2
Causes

Researchers have been attempting to find the causes of autism since it was first identified by Kanner in 1943. Although Kanner initially suggested autism to have a biological basis; most early efforts to identify the causes of autism focused on inadequate nurturance by emotionally cold and indifferent parents (Ozonoff & Rogers, 2003). However, in the words of Ozonoff and Rogers (2003): "It is now abundantly clear that autism is a biological disorder and is not caused by parenting deficiencies or other social factors" (p. 18). Today, it is accepted that the behavioral manifestations of autism are a consequence of abnormal brain development, structure, and function. The brain structures implicated in autism are illustrated in Figure 2.1 (Strock, 2004).

Although it is clear that autism has an organic etiology, the underlying causes of these neurological differences, and exactly how they manifest themselves, is much more controversial. Literature reviews conducted by Muhle, Trentacoste, and Rapin (2004), Rapin and Katzman (1998), and Newschaffer, Fallin, and Lee (2002) suggest the etiology of autism to be complex and multifaceted, resulting from the interaction of genetic, neurological, and environmental factors. Specifically, it has been suggested that some combination of genetic predisposition(s) and gene by environmental interaction(s) result in the brain abnormalities, which in turn are the causes of the range of behaviors we currently refer to as autism spectrum behaviors. These hypothetical relationships are summarized in Figure 2.2.

Genetics

There is strong evidence that autism is heritable (Muhle et al., 2004). Ozonoff and Rogers (2003) suggest that there are four primary lines of research pointing to the role of genetic factors in autism. First, they refer to research that has documented a 3 to 6 percent increased risk for autism among the siblings of children with an autism spectrum disorder, a rate that far exceeds that found in the general population. Second, they site research that has found that if one identical twin has Autistic Disorder, 60 percent of the time the other twin will also have this condition. This percentage jumps to 90 percent when both twins are viewed from

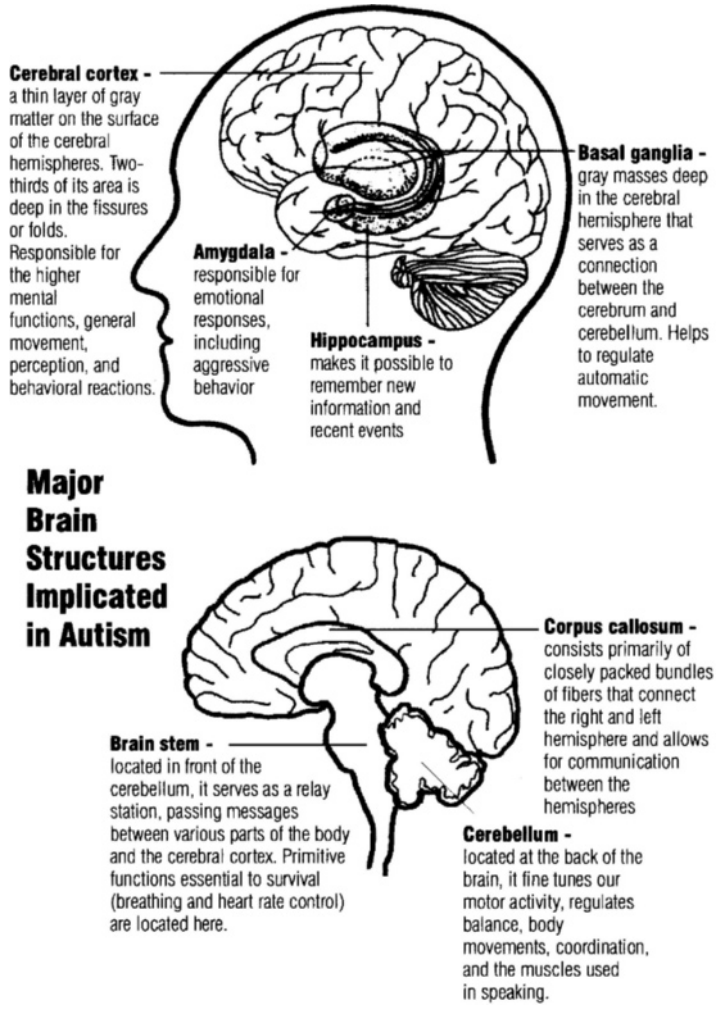

FIGURE 2.1. The brain structures implicated in autism. [Reprinted from Margaret Strock (2004), *Autism Spectrum Disorders.* Bethesda, MD: NIMH (p. 29). This work is in the public domain.]

the perspective of the broader autism spectrum. Conversely, among fraternal twins (who have developed from two separate ova), the risk of both twins having autism is no greater than that found among non-twin siblings.

Third, Ozonoff and Rogers (2003) acknowledge research that has documented autism to be associated with a variety of genetic and chromosomal abnormalities. However, it is important to note that current estimates suggest that less than 10 percent of all autism cases are caused by a diagnosable medical condition, chromosomal abnormality, or genetic defect (e.g., tuberous sclerosis, fragile X;

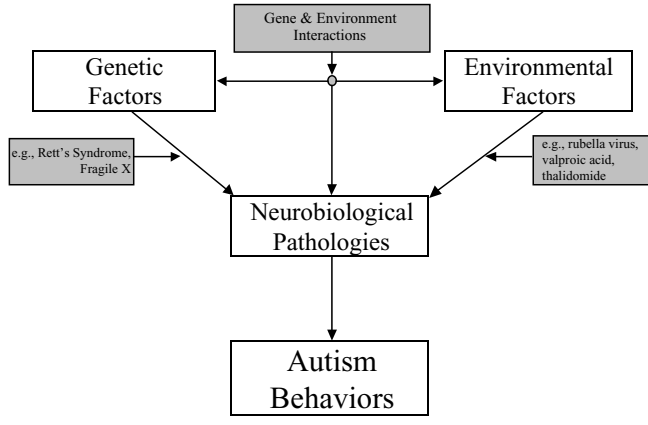

FIGURE 2.2. The hypothetical relationships between genetics, the environment, and the brain abnormalities that are the likely causes of autism.

Muhle et al., 2004). Finally, they cite research suggesting that besides autism, the families of individuals with autism tend to demonstrate a set of cognitive and social differences that are not seen in other family groups. Although these data are very powerful, at present the identity and number of genes associated with autism is not known and is the focus of much scientific inquiry.

Identification of Autism Genes

The human genome is composed of 23 pairs of chromosomes (numbered 1 to 22, with X and Y designating the sex chromosomes). Combinations of 30,000 to 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 (Exploring Autism, 2002; The National Autistic Society, 2004). To better understand the genetics of autism, researchers currently employ several different methods. Muhle and colleagues (2004) divide these methods into: (a) cytogenetic studies, (b) genome searches, and (c) candidate gene searches.

Cytogenetic studies. This type of research examines chromosome number and/or structure to identify abnormalities that may be associated with autism. Using various viewing techniques, researchers examine the chromosomes of individuals with autism and search for visible breakpoints, translocations, duplications, and deletions (Exploring Autism, 2002). When such abnormalities are found, the hunt for specific autism genes within that region begins. Muhle and colleagues (2004) suggest that among individuals with autism, abnormalities are "fairly frequent" on chromosome 15 (15q) (p. 472). Currently it is speculated that there are at least

TABLE 2.1. Genes suspected to be involved in autism.

Gene(s)	Chromosome(s)
5-hydroxytryptamine (serotonin) transporter (*5HTT*) gene	17
Gamma-aminobutyric acid A receptor b3 (*GABRB3*) gene	15
Reelin (*RELN*) gene	7
Homeobox (*HOX*) genes	7, 17, 2
Fragile X genes	X
C-Harvey-ras (*HRAS*) gene	11

Sources: Muhle et al. (2004) and Newschaffer et al. (2002).

22 chromosome regions containing genes associated with autism (Xu, Zwaigenbaum, Szatmari, & Scherer, 2004). It is important to note that while cytogenetic studies are helpful in identifying regions of interest in and of themselves, these techniques cannot identify the specific genes that may cause autism.

Genome searches. This type of research examines the genetic material of families that include individuals with autism. Within these families, DNA sequences (or markers) along different chromosomes are examined by researchers for slight differences (referred to as polymorphisms). Researchers then try to find differences that are consistently found among family members who have autism, but not among those without the disorder. By determining how close the polymorphism, unique to the autism family members, are to a specific gene (done via statistical methods), the polymorphism can be "linked" to that gene (Exploring Autism, 2002). When such linkages are made, the hunt for a specific autism gene within that chromosome region begins. Muhle and colleagues (2004) suggest that at least 10 different genes have been associated with autism using this technique, with the putative speech and language region (7q31–q33) "most strongly linked with autism" (p. 472). Here again it should be noted that these studies are helpful in identifying chromosomal regions of interest. However, linking a given polymorphism and a given gene does not mean that a specific gene has been found. Rather, it means that it is likely that such a gene is nearby.

Candidate gene searches. This research begins with the assumption that certain specific genes are likely to be associated with autism. These prior assumptions are based upon clinical and empirical evidence (including whole genome searches and cytogenetic analysis) that a specific gene is associated with the development of specific autism symptoms. Using this method, several research teams have found associations between autism and at least six different genes or gene groups. These genes are listed in Table 2.1. However, there has been no consistent replication of positive findings for any of these genes (Newschaffer et al., 2002).

Concluding Comments Regarding the Role of Genetics

It is not likely that autism is a purely genetic disorder (Ozonoff & Rogers, 2003). With the exception of Rett's Syndrome [which is caused in the majority of cases by

changes to a gene on the X chromosome (Xq28)], there is no conclusive evidence that autism is associated with any specific genetic defect. Rather, the available data suggests that multiple genetic factors cause a majority of cases of autism (Muhle et al., 2004). Models of how this might work include an additive threshold model (wherein a certain number of factors are needed to reach a critical threshold for autism to develop) and an epistatic model (wherein multiple predisposing genes interact with each other to cause autism; Newschaffer et al., 2002). Also yet to be identified are the potential environmental and biological triggers that may interact with these genetic predispositions and result in the symptoms defined as autism.

Environment

Among family members (including identical twins), the manifestations of autism can vary substantially. This fact strongly argues that simple models of inheritance do not account for this spectrum of disorders (London & Etzel, 2000) and has facilitated a recent increase in studies of possible environmental factors in autism. This line of study is reinforced by prior research documenting that environmental factors (e.g., alcohol) can cause developmental disabilities (e.g., fetal alcohol syndrome). However, to the extent the environment does have a role in causing autism, it has been suggested that it does so by interacting with certain genes. Thus, a certain gene or gene combinations may generate a susceptibility to autism that is in turn triggered by a certain environmental factor or factors (Newschaffer et al., 2002). Environmental factors currently being considered include obstetric suboptimality, prenatal, and postnatal factors.

Obstetric Suboptimality

According to Newschaffer and colleagues (2002), the combination of evidence suggesting autism to have its origins in prenatal development and the lack of any specific factor as being the cause of autism has led to the study of summary measures of the pregnancy and delivery's "optimality" (e.g., maternal age, maternal disease, neonatal respiratory distress). Most studies that have considered obstetric suboptimality have found lower optimality among children with autism when compared with normal controls (Glasson et al., 2004; Newschaffer et al., 2002). However, whether this is a cause or a consequence of autism remains unknown, and Hansen and Hagerman (2003) suggest that these variables " . . . likely represent additive brain trauma to a vulnerable child rather than a distinct etiology of ASD" (p. 99).

Prenatal Factors

Maternal infection and drug exposure are two prenatal factors reported by Newschaffer and colleagues (2002) as having been the focus of prior study. Regarding the former, rubella has been specifically associated with autism. However,

Newschaffer et al. conclude: "The low frequency of reports suggests that infectious diseases known to be associated with neuropathology are not a major independent cause of ASD" (p. 145). Cytomegalovirus, herpes, and HIV have also been associated with autism (Hansen & Hagerman, 2003).

Regarding drug exposure, taking thalidomide during the 20th to 24th weeks of pregnancy has been correlated with an increased risk of autistic disorder (Miller & Stömland, 1999). Valproic acid (know by the brand names Depakene and Depakote) and alcohol abuse have also been suggested to increase the risk of autism (Hansen & Hagerman, 2003; Newschaffer et al., 2002).

Postnatal Factors

Herpes encephalitis and other infections (e.g., chickenpox) have been associated with autism. However, current research does not support the potential etiological role of chemical exposures, the measles-mumps-rubella vaccine, nor mercury and thimerosal-containing vaccines (Newschaffer et al., 2002). Epidemiological data from the US and Europe have not found relationships between thimerosal nor vaccines and autism. According to the Institute of Medicine's Immunization Safety Review Committee (2004), ". . . the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism" (p. 16), and ". . . that the evidence favors rejection of a causal relationship between MMR vaccine and autism" (p. 16). Finally, Matsuishi and colleagues (1999) report that children with autistic disorder have a significantly higher incidence of meconium aspiration syndrome, which is associated with fetal hypoxia, when compared with the children in the control group. Again, it is not clear if the association is a cause or consequence associated with the development of autism.

Concluding Comments Regarding the Role of the Environment

Currently, there is very little evidence supporting any one environmental factor as playing a primary role in the development of autism. Thus, to the extent environmental factors (both those that affect the mother and those that affect the child who develops autism) are playing a causal role in the development of autism, it seems likely that they interact with a variety of genetic factors (both those carried by the mother and those carried by the child who will develop autism). The relationships between the environments of the mother and the child and the genetics of both is illustrated in Figure 2.3, which offers the model of potential etiologic effects put forward by Newschaffer and colleagues (2002).

Neurobiology

Contemporary scholars generally agree that autism's behavioral abnormalities are the result of developmental brain pathologies (Akshoomoff, Pierce, & Courchesne, 2002; Courchesne, Carper, & