicate both orbitofrontal and dorsolateral prefrontal dysfunction in ADHD. In contrast, the mesial prefrontal region, where lesions predict dysfluency and the slowing of spontaneous behavior, is not implicated in ADHD.

Given the complexity of prefrontal circuitry (60), along with the limitations of neuropsychological inference, we cannot endorse a simple lesion model of ADHD. The "prefrontal" abnormalities in ADHD may result from abnormalities of prefrontal cortex, but they may also reflect the dysfunction of brain areas with projections to prefrontal cortex. Given the known role of subcortical networks as modulators of prefrontal functioning, the term *frontosubcortical* seems appropriate for ADHD. This term denotes a behavioral or cognitive dysfunction that looks "frontal" but may be influenced by subcortical projections.

The neuropsychological findings in ADHD provide a fertile resource for speculations about the role of subcortical structures. For example, the cingulate cortex influences motivational aspects of attention and in response selection and inhibition. The brainstem reticular activating system regulates attentional tone and reticular thalamic nuclei filter interference. Working memory deficits implicate a distributed network including anterior hippocampus, ventral anterior and dorsolateral thalamus, anterior cingulate, parietal cortex, and dorsolateral prefrontal cortex. Moreover, the attentional problems of children with ADHD may implicate a wider distribution of neural networks. A system mainly involving right prefrontal and parietal cortex is activated during sustained and directed attention across sensory modalities. The inferior parietal lobule and superior temporal sulcus are polymodal sensory convergence areas that provide a representation of extrapersonal space and play an important role in focusing on and selecting a target stimulus.

Neuroimaging Studies

Fortunately, hypotheses based on neuropsychological inference can be tested with neuroimaging paradigms. Because neuroimaging studies provide direct assessments of brain

TABLE 43.1. STRUCTURAL NEUROIMAGING STUDIES OF ADHD

Study	Diagnosis	Method	Findings
Shaywitz et al. (199)	ADD	CT	No abnormalities found
Nasrallah et al. (200)	HYP	CT	Sulcal widening, cerebellar atrophy
Lou et al. (201)	ADD	CT	Slight frontal cortex atrophy
Hynd et al. (202)	ADD/H	MRI	Smaller frontal cortex Loss of normal asymmetry in frontal cortex
Hynd et al. (203)	ADHD	MRI	Smaller corpus callosum
Aylward et al. (204)	ADHD	MRI	Smaller left globus pallidus
Singer et al. (205)	ADHD+TS	MRI	Smaller left globus pallidus
Baumgardner (206)	ADHD	MRI	Small corpus callosum
Semrud-Clikeman et al. (207)	ADHD	MRI	Small corpus callosum
Castellanos et al. (208)	ADHD	MRI	Smaller right prefrontal cortex, right caudate, and globus pallidus
Mostofsky et al. (209)	ADHD	MRI	Smaller inferior posterior vermis of cerebellum
Nopoulos et al. (70)	ADHD	MRI	Neural migration anomalies and excess cerebrospinal fluid in the posterior fossa but no differences in cavum septi pellucidi
Overmeyer et al. (210)	ADHD	MRI	No corpus callosum abnormalities
Mataro et al. (211)	ADHD	MRI	Larger right caudate nucleus
Kayl et al. (212)	ADHD[a]	MRI	Increased severity of attention problems was associated with small total callosal areas
Berquin et al. (213)	ADHD	MRI	Smaller inferior posterior vermis of cerebellum
Casey et al. (214)	ADHD	MRI	Poor response inhibition associated with right sided abnormalities prefrontal cortex, caudate, and globus pallidus, but not putamen
Filipek et al. (215)	ADHD	MRI	Smaller left caudate, right frontal cortex, and bilateral peribasal ganglia and parietal-occipital regions

ADD, DSM-III attention-deficit disorder; ADD/H, DSM-III ADD with hyperactivity; ADHD, DSM-III-R attention-deficit hyperactivity disorder; CT, computed tomography; HYP, DSM-II hyperkinesis; MRI, magnetic resonance imaging; TS, Tourette syndrome.
[a]In this study, ADHD was secondary to neurofibromatosis.

structure and function, they are ideal for testing hypotheses about the locus of brain dysfunction. Table 43.1 reviews 18 structural neuroimaging studies of children, adolescents, and adults with ADHD that used computed tomography or magnetic resonance imaging. Among these studies, the most consistent findings implicated frontal cortex, usually limited to the right side, cerebellum, globus pallidus, caudate, and corpus callosum. Several other regions were less consistently implicated. Consistent with these findings, the I/LnJ mouse strain shows total callosal agenesis along with behavioral features that resemble ADHD (61). These mice show learning impairments, impulsiveness, and hyperactivity. Metabolic mapping studies suggest that their behavioral deficits are associated with lower 2-deoxyglucose uptake in the left striatum and the frontal and parietal cortex (61).

Table 43.2 reviews 14 functional neuroimaging studies of ADHD using regional cerebral blood flow, positron emission tomography, single photon emission tomography, functional magnetic resonance imaging, or electroencephalography. The most consistent findings were hypoactivity of frontal cortex and subcortical structures, usually on the right side. Because Ernst et al. found significant brain dysfunction for girls, but not boys, with ADHD (62), and Baving et al. found gender differences in lateralization (63), future studies will need to assess gender differences and to determine how they may be related to the male predominance of the disorder.

Ernst et al. noted that findings of frontal hypoactivity are stronger in adult ADHD compared with adolescent ADHD (64). They offered two explanations for this finding. First, the adolescent samples studied may have been more heterogeneous than the adult samples. Although all the adults had persistent ADHD, some of the adolescent cases may have remitted by adulthood. Thus, frontal dopaminergic hypoactivity may be associated with persistent ADHD only. Alternatively, Ernst et al. speculated that, because of brain maturation, the locus of ADHD's dopamine abnormality may shift from the midbrain in childhood to the prefrontal cortex in adults.

