Chapter 2
Causes

To date no single factor has been identified as *the* cause of ADHD. Rather, as is the case for other psychopathologies (e.g., schizophrenia, autism, PTSD, bipolar disorder), ADHD is thought to be the result of complex interactions between genetic, environmental, and neurobiological factors (Kieling, Goncalves, Tannock, & Castellanos, 2008; Mick & Faraon, 2008; Shastry, 2004; Spencer, Biederman, Wilens, & Farone, 2002). Specifically, it appears that the genetic and environmental etiologies of ADHD lead to the neurobiological differences, which in turn manifest as ADHD symptoms (Biederman & Faraone, 2002). These hypothetical relationships are illustrated in Fig. 2.1, which suggests that genetic and neurobiological variables appear to be the greatest contributors to ADHD symptoms (Barkley, 2006). Further, it is clear that environmental variables play a less significant role in the development of most cases of ADHD and it is not known if environmental insults are required for ADHD to emerge (Das Banerjee, Middleton, & Faraone, 2007). To the extent they are involved it seems likely that they contribute to ADHD symptoms by interacting with genetic predispositions. However, in a few cases (i.e., significant neurological injury) ADHD can arise without genetic predisposition (Max et al., 2005a, 2005b). While psychosocial factors do not appear to cause ADHD per se, they clearly have the potential to effect symptom expression (Barkley, 2006).

Genetics

There is strong evidence that genetics plays a powerful etiological role in ADHD (Biederman, 2005; Daley, 2006; Mick & Farone, 2008; National Institute of Mental Health [NIMH], 2006). Evidence in support of this conclusion comes from a variety of sources including family, twin, adoption, genome, and candidate gene search studies.

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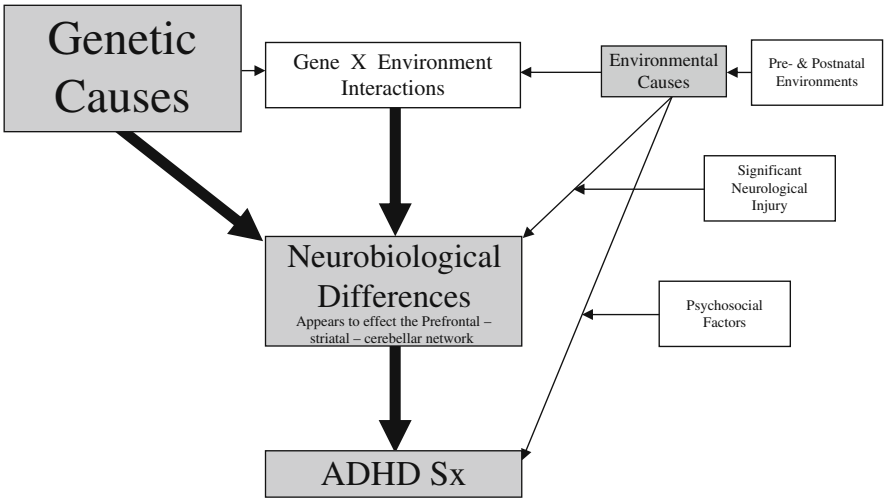


Fig. 2.1 This figure illustrates the hypothetical relationships between genetics, the environment, and the neurobiological differences associated with ADHD. Each of these factors likely has a role in the development and/or manifestation of ADHD and its symptoms

Family Studies

Because children share 50% of their genes with each parent, for genes to be important in the development of ADHD it must run in families (Acton, 1998). Despite changes in diagnostic criteria (as described in Chapter 1), Biederman's (2005) overview of the literature found consistent agreement that the parents and siblings of children with ADHD have a two- to eight-fold increased risk for the disorder. For example, the incidence of ADHD among the parents and siblings of children diagnosed with ADHD is reported to be 25–26% respectively (Biederman, Faraone, Keenan, Knee, & Tsuang, 1990; Welner, Welner, Steward, Palkes, & Wish, 1977). Even more impressive is the report that the incidence of ADHD among children of parents with ADHD is 55% (Biederman et al., 1995). Thus, a family history of ADHD is an important variable to consider when diagnosing this disorder.

Twin Studies

These studies compare identical (monozygotic) twins to fraternal (dizygotic) twins. While identical twins share 100% of their genes, fraternal twins (as is the case with other siblings) share only 50% of their genes. The extent to which identical twin pairs are more likely to have ADHD than fraternal twin pairs is used to estimate "heritability" or the proportion of individual differences in ADHD within a population that can be attributed to genetic differences.

Tharpar, Harrington, Ross, and McGuffin's (2000) literature review suggested the heritability of ADHD to range from 64 to 91%, while Faraone and colleagues' (2005) review of 20 twin studies found a mean heritability estimate of 76%. More recently, Barkley's (2006) review of 18 twin studies suggested the average heritability of ADHD to be "at least" 80–90% (p. 227). From these data it can be concluded that a substantial proportion of the individual differences in ADHD may be attributed in some way to individual genetic differences. It is interesting to note that among fraternal twins (who have developed from two separate ova), the risk of both twins having ADHD is reported by Gilger, Pennington, and DeFries (1992) to be no greater than that found among non-twin siblings (i.e., 29%), despite sharing the same maternal environment during pregnancy.

Adoption Studies

Because family members share, if not the same, very similar environments it is possible that ADHD is transmitted by the common environment and not by common genes. To test this hypothesis adoption studies have been conducted. If genetics (and not shared environment) is the primary factor in the development of ADHD, then siblings with ADHD reared apart should be more similar than adopted siblings reared in the same family (Acton, 1998).

Early adoption studies focused on hyperactivity and confirmed that the biological relatives of children who were hyperactive were more likely to have hyperactivity than the adopted relatives of these children (Cantwell, 1975; Morrison & Stewart, 1971). A more recent study employing *DSM III-R* ADHD diagnostic criteria also found that the biological relatives of children with ADHD are more likely to have ADHD than their adopted relatives (Sprich, Biederman, Crawford, Mundy, & Faraone, 2000).

In sum, family, twin, and adoption studies indicate a strong genetic influence in the development of ADHD. In fact, according to Spencer and colleagues (2002), it "is more attributable to genetic factors than are depression, generalized anxiety disorder, breast cancer, and asthma" (p. 6). However, these studies do not identify the specific chromosome regions, or more precisely the specific genes, that are associated with this disorder. To do so genome and candidate gene search studies have been conducted.

Genome Search Studies

The human genome is comprised of 23 pairs of chromosomes (numbered 1–22, with X and Y designating the sex chromosomes). Combinations of 30,000–40,000 different genes form each chromosome. Composed of deoxyribonucleic acid (DNA), genes function as blueprints for growth and development. If a particular gene is changed in some way, its ability to direct normal development is affected. Similarly,

if a chromosome is damaged in some way, it can affect normal development by altering the numerous genes located in that part of the chromosome (Brock, Jimerson, & Hansen, 2006).

Genome search studies examine all chromosomal locations of families that include individuals with ADHD without any prior assumptions being made about what specific genes underlie ADHD (Biederman & Faraone, 2002). Within these families, DNA sequences (or markers) along different chromosomes are examined by researchers for slight differences (or polymorphisms). Researchers then try to find differences that are consistently found among family members who have ADHD, but not among those without this disorder. By determining how close these polymorphisms unique to the ADHD family members are to a specific gene (done via statistical methods), it can be "linked" to that gene. When such linkages are made the hunt for specific ADHD genes within that chromosome region (or candidate gene searches) can be conducted (Brock et al., 2006).

Waldman and Gizer's (2006) review of the genetics of ADHD report the results of four genome scans for ADHD from three different samples. While there were many discrepant findings, it was reported that three chromosomal regions in two of three samples showed common linkages (i.e., 5p13, 11q22–25, and 17p11).

Candidate Gene Searches

This research begins with the assumption that certain specific genes are likely to be associated with ADHD. These prior assumptions are based upon clinical and empirical evidence (including whole genome searches) that a specific gene is associated with the development of specific ADHD symptoms. Some of the more common candidates to be studied are those genes known to regulate the brain chemicals (e.g., dopamine) and regions (e.g., frontal-subcortical networks) thought to be associated with ADHD.

Mick and Faraone's (2008) review of the literature candidate gene studies of ADHD identifies five different genes for which there appears to be substantial evidence implicating them in the etiology of this disorder. These genes are:

1. *Dopamine D4 Receptor* (DRD4, prevalent in frontal-subcortical networks and associated with the personality trait of novelty seeking),
2. *Dopamine D5 Receptor* (DRD5, abnormalities in this brain chemical are thought to underlie ADHD),
3. *Dopamine SLC6A3 Transporter* (regulates dopamine and is affected by stimulant medication),
4. *Synaptosomal-Associated Protein of 25kD* (SNAP-25, which effects dopamine and serotonin levels and might cause hyperactivity),
5. *Serotonin HTR1B Receptor* (thought to underlie the impulsive symptoms of ADHD).

However, it is important to note that Mick and Faraone caution that the associations with these genes and ADHD are small "and consistent with the idea that genetic vulnerability to ADHD is medicated by many genes of small effects" (pp. 275–276).

Concluding Comments Regarding the Role of Genetics

While family, twin, and adoption studies offer persuasive evidence that ADHD is highly heritable, genome and candidate gene searches suggest that the genetics of ADHD is complex. At this point in time it is safe to say that this disorder is likely mediated by many different genes (Faraone et al., 2005; Mick & Faraone, 2008). Further, one recent study of note suggested the possibility that the genetics of ADHD is a dynamic process wherein different genes are being turned on across development (Kuntsi, Rijsdijk, Ronald, Asherson, & Plomin, 2005). Finally, as illustrated in Fig. 2.1, it would appear that ADHD is not entirely heritable and that there may be some role for environmental factors and/or gene by environment interactions as a cause of ADHD (Das Banerjee et al., 2007; Larsson, Larsson, & Lichtenstein, 2004).

Environment

Among family members the manifestations of ADHD can vary substantially. This fact argues that simple models of inheritance do not account for all of the individual differences in ADHD symptoms (Barkley, 2006), and has supported the hypothesis that environmental variables may be playing a role in the development of ADHD (Das Banerjee et al., 2007). Further supporting a causal role for the environment is prior research documenting that environmental factors (e.g., alcohol) can cause developmental disabilities (e.g., fetal alcohol syndrome).

Environmental variables thought to be playing a role in ADHD symptom expression include both biological and psychosocial factors (Biederman & Faraone, 2002; Das Banerjee et al., 2007). However, according to Barkley (2006), "We are very near to reaching the time when we can conclude unequivocally that ADHD cannot and does not arise from purely social factors. . ." (p. 220). Two other environmental variables that have not received support as being a cause of ADHD include diet and television viewing.

Biological Factors

A variety of biological factors have been associated with an increased risk for ADHD. These include pre-, peri-, and post-natal complications; toxins; and brain injury.

Pre-, peri- and post-natal complications. A variety of pregnancy, birth, and neonatal complications have been associated with a predisposition to ADHD. These include duration of labor, fetal distress, fetal post-maturity, forceps delivery, toxemia or eclampsia, poor maternal health, younger maternal age, and low birth weight (Barkley, 2006; Biederman & Faraone, 2002). Each of these complications can be associated with hypoxic insults, which in turn are hypothesized to affect the brain structures implicated in ADHD (Das Banerjee et al., 2007). For example, Ben Amor and colleagues (2005), report that the mean number of neonatal complications is significantly greater among children with ADHD as compared to their unaffected siblings (3.9 vs. 2.5, $p = .006$). In particular, numerous studies have suggested that low birth weight is a risk factor for ADHD (Biederman & Faraone, 2005). For example, from a case-controlled family study Mick, Biederman, Prince, Fischer, and Faraone (2002) estimated that 13.8% of ADHD cases in the U.S. population could be attributed to low (<2500 g/5.5 lbs) birth weight. More recently, Shum, Neulinger, O'Callaghan, and Mohay (2008) reported children born very early ($\leq$27 weeks) or with an extremely low birth weight ($\leq$1000 g or 2.2 pounds) had more problems with attention (as measured by psychological tests and parent/teacher rating scales) than a control group at 7–9 years of age.

It is important to acknowledge, however, that by themselves low birth weight and the other pre-, peri-, and post-natal complications, lead to a relatively small proportion of children with ADHD (APA, 2000).

Toxins. According to Das Banerjee and colleagues' (2007) review of the literature, exposure to several different toxins have been associated with an increased risk for ADHD, including lead, mercury, manganese, and polychlorinated biphenyls (PCBs). However, it is important to acknowledge that most children with ADHD do not have such exposures. Further, many individuals with high lead levels for example, do not demonstrate ADHD symptoms (Biederman & Faraone, 2005). Barkley's (2006) review of the literature suggests that no more than 4% of the variance in ADHD symptom expression can be explained by elevated lead levels.

Prenatal exposures to tobacco smoke and alcohol have also been suggested to be risk factors for ADHD (Das Banerjee et al., 2007). For example, Linnet and colleagues' (2003) review of 24 studies offers strong evidence in support of the hypothesis that prenatal tobacco smoke exposure is associated with ADHD. Further, several prospective studies of infants demonstrate that fetal exposure to maternal alcohol use leads to behavior problems consistent with ADHD symptoms (Biederman & Faraone, 2005). Finally, among children with ADHD, there is an increased likelihood of having been exposed to alcohol as a fetus (Mick, Biederman, Faraone, Sayer, & Kleinman, 2002).

Brain injury. As was mentioned in Chapter 1, following an encephalitis epidemic in 1917 and 1918, it was observed that a number of children who survived this infection developed ADHD-like behaviors. Consequently early theories of the cause of ADHD focused on brain injury. However, it is now clear that such trauma accounts for only a small percentage (fewer than 5%) of individuals with ADHD (Barkley, 1990). Nevertheless, this disorder has been documented to occur secondary to brain injury (e.g., head trauma, stroke) in childhood, with the occurrence of ADHD being

positively correlated with increased injury severity (Max et al., 1997, 1998, 2002). In two recent studies of children (ages 5–14 years) with brain injury, 15–21% were found to demonstrate "secondary ADHD" (Max et al., 2005a, 2005b). It is important to acknowledge, however, that ADHD itself may be a risk factor for TBI, so genetic and brain injury causes may not be entirely independent.

Psychosocial Factors

Some studies have suggested that the severity of ADHD is associated with family stressors and other psychosocial variables. For example, making use of Rutter's (Rutter, Cox, Tupling, Berger, & Yule, 1975) "adversity indicators" (i.e., severe marital discord, low social class, large family size, paternal criminality, and maternal mental disorder), Biederman, Faraone, and Monuteaux (2002) found that the risk of ADHD increased as the number of adversity factors increased, and Pressman and colleagues (2006), in a study of families with two children diagnosed with ADHD conclude, "There are strong links between impairment in children with ADHD and family environment" (p. 346).

In interpreting these results, it is important to keep in mind that it is possible that the same genetic influences that cause ADHD may also be associated with these psychosocial factors. In the words of Biederman et al. (2002),

> Although our results show that psychosocial adversity is associated with ADHD risk, it is not possible to separate the effects of genetic and environmental influences on our measures of adversity. That is, the pathogenic genes that make a child susceptible to ADHD can lead to psychopathology in the parents and adversity in the family environment. (p. 1561)

Given these observations and the powerful data regarding the heritability of ADHD, it is generally concluded that psychosocial factors do not cause ADHD per se (Barkley, 2006). However, it is safe to say that the severity of symptoms is related to the stress and social adversity experienced among the families of children with ADHD (Jensen, 2000; Remschmidt & the Global ADHD Working Group, 2005). In other words, while they would not appear to cause ADHD, psychosocial factors clearly effect the expression of this disorder.

Diet

It has been suggested that for the vast majority of children, ADHD is neither caused nor exacerbated by refined sugar or food additives (Das Banerjee et al., 2007). In 1982, the National Institutes of Health held a consensus conference and concluded that diet restrictions help only about 5% of children with ADHD, and that such children are mostly those with food allergies. Other more recent studies have supported this conclusion (NIMH, 2006).

Television Viewing

An association between early television viewing (at ages 1 and 3 years) and later attention problems (at age 7 years) has been reported by Christakis, Zimmerman, DiGiuseppe, & McCarty (2004). However, this study did not measure ADHD symptoms per se. Further, additional research has not been able to document a relationship between ADHD and television viewing, which has lead to the conclusion that it is not a risk factor for ADHD (Das Banerjee et al., 2007).

Concluding Comments Regarding the Role of the Environment

Currently, there is very little evidence supporting any one environmental factor as playing a significant etiological role in ADHD. As illustrated in Fig. 2.2, genetics (i.e., having a family history of ADHD) is a much more powerful risk factor than any of the environmental variables. With the exception of significant neurological injuries, such as head trauma and stroke, to the extent environmental factors have a causal role, it seems likely that they do so by interacting with genetic factors (Das Benerjee et al., 2007). Psychosocial factors seem more likely to effect the symptom expression of ADHD, than to be a cause of the disorder per se. Diet and television viewing do not appear to play a role in the etiology of ADHD.

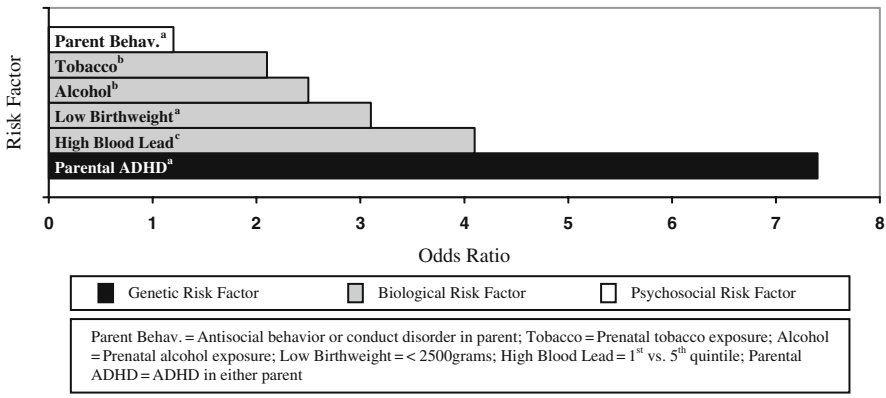


Fig. 2.2 Selected odds ratios, determined by logistic regression analysis, obtained by three studies ([a]Mick, Biederman, Prince, et al., 2002; [b]Mick, Biederman, Faraon et al., 2002; [c]Braun, Kahn, Forehlic, Auinger, & Lanphear, 2006) for genetic, psychosocial, and biological ADHD risk factors. Odds ratios greater than one imply that the factor is more likely to be present among children with ADHD than among those without this disorder

Neurobiology

Researchers generally agree that ADHD's behavioral abnormalities are the result of developmental brain pathologies (presumably caused by the genetic differences and/or environmental insults previously discussed). In particular, it has been suggested that ADHD is linked to dysfunction of the frontal – striatal – cerebellar circuits (Kieling et al., 2008; Krain & Castellanos, 2006) and associated deficits in specific neurotransmitters (e.g., dopamine and norepinephrine; Barkley, 2006). Neuropsychological, neurophysiological, and neurochemical research methods have all been used to understand the neurobiology of ADHD.

Neuropsychology

Neuropsychological research suggests that the inattention, hyperactivity, and impulsivity that characterize ADHD are the result of underlying deficits in behavioral inhibition, resistance to distraction, and executive functioning. These psychological functions have been linked to the prefrontal cortex, and its networks within the striatum and cerebellum (Barkley, 2006; Krain & Castellanos, 2006). This research has provided specific direction to neurophysiological research.

Neurophysiology

Making use of advances in functional imaging technology, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single photon emission computer tomography (SPECT), much has been learned in recent years about the neurophysiology of ADHD (NIMH, 2006). In fact, there is now convincing evidence that ADHD is associated with significant differences in brain development. These include overall brain size; and specific prefrontal, striatal, and cerebellar differences. These specific brain regions are illustrated in Fig. 2.3.

Decreased overall brain size. When compared to age- and sex-matched peers without ADHD, individuals with ADHD have about a 3–8% smaller brain volume (Kieling et al., 2008). By in large these differences are consistent throughout childhood and adolescence, and do not appear to be related to medication status (i.e., whether or not the individual had taken medication to manage ADHD symptoms; Castellanos et al., 2002). As measured by behavior rating scales and neuropsychological tests, more severe ADHD symptoms are associated with smaller brain volumes (Bush, Valera, & Seidman, 2005). Future research will be necessary to determine if these brain size differences are stable into adulthood.

Prefrontal cortex. Consistent with neuropsychological research findings, neurophysiological research has tended to focus on the frontal lobes of the brain and those associated networks responsible for attention, behavioral inhibition, resistance to distraction, and executive functioning. The prefrontal cortex has been found to be

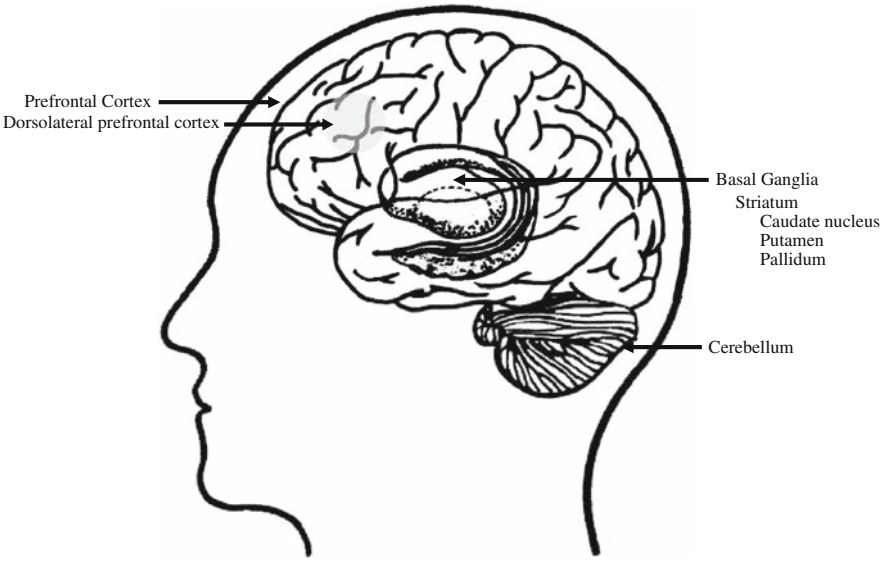


Fig. 2.3 Major brain structures implicated in ADHD

significantly smaller among children with ADHD as compared to controls. This brain structure is near the front of the frontal lobes and is thought to be responsible for executive functions. In Seidman, Valera, and Makris' (2005) review of the literature, all studies that have measured at least one part of the prefrontal cortex found this structure to be smaller among children with ADHD. More specifically, brain size reductions in particular regions of the prefrontal cortex, such as the dorsolateral prefrontal cortex, have been implicated in the pathophysiology of ADHD (Bush et al., 2005; Kieling et al., 2008; Krain & Castellanos, 2006; Seidman et al., 2005).

Basal ganglia (striatum). The caudate nucleus, putamen, and the pallidum, which serve as the entry point to the basal ganglia, have also been implicated in ADHD (Krain & Castellanos, 2006). This brain structure is located deep within the cerebral hemispheres and serves as a connection between the cerebrum and cerebellum (NIMH, 2004). Damage to this structure is associated with secondary ADHD and in animal studies has been found to produce hyperactivity. In Seidman and colleagues' (2005) review, 9 out of 13 studies found individuals with ADHD to have smaller caudate volumes, and all 4 studies of the pallidum found children with ADHD to have smaller volumes. Interestingly, the one brain structure that appears to normalize in size by mid-adolescence is the caudate nucleus, which has lead to speculation that this may be the neurophysiological basis for why symptoms of hyperactivity diminish with increasing age (Castellanos et al., 2002).

Cerebellum. In addition to its role in the coordination of motor movements, this brain structure is also involved in timing and attention shifting via its connections with frontal regions (Krain & Castellanos, 2006). This structure is located at the

lower back part of the brain, and in Seidman and colleagues' (2005) review, all five research groups studying the cerebellum noted structural abnormalities including reduced volume.

Neurochemistry

Based primarily on the responses of children with ADHD to medications that increase the availability of dopamine and norepinephrine, neurochemical explanations for ADHD have also been proposed (Biederman & Farone, 2005). These medications include methylphenidate (Ritalin), pemoline (Cylert), and dextroamphetamine (Dexedrine®), which increase the release and inhibit the reuptake of dopamine (thereby increasing the availability of this brain chemical). They also include atomoxetine (Strattera®), which is a norepinephrine reuptake inhibitor (i.e., it elevates this neurotransmitter by inhibiting its reuptake from the synaptic cleft thereby increasing its availability). Further evidence supporting the neurochemical basis of ADHD include (a) studies suggesting decreased brain dopamine in the cerebral spinal fluid of children with ADHD (as compared to children without this disorder), (b) animal studies (which, for example, have shown that methyphenidate increases norepinephrine and dopamine out flow within the prefrontal cortex), and (c) the fact that the genes implicated in ADHD are known to regulate brain chemicals (Barkley, 2006; Berridge et al., 2006; Biederman & Faraone, 2005; Remschmidt et al., 2005).

Concluding Comments Regarding the Role of Neurobiology

In addition to being highly heritable, there is strong evidence in support of a neurobiologic basis for ADHD. Recent imaging research has documented that differences in overall brain size and specific brain regions appear to distinguish children with ADHD from those without this disorder. These studies have suggested that the behavioral manifestations of ADHD are the result of dysfunction in the frontal – striatal – cerebellar circuits. Also implicated in the pathophysiology of ADHD are deficits in specific neurotransmitters (e.g., dopamine and norepinephrine). The fact that the medications used to treat ADHD increase the availability of these brain chemicals offers further evidence in support of a neurobiological basis for this disorder.

Concluding Comments

The etiology of ADHD is complex and a precise understanding of what causes this disorder, particularly in individual cases, has not yet been obtained. However, at this point in time it is safe to say that ADHD is a highly heritable neurobiological disorder. To the extent that biological factors in the environment plays a role

in the etiology of ADHD, in all but a few cases (i.e., traumatic brain injury) they likely do so by interacting with specific genetic factors. In concluding this chapter it is also important to acknowledge that much has been learned about what does *not* cause ADHD. Specifically, diet, poor parenting or dysfunctional family environments, and excessive television viewing do not appear to cause ADHD per se. Clearly such factors can make ADHD symptoms better or worse, but they do not cause the neurobiological differences associated with this disorder.



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