Anterior cingulate cortex, lying on the medial surface of the frontal lobe, has strong connections to dorsolateral prefrontal cortex. Bush et al. used a Stroop task to compare anterior cingulate cortex activation in adults with ADHD and those who did not have ADHD (65). In contrast to controls, the adults with ADHD failed to activate the anterior cingulate cortex. Notably, in the prior study by Zametkin et al. (66), cingulate cortex was one of only four (of 60) regions evaluated that still showed regional hypoactivity after global normalization.

The neurochemical basis of brain dysfunction in ADHD was studied by Dougherty et al. (67). They measured DAT density by single photon emission computed tomography with the radiopharmaceutical iodine 123–labeled altropane. Their findings were consistent with the catecholamine hy-

TABLE 43.2. FUNCTIONAL NEUROIMAGING STUDIES OF ADHD

Study	Diagnosis	Method	Findings
Lou et al. (201)	ADD	rCBF	Hypoperfusion in frontal cortex and caudate, hyperperfusion in occipital cortex
Lou et al. (216)	ADHD	rCBF	Hypoperfusion in right striatal region, hyperperfusion in occipital cortex, left sensorimotor, and primary auditory regions
Lou et al. (217)	ADHD	rCBF	Hypoperfusion in striatal and posterior periventricular regions; hyperperfusion in occipital cortex, left sensorimoter, and primary auditory regions
Zametkin et al. (66)	ADHD	PET	Lower glucose metabolism in premotor and superior prefrontal cortex, right thalamus, right caudate, right hippocampus, and right cingulate
Ernst et al. (62)	ADHD	PET	ADHD girls (but not boys) show lower glucose metabolism in right prefrontal cortex, right temporal cortex, right and left posterior putamen, and middle cingulate
Amen et al. (218)	ADHD	SPECT	Decreased perfusion in prefrontal cortex
Rubia et al. (219)	ADHD	fMRI	Lower activation in right mesial prefrontal cortex, right inferior prefrontal cortex, and left caudate
Baving et al. (63)	ADHD	EEG	Boys show a less right-lateralized frontal activation pattern; girls show a more right-lateralized frontal activation pattern than healthy control girls
Schweitzer et al. (220)	ADHD	rCBF	Task-related changes in rCBF in non-ADHD men without ADHD were prominent in frontal and temporal regions; changes in ADHD men were more widespread, suggesting the use of compensatory mental and neural strategies
Silberstein et al. (221)	ADHD	EEG	Increased speed of prefrontal processing in non-ADHD children, ADHD following priming stimulus, and a deficit in such processes in ADHD children
Vaidya et al. (222)	ADHD	fMRI	ADHD is characterized by atypical frontal-striatal function, and methylphenidate affects striatal activation differently in ADHD than in healthy children
Ernst et al. (223)	ADHD	PET	More accumulation of [^{18}F]DOPA in the right midbrain correlated with symptom severity
Bush et al. (65)	ADHD	fMRI	ADHD adults show weak activation of anterior cingulate cognitive division during counting Stroop task
Dougherty et al. (67)	ADHD	SPECT	Dopamine transporter density in striatum greater in ADHD adults

ADD, DSM-III attention-deficit disorder; ADHD, DSM-III-R attention-deficit hyperactivity disorder; EEG, Electroencephalogram; fMRI, functional magnetic resonance imaging; PET, position emission tomography, rCBF, regional cerebral blood flow; SPECT, photon emission computed tomography.

pothesis of ADHD in showing the DAT to be elevated by about 70% in adults with ADHD.

The functional studies are consistent with the structural studies in implicating frontosubcortical system in the pathophysiology of ADHD. Taken together, the brain imaging studies fit well with the idea that dysfunction in frontosubcortical pathways occurs in ADHD. They are also consistent with the report of a father and son, both having methylphenidate-responsive ADHD secondary to frontal lobe epilepsy (68). Notably, the frontosubcortical systems that control attention and motor behavior are rich in catecholamines, which have been implicated in ADHD by the mechanism of action of stimulants.

In a novel approach to assessing brain regions implicated in ADHD, Herskovits et al. used magnetic resonance imaging to assess the spatial distribution of lesions in children who developed ADHD after closed-head injuries (69). Compared with head-injured children who did not develop ADHD, the children with ADHD had more lesions in the right putamen and a trend for more lesions in the right caudate nucleus and right globus pallidus.

Very little is known about when ADHD-related brain abnormalities emerge. To address this issue, Nopoulos et al. assayed four brain abnormalities believed to occur before birth: neural migration anomalies, corpus callosum agenesis or partial agenesis, enlarged cavum septi pellucidi, and malformations of the posterior fossa (70). Neural migration anomalies and malformations of the posterior fossa were more common among patients with ADHD compared with control subjects. Both these abnormalities were rare. However, given that several other studies showed partial agenesis of the corpus callosum or anomalies of the cerebellar vermis (also formed before birth), it seems reasonable to conclude that at least some children with ADHD have a very early onset of brain abnormalities.

GENETICS

Family Studies

Figure 43.1A shows rates of hyperactivity among the siblings of hyperactive probands (71–75). Figure 43.1B shows an elevated prevalence of ADHD among mothers and fathers of children with ADHD that provides further support for the familiality of the disorder and evidence that the adult diagnosis is valid. These studies leave no doubt that ADHD

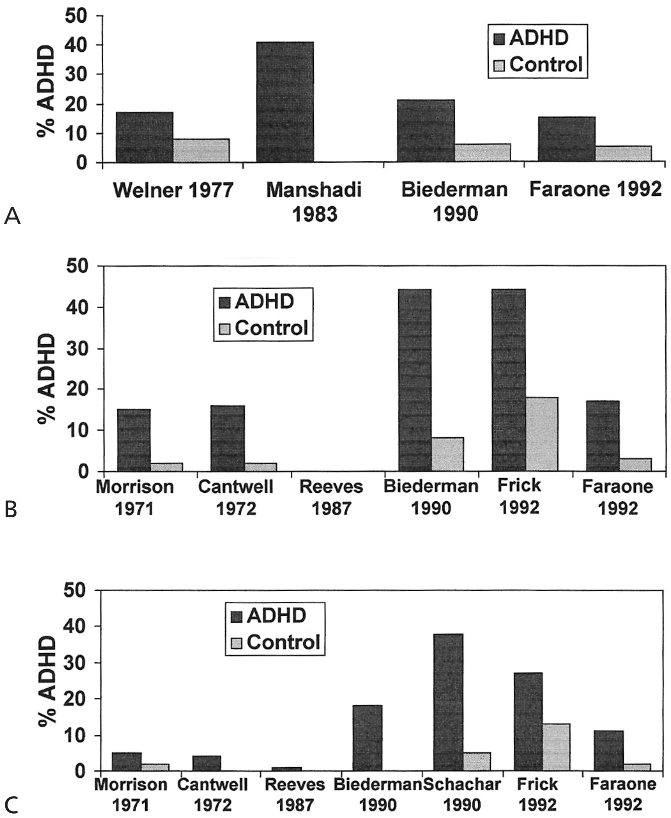

FIGURE 43.1. ADHD in relatives of ADHD and controls children. **A:** ADHD in siblings. **B:** ADHD in fathers. **C:** ADHD in mothers.

is familial. Moreover, studies of more distant relatives are consistent with this idea as well (76).

Family studies of ADHD suggest that its psychiatric comorbidities may help to clarify its genetic heterogeneity. The Harvard/Massachusetts General Hospital (Boston) ADHD family project studied two independent samples of children with attention-deficit disorder (ADD) as defined by the DSM-III (74) and ADHD as defined by the DSM-III-R (77). These data show that (a) ADHD and major depression share common familial vulnerabilities (78,79), (b) children with ADHD who have conduct (80,81) and bipolar (82,83) disorders may comprise a distinct familial subtype of ADHD, and (c) ADHD is familially independent of anxiety disorders (84) and learning disabilities (85). Thus, stratification by conduct and bipolar disorders may cleave the universe of children with ADHD into more familially homogeneous subgroups. In contrast, major depression may be a nonspecific manifestation of different ADHD subforms. In a sample of 132 ADHD sib-pair families, Smalley et al. reported further evidence that ADHD with conduct disorder is a distinct subtype (86). These investigators also examined comorbidity with learning disability, but these data produced equivocal results.

Faraone et al. proposed that stable or persistent ADHD may be a useful subtype of ADHD for genetic studies (87). These investigators reasoned that cases that remit before adolescence could have a smaller genetic component to their disorder than persistent cases. Evidence supporting this hypothesis derives from several studies. In a prospective follow-up study, Biederman et al. showed that by midadolescence, 85% of boys with ADHD continued to have ADHD; 15% remitted (88). The prevalence of ADHD among parents was 16.3% for the persistent ADHD probands and 10.8% for the remitted ADHD probands. For sibs, the respective prevalences were 24.4% and 4.6%. Thus, these data suggest that children with persistent ADHD have a more familial form of ADHD than those whose ADHD remits by adolescence.

Consistent with this finding, Biederman et al. showed that children of parents with clinically referred, childhood-onset, ADHD were at high risk of meeting diagnostic criteria for ADHD: 84% of the adults with ADHD who had children had at least one child with ADHD, and 52% had two or more children with ADHD (89). The 57% rate of ADHD among children of adults with ADHD was much higher than the more modest 15% risk for ADHD in siblings of referred children with this disorder. These findings were consistent with a prior study by Manshadi et al. (72). They studied the siblings of 22 alcoholic adult psychiatric patients who met DSM-III criteria for ADD, residual type. The authors compared these patients with 20 patients matched for age and comorbid psychiatric diagnoses. Forty-one percent of the siblings of the adult ADD probands were diagnosed with ADHD compared with 0% of the non-ADHD comparison siblings.

In another retrospective study, Biederman et al. compared adolescents with ADHD having retrospectively reported childhood-onset ADHD with children with ADHD (90). These investigators found that the relatives of adolescent probands had higher rates of ADHD compared with the relatives of child probands. Thus, a prospective study of children and retrospective studies of adolescents and adults suggested that, when ADHD persists into adolescence and adulthood, it is highly familial. This idea is consistent with one of Ernst's explanations for the finding that frontal dopaminergic hypoactivity is stronger in adult ADHD compared with adolescent ADHD; that is, frontal dopaminergic hypoactivity may be associated with persistent ADHD.

Twin and Adoption Studies

Although family studies provide much useful information, they cannot disentangle genetic from environmental sources of transmission. To do so, we must turn to twin and adoption studies. There are two types of twins: identical or monozygotic twins share 100% of their genes in common. In contrast, fraternal or dizygotic twins are no more genetically alike than siblings and therefore share only 50% of

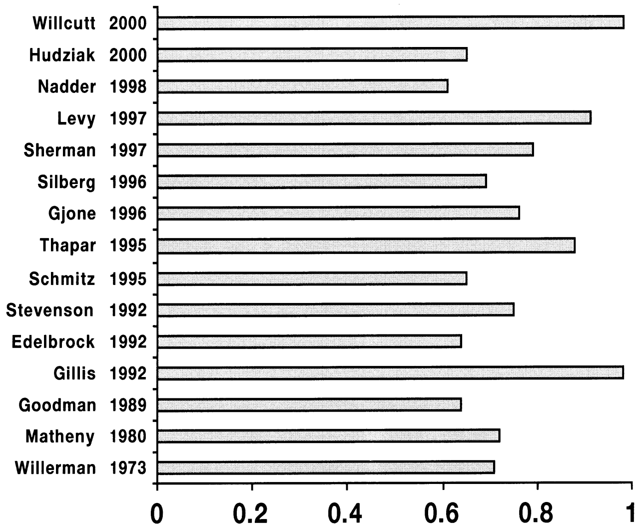

FIGURE 43.2. Heritability of ADHD.

their genes. Thus, the occurrence of twinning creates a natural experiment in psychiatric genetics (91). If a disorder is strongly influenced by genetic factors, then the risk to cotwins of ill probands should be greatest when the twins are monozygotic. The risk to dizygotic twins should exceed the risk to controls but should not be greater than the risk to siblings.

Twin data are used to estimate *heritability,* which measures the degree to which a disorder is influenced by genetic factors. Heritability ranges from zero to one, with higher levels indicating a greater degree of genetic determination. Figure 43.2 presents heritability data from 11 twin studies of ADHD. These data attribute about 80% of the origin of ADHD to genetic factors.

Goodman and Stevenson found the heritability of hyperactivity to be 64% (92,93). In a repeat analysis of these data, Stevenson reported that the heritability of mother-reported activity levels was 75%, and the heritability of a psychometric measure of attention was 76% (94). In a study of ADHD in twins who also had reading disability, Gilger et al. estimated the heritability of attention-related behaviors as 98% (95). In a study of 288 male twin pairs, Sherman et al. examined inattentive and impulsive-hyperactive symptoms using both mother and teacher reports (96). Within both raters, the heritability of the impulsivity-hyperactivity dimension exceeded that of the inattention dimension; however, mothers' ratings showed higher heritability than did teachers' ratings. Specifically, mothers' ratings produced a heritability of 91% for impulsivity and hyperactivity and 69% for inattention. Teachers' ratings yielded a heritability of 69% for impulsivity and hyperactivity and 39% for inattention. Using the Child Behavioral Checklist as a dimensional measure, Hudziak and colleagues found a similar heritability (60% to 68%) for mother-reported attention problems (97).

Other studies of inattentive and hyperactive symptoms found a high heritability and minimal impact of the shared environment (98,99). Rhee et al. examined gender differences in heritability using twin and sibling pairs from Australia (99). Specific genetic and environmental influences were highly similar for boys and girls. Slight differences that emerged were related to more influence of the shared environment in girls and some evidence genetic dominance in boys.

Several twin studies examined the genetic contribution to the comorbidity of ADHD and other disorders. Data from Gilger et al. (95) were consistent with a prior family study (85) in suggesting that ADHD and reading disability were genetically independent; however, the existence of a genetically mediated subtype of both disorders could not be excluded. In contrast, two twin studies suggested that ADHD and reading disability share some genes in common (100,101). That this relationship may be complex is suggested by the report by Willicutt et al. of genetic overlap between reading disability and inattention but not between reading disability and hyperactive impulsive symptoms (102).

Nadder et al. examined whether ADHD and comorbid conduct and oppositional defiant disorder symptoms shared genetic risk factors (98). These investigators found that 50% of the correlation between the ADHD and comorbid conduct was the result of shared genes. Similarly, the twin study of Silberg et al. found that genes influencing variation in hyperactivity scores were also responsible for variation in conduct problems (103). Between 76% and 88% of the correlation between hyperactivity and conduct scores were attributed to genes. These investigators concluded that the results were consistent with the existence of a biologically based group of children who manifest both hyperactivity and conduct disturbances. Further evidence that the ADHD plus comorbid conduct subgroup may be etiologically meaningful comes from a study showing differences in serotonergic functioning between aggressive and nonaggressive children with ADHD (104).

Like twinning, adoption provides another useful experiment for psychiatric genetics (91). Whereas parents can confer a disease risk to their biological children by both biological and environmental pathways, to adoptive children they can confer risk only by an environmental pathway. Thus, by examining both the adoptive and the biological relatives of ill probands, we can disentangle genetic and environmental sources of familial transmission.

Adoption studies of ADHD also implicate genes in its origin. The adoptive relatives of children with ADHD are less likely to have ADHD or associated disorders than are the biological relatives of children with ADHD (105,106). Biological relatives of children with ADHD also do more poorly on standardized measures of attention than do adoptive relatives of children with ADHD (107).

Segregation Analysis Studies

Segregation analysis provides evidence of genetic transmission by demonstrating that the pattern of illness in families is consistent with known genetic mechanisms. An early approach to this was reported by Morrison and Stewart, who concluded that polygenic inheritance was a likely mode of transmission for ADHD (108). Contrasting data were presented by Deutsch et al. (109). They found preliminary evidence for a single dominant gene regulating the transmission of ADHD and minor physical anomalies in 48 families. Similarly, Faraone et al. reported that the familial distribution of ADHD was consistent with the effects of a single major gene (75). Similar results were since reported in a twin study by Eaves et al. (110) and in a pedigree study by Hess et al. (111). Consistent findings also emerged from South America (112). Based on a sample of families from Colombia, the only models of inheritance that could not be rejected were those of dominant and codominant major gene effects. Finally, when families of ADHD probands were ascertained by the father's diagnosis of substance abuse, Maher et al. found that a sex-dependent mendelian codominant model was the best explanation for the pattern of transmission of ADHD (113).

Although the segregation analyses of ADHD suggest that a single gene of major effect is involved in the origin of ADHD, the differences in fit among genetic models was modest. This was especially true for the comparison of multifactorial and single gene inheritance. Several interpretations of these results are possible. If ADHD had more than one genetic cause, then the evidence of any single mode of transmission could be relatively weak. Alternatively, ADHD may be caused by several interacting genes of modest effect. This latter idea is consistent with ADHD's high population prevalence (2% to 7% for ADHD) and high concordance in monozygotic twins but modest recurrence risks in first-degree relatives.

The studies by Deutsch et al. and Faraone et al. predicted that only about 40% of children carrying the putative ADHD gene would develop ADHD. This finding and other features of the genetic epidemiology of ADHD suggest that such a gene likely interacts with other genes and environmental factors to produce ADHD. Moreover, the segregation studies indicated that about 2% of people without the ADHD gene would develop ADHD, a finding suggesting that nongenetic forms of ADHD may exist.

Chromosomal Anomalies and Molecular Genetic Studies

Anomalies in the number or gross structure of chromosomes usually lead to very early-onset disorders having severe clinical manifestations (e.g., mental retardation, gross physical anomalies). No systematic studies of gross chromosomal anomalies in ADHD have been conducted, but there are several reports that such anomalies cause hyperactivity and inattention. Examples include the fragile X syndrome, duplication of the Y chromosome in boys, and loss of an X chromosome in girls. These associations are intriguing but rare. Thus, they can account for only a very small proportion of cases of ADHD.

Molecular genetic studies use the methods of linkage and association to search for aberrant genes that cause disease. Such studies of ADHD are relatively new and far from definitive. Hauser et al. demonstrated that a rare familial form of ADHD is associated with generalized resistance to thyroid hormone, a disease caused by mutations in the thyroid receptor-β gene (114). The thyroid receptor-β gene cannot, however, account for many cases of ADHD because the prevalence of generalized resistance to thyroid hormone is very low among patients with ADHD (1 in 2,500) (115), and, among pedigrees with generalized resistance to thyroid hormone, the association between ADHD and the thyroid receptor-β gene has not been consistently found (116).

Several research teams have examined candidate genes in dopamine pathways because, as discussed earlier, animal models, theoretic considerations, and the effectiveness of stimulant treatment implicate dopaminergic dysfunction in the pathophysiology of this disorder. Several groups have reported an association between ADHD and dopamine D4 receptor gene *(DRD4)* gene (117–123). Notably, each study showed the 7-repeat allele of *DRD4* to be associated with ADHD despite the use of different diagnostic systems (DSM-IIIR and DSM-IV) and measures of ADHD (rating scales and structured interviews). However, like many findings in psychiatric genetics (91), these positive findings are offset by some negative studies (124–128).

The positive *DRD4* findings could be caused by another gene in linkage disequilibrium with *DRD4* or another variant within *DRD4.* However, because the *DRD4* 7-repeat allele mediates a blunted response to dopamine, it is a biologically reasonable risk factor for ADHD (129). The 7-repeat allele has also been implicated in novelty seeking, a personality trait related to ADHD (130,131). Moreover, both norepinephrine and dopamine are potent agonists of *DRD4* (132).

When the D4 gene is disabled in a knockout mouse model, dopamine synthesis increases in the dorsal striatum, and the mice show locomotor supersensitivity to ethanol, cocaine, and methamphetamine. (133). D4 knockout mice also show reduced novelty-related exploration (134), a finding consistent with human data suggesting a role for D4 in novelty-seeking behaviors.

Cook et al. reported an association between ADHD and the 480-bp allele of the *DAT* gene using a family-based association study (135). This finding was replicated by Gill et al. (136), Daly et al. (126), and Waldman et al. (137), but not in other studies (124,138). In the study by Waldman et al. (137), hyperactive-impulsive symptoms but not inattentive symptoms were related to the number of DAT high-risk alleles. Further support for a link between the *DAT* gene and ADHD comes from a study that relates this gene to poor methylphenidate response in children with ADHD (139) and from the neuroimaging study (Table 43.2) showing that DAT activity in the striatum is elevated by 70% in adults with ADHD (67).

In mice, eliminating *DAT* gene function leads to several features suggestive of ADHD: hyperactivity, deficits in inhibitory behavior, and a paradoxical response to stimulants (i.e., stimulants reduce hyperactivity) (37,140). Studies of this knockout mouse model show the potential complexities of gene–disease associations. The loss of the *DAT* gene has many biological effects: increased extracellular dopamine, a doubling of the rate of dopamine synthesis (141), decreased dopamine and tyrosine hydoxylase in striatum (142), and a nearly complete loss of functioning of dopamine autoreceptors (143). Because ADHD is believed to be a hypodopaminergic disorder, the decreased striatal dopamine may be most relevant to the disorder.

Gainetdinov et al. showed that enhancement of serotonergic transmission mediates the mouse's paradoxical response to stimulants (37). These researchers attributed this to the effects of stimulants on the serotonin transporter. To complicate matters further, Bezard et al. showed that *DAT* knockout mice did not experience MPTP-induced dopaminergic cell death (144), and another study found a gradient effect such that mice with zero, one, and two functional *DAT* genes showed increasing susceptibility to MPTP (145). These latter findings suggest that individual differences in the *DAT* gene may mediate susceptibility to neurotoxins having an affinity for the DAT.

A population-based association study has also implicated the A1 allele of the dopamine D2 receptor gene in ADHD (146). Absence of the D2 gene in mice leads to significantly reduced spontaneous movements, a finding suggesting that D2 plays a role in the regulation of activity levels (147, 148). Mice without D2 genes also show decreased striatal DAT functioning (149), a finding that illustrates the potential effects of gene–gene interaction on simple phenotypes such as locomotion in mice. In addition, Calabresi et al. used the D2 knockout mouse to study the role of the D2 receptor in striatal synaptic plasticity (150). In these mice, these researchers found abnormal synaptic plasticity at corticostriatal synapses and long-term changes in synaptic efficacy in the striatum.

The only human study of the D3 receptor gene found no evidence of an association with ADHD (151). However, homozygous mice lacking D3 receptors displayed increased locomotor activity, and heterozygous mice showed less pronounced hyperactivity. These results led Accili et al. to conclude that D3 receptors play an inhibitory role in the control of certain behaviors (152).

Four human studies of ADHD have examined the catechol-O-methyltransferase (COMT) gene, the product of which is involved in the breakdown of dopamine and norepinephrine. Although one study found that ADHD was associated with the Val allele (153), others have found no association between the *COMT* polymorphism and ADHD in Irish (154), Turkish (155), and Canadian (156) samples. Despite the negative finding, the positive finding is intriguing because the Val allele leads to high COMT activity and an increased breakdown of catecholamines.

Another study found an association with the DXS7 locus of the X chromosome, a marker for monoamine oxidase that encode enzymes that metabolize dopamine and other neurotransmitters (157). Finally, Comings and colleagues found associations and additive effects of polymorphisms at three noradrenergic genes (the adrenergic α_{2A}, adrenergic α_{2C}, and dopamine-β-hydroxylas) on ADHD symptoms in a sample of patients with Tourette syndrome (158), but they found no association between the tyrosine hydroxylase gene and ADHD in this sample (159).

Some investigators have used the coloboma mouse model to investigate the genetics of ADHD. These mice have the coloboma mutation, a hemizygous, 2-centimorgan deletion of a segment on chromosome 2q. The mutation leads to spontaneous hyperactivity (which is reversed by stimulants), delays in achieving complex neonatal motor abilities, deficits in hippocampal physiology that may contribute to learning deficiencies, and deficits in Ca^{2+}-dependent dopamine release in dorsal striatum (160).

The coloboma deletion region includes the gene encoding SNAP-25, a neuron-specific protein implicated in exocytotic neurotransmitter release. Hess et al. suggested that interference with SNAP-25 may mediate the mouse's hyperactivity (161). As predicted by this hypothesis, when these investigators bred a SNAP-25 transgene into coloboma mice, the animals' hyperactivity was reduced. Moreover, other work suggested that reduced SNAP-25 expression leads to striatal dopamine and serotonin deficiencies, which may be involved in hyperactivity (162).

Hess et al. tested the idea that the human homologue of the mouse coloboma gene could be responsible for ADHD by completing linkage studies of families with ADHD by using markers on human chromosome 20p11-p12, which is syntenic to the coloboma deletion region (111). These investigators used five families for which segregation analysis suggested that ADHD was the result of a sex-influenced, single gene. However, no significant linkage was detected between ADHD and markers on chromosome 20p11-p12.

ENVIRONMENTAL RISK FACTORS

Although genetic studies of ADHD unequivocally show that genes are risk factors for the disorder, they also show that the environment has a strong influence on the emergence of the disorder. This conclusion follows from studies of identical twins, which show that when one twin has ADHD, the probability of the other, genetically identical, twin's having ADHD is only about 60%. This less than perfect identical twin concordance implicates environmental risk factors. The nature of these risk factors has emerged from studies assessing features of the biological and psychosocial environment that may increase the risk of ADHD.

Biological Adversity

The idea that certain foods could cause ADHD received much attention in the popular press after claims were made that ADHD could be cured by eliminating food additives from the diet. The Feingold diet for ADHD was popularized by the media and was accepted by many parents of ill children. Systematic studies, however, showed the diet was not effective and concluded that food additives do not cause ADHD (163). Another popular theory posited that excessive sugar intake would lead to ADHD symptoms. Although some positive studies supported this idea, the bulk of systematic, controlled research did not (164).

In contrast to the mostly negative studies of dietary factors, some toxins have been implicated in the origin of at least some cases of ADHD. Several groups have shown that lead contamination leads to distractibility, hyperactivity, restlessness, and lower intellectual functioning (165). However, many children with ADHD do not show lead contamination, and many children with high lead exposure do not develop ADHD. Thus, lead exposure cannot account for the bulk of cases of ADHD.

The literature examining the association of ADHD with pregnancy and delivery complications (PDCs) presents conflicting results; it tends to support the idea that PDCs can predispose children to ADHD (166–168), although some investigators do not (169). The PDCs implicated in ADHD frequently lead to hypoxia and tend to involve *chronic* exposures to the fetus, such as toxemia, rather than *acute,* traumatic events, such as delivery complications.

For example, Conners reported that mothers of children with ADHD had high rates of toxemia during pregnancy (166). Hartsough and Lambert described eight PDCs associated with ADHD: maternal illness, toxemia, eclampsia, older maternal age, parity of child, fetal postmaturity, duration of labor, and fetal distress during labor or birth (170). Nichols and Chen found that hyperactivity was significantly associated with low birth weight (171), and Chandola et al. reported antepartum hemorrhage, maternal age, length of labor, sex, and 1-minute Apgar scores to be significant prenatal and perinatal risk factors for subsequent referral for hyperactivity (172).

Sprich-Buckminster et al. showed that the association between ADHD and PDCs was strongest for children with ADHD who had psychiatric comorbidity (168). PDCs were also elevated among children with ADHD who had no family history of ADHD. These investigators concluded that PDCs may be more common among those children with ADHD having a weaker genetic predisposition, but this hypothesis was not confirmed in another study by the same group (167). The latter study found that children with ADHD and a history of PDCs showed more school failure and psychometric evidence of cognitive impairment than other children with ADHD. In addition to confirming the etiologic role of medical complications, this study showed that psychosocial stress during pregnancy predicted subsequent ADHD and poor cognitive performance in children. Notably, catecholamines are secreted in response to stress, and mouse studies showed that catecholamine administration produces uterine vasoconstriction and fetal hypoxia (173).

One extensively studied risk factor has been maternal smoking during pregnancy. By exposing the fetus to nicotine, maternal smoking can damage the brain at critical times in the developmental process. The smoking mother is at increased risk of antepartum hemorrhage, low maternal weight, and abruptio placentae (173). Her fetus is at risk of low birth weight (173,174), and because smoking increases carboxyhemoglobin levels in both maternal and fetal blood, it places the fetus at risk of hypoxia (175). Consistent with these effects, maternal smoking during pregnancy predicts behavioral and cognitive impairment in children and ADHD (41,176).

Animal studies in pregnant mice and rats have shown a positive association between chronic exposure to nicotine and hyperactivity in offspring (42). Neonatal nicotine exposure prevents the development of low-affinity nicotine receptors (177), and chronic exposure results in tolerance to the drug and an increase in brain nicotinic receptors (178–181). Because nicotinic receptors modulate dopaminergic activity and dopaminergic dysregulation may be involved in the pathophysiology of ADHD, it is theoretically compelling to consider maternal smoking as a risk factor for ADHD.

Little is known about the potential role of *in utero* exposure to viral infections. Because maternal viral infections can affect the fetus and can have an adverse impact on the developing brain, viral infections could be associated with later psychopathology. Because viral infections occur more commonly in winter than in other seasons, season-of-birth data have been used to implicate *in utero* viral infection for several disorders including schizophrenia (182), autism (183), and dyslexia (184)

Although Mick et al. found no evidence of a strong seasonal pattern of birth in children with ADHD (185), they did find statistically significant peaks for September births in children with ADHD who had comorbid learning disabilities and in children with ADHD who had no additional psychiatric comorbidity. Thus, it is possible that winter infections during the first trimester of pregnancy may account for some subtypes of ADHD. Mick et al. found no evidence favoring the idea that putative viral exposure led to a nonfamilial form of ADHD. In contrast, they found a weak trend toward an increase in winter births for children with ADHD who have a positive family history of ADHD. If replicated, this finding suggests that a seasonally mediated infection at birth may be an environmental "trigger" for the genetic predisposition to the disorder.

Psychosocial Adversity

The delineation of psychosocial features in the child's environment associated with more impaired outcome in children with ADHD has potentially important clinical, scientific, and public health implications. Such efforts can help to identify etiologic risk factors associated with more impaired outcome in ADHD and can characterize early predictors of persistence and morbidity of this disorder. Moreover, finding environmental risk factors for ADHD could help to design improved preventive and therapeutic intervention programs.

The classic studies by Rutter et al. of the Isle of Wight and the inner borough of London provide a compelling example of how psychosocial risk factors influence child psychopathology (186). Compelling examples of how psychosocial risk factors affect child psychopathology, these studies examined the prevalence of mental disorders in children living in two very different geographic areas. This research revealed six risk factors within the family environment that correlated significantly with childhood mental disturbances: (a) severe marital discord, (b) low social class, (c) large family size, (d) paternal criminality, (e) maternal mental disorder, and (f) foster placement. This work found that it was the aggregate of adversity factors, rather than the presence of any single one, that impaired development. Other studies also found that as the number of adverse conditions accumulated, the risk of impaired outcome in the child increased proportionally (187). Biederman et al. found a positive association between Rutter's index of adversity and ADHD, measures of ADHD-associated psychopathology, impaired cognition, and psychosocial dysfunction (188).

Other cross-sectional and longitudinal studies have identified variables such as marital distress, family dysfunction, and low social class as risk factors for psychopathology and dysfunction in children. For example, the Ontario Child Health Study in Canada showed that family dysfunction and low income predicted persistence and onset of one or more psychiatric disorders over a 4-year follow-up period (189). Other work implicated low maternal education, low social class, and single parenthood as important adversity factors for ADHD (171,190). These studies suggested that the mothers of children with ADHD had more negative communication patterns, more conflict with their children, and a greater intensity of anger than did control mothers.

Biederman et al. showed that long-term conflict, decreased family cohesion, and exposure to parental psychopathology, particularly maternal psychopathology, were more common in ADHD-affected families compared with control families (191). The differences between children with ADHD and control children could not be accounted for by either socioeconomic status or parental history of major psychopathology. Moreover, increased levels of family-environment adversity predicted impaired psychosocial functioning. Measures indexing long-term family conflict showed a more pernicious impact on the exposed child than those indexing exposure to parental psychopathology. Indeed, marital discord in families has consistently predicted disruptive behaviors in boys (192). This research shows that the extent of discord and overt conflict, regardless of whether the parents are separated, predicts the child's risks of psychopathology and dysfunction (193).

Thus, dysfunctional family environments appear to be a nonspecific risk factor for psychiatric disorders and psychological distress. Reid and Crisafulli reported a metaanalysis of the impact of marital discord on the psychological adjustment of children and found that parental conflict significantly predicted a variety of child behavior problems (194). The Ontario Child Health Study provided a prospective example of the impact of parental conflict on children's mental health: family dysfunction (and low income) predicted persistence and onset of one or more psychiatric disorders over a 4-year period (189).

Low maternal warmth and high maternal malaise and criticism were previously associated with ADHD in children (195), and an epidemiologic study examining family attributes in children who had undergone stressful experiences found that children's perceptions of mothers, but not fathers, differentiated stress-resilient and stress-affected children (196).

An extensive literature documents maternal depression as a risk factor for psychological maladjustment and psychiatric disorder in children (197). This is consistent with the known familial link between ADHD and depression (79). Some investigators have suggested that depressed mood may lead mothers to perceive their children as more deviant than warranted by the child's behavior. Richters, however, reviewed 22 studies of this issue and concluded that, owing to methodologic problems with research in the area, there was no empiric foundation for this claim (198).

Other data revealed a link between maternal depression and child functioning that was independent of the mother's perceptions. These data suggested that depressed mothers accurately perceive symptomatic behavior but react to it in a negative manner that worsens the condition of the child. This conclusion was echoed by Gelfand and Teti (197). Their comprehensive review of relevant literature found many studies to document the assertion that depressed mothers have attitudes of insensitivity, disengagement, disapproval, and hostility toward their children. They also found maternal depression to be associated with undesirable parenting practices such as intrusiveness, unresponsiveness, and inept discipline. In addition, their review supported the idea that depressed mothers had negative perceptions of their children.

Other work shows that ADHD in children predicts depression in mothers, but maternal depression provides no additional information for predicting ADHD in siblings of ADHD probands. This finding suggests that maternal depression is a heterogeneous disorder. It may be that some mothers have a disorder that is genetically linked to ADHD, whereas others may experience depression resulting from the stress of raising a child with ADHD (and perhaps living with an ADHD-affected or antisocial husband). Furthermore, it is possible that maternal depression exacerbates family conflict and poor parenting, both of which could exacerbate ADHD symptoms.

Notably, although many studies provide strong evidence of the importance of psychosocial adversity for ADHD, these factors tend to emerge as universal predictors of children's adaptive functioning and emotional health, not predictors that are specific to ADHD. Thus, they can be conceptualized as nonspecific triggers of an underlying predisposition or as modifiers of the course of illness.

SUMMARY AND CONCLUSIONS

It is not yet possible to describe the origin and pathophysiology of ADHD completely. Nevertheless, converging evidence from the studies reviewed in this chapter supports several empiric generalizations, which should be useful in guiding future research and theory.

Catecholamine Hypothesis

Much research supports the idea that catecholaminergic systems mediate the onset and expression of ADHD symptoms. The key data supporting this idea are as follows: (a) anti-ADHD medications have noradrenergic and dopaminergic effects; (b) lesion studies in mouse and monkey models implicate dopaminergic pathways; (c) the SHR rat shows deficits in catecholaminergic systems; (d) D2, D3, and D4 knockout mice studies show that these genes regulate locomotor activity; and (e) human studies implicate the *DRD4* and *DAT* genes in the origin of ADHD.

Although the role of catecholamine systems cannot be disputed, future work must also consider other neurotransmitter systems that exert upstream effects on catecholamines. Two prime candidates are nicotinic and serotonergic systems. Nicotinic agonists help to control the symptoms of ADHD, and nicotinic activation enhances dopaminergic neurotransmission. Serotonergic drugs have not been shown to be effective anti-ADHD agents, but knockout mice studies suggest that the paradoxical effects of stimulants on hyperactivity are mediated by serotonergic neurotransmission. Moreover, SNAP-25, which has been implicated in studies of the coloboma mouse, leads to striatal dopamine and serotonin deficiencies. These data call for further studies of serotonergic and nicotinic systems.

Brain Systems

Several types of study provide information about the locus of ADHD's pathophysiology in the brain: neuropsychological studies, neuroimaging studies, and animal models. Taken together, these studies support the idea that ADHD arises from the dysregulation of frontal cortex, subcortical structures, and networks connecting them. This idea fits with the pharmacotherapy of ADHD because a plausible model for the effects of stimulants is that, through dopaminergic or noradrenergic pathways, these drugs increase the inhibitory influences of frontal cortical activity on subcortical structures.

Additional data supporting frontal-subcortical involvement in ADHD are as follows: (a) neuropsychological studies implicate orbitofrontal and dorsolateral prefrontal cortex or regions projecting to these regions; (b) the monkey model of ADHD implicates frontal-striatal neural networks; (c) studies of the SHR rat implicate caudate, putamen, nucleus accumbens, and frontal cortex; patients with frontal lobe damage show ADHD-like behaviors; (d) structural neuroimaging implicates frontal cortex, usually limited to the right side, cerebellum, globus pallidus, caudate, and corpus callosum; (e) the I/LnJ mouse strain shows total callosal agenesis along with behavioral features that resemble ADHD; (f) functional neuroimaging finds hypoactivity of frontal cortex, anterior cingulate cortex, and subcortical structures, usually on the right side; (g) ADHD secondary to brain injury shows lesions in right putamen, right caudate nucleus, and right globus pallidus; (h) disabling the D4 gene in mice leads to increased dopamine synthesis in dorsal striatum; (i) mice without D2 genes also show decreased striatal DAT functioning, abnormal synaptic plasticity at corticostriatal synapses, and long-term changes in synaptic efficacy in the striatum; and (j) the coloboma mouse shows deficient dopamine release in dorsal striatum.

Etiologic Factors

In a word, the origin of ADHD is complex. Although rare cases may have a single cause such as lead exposure, generalized resistance to thyroid hormone, head injury, and frontal lobe epilepsy, most cases of ADHD are probably caused by a complex combination of risk factors.

From the many twin studies of ADHD, we know for certain that genes mediate susceptibility to ADHD. Molecular genetic studies suggest that two of these genes may be the *DRD4* gene and the *DAT* gene. To confirm these findings, we need much more work because, even if the positive studies are correct, they may implicate neighboring genes instead of those targeted by the studies. It seems unlikely that a single ''ADHD gene'' causes ADHD with certainty. Instead, it seems likely that several genes act together to form the genetic substrate of the disorder.

When the ADHD-related variants of these genes are discovered, they will probably be ''normal'' variants and will most certainly not have the devastating effects seen in knockout mouse models. For example, suppose future work confirms that the 7-repeat allele is a risk factor for ADHD. We would consider this a normal variant because about 20% of people who do not have ADHD carry this version of the *DRD4* gene. Most of these people do not develop ADHD despite the blunted dopaminergic transmission associated with that allele, and many patients with ADHD do not carry the allele. Thus, the 7-repeat allele cannot be a necessary or sufficient cause of the disorder. Instead, it acts in concert with other genes and environmental risk factors to bring forth ADHD.

Like genetic studies, studies of environmental risk factors suggest that most of these risks exert small but significant influences on the origin of ADHD. For example, most children with a history of PDCs do not develop ADHD, and most children with ADHD do not have a history of ADHD. Nevertheless, research suggests that such complications are more common among children with ADHD.

These considerations lead us to conclude that the origin of ADHD is multifactorial. A simple multifactorial model posits ADHD to arise a pool of genetic and environmental variables—each of small effect—that act in concert to produce vulnerability to ADHD. If a person's cumulative vulnerability exceeds a certain threshold, he or she will manifest the signs and symptoms of ADHD. According to the multifactorial model, no single factor is a necessary or sufficient cause for ADHD, and each of the etiologic factors is interchangeable (i.e., it does not matter which factors one has; only the total number is important). Whether risk factors combine in an additive or interactive manner is unknown.

The mouse models of ADHD we described provide examples of multifactorial causation in a simple system. One model showed that individual differences in the *DAT* gene could directly produce a hypodopaminergic state; these studies showed that dopamine transporter variants differ in their affinity for neurotoxins. Thus, dopamine transporter abnormalities could interact with environmental toxins to produce hyperactivity. Another line of work shows that catecholamines are secreted in response to stress, and catecholamine administration produces fetal hypoxia. Human studies implicate both stress during pregnancy and fetal hypoxia as risk factors for ADHD.

These simple examples suggest that unraveling the complexities of multifactorial causation will be a difficult task for ADHD researchers. However, because technological developments in neuroscience and molecular genetics are moving at a rapid pace, the next decade of work should provide us with more accurate assessments of the brain along with a complete sequence of the human genome. These advances should set the stage for breakthroughs in our understanding of the neurobiology of ADHD and in our ability to treat affected persons.

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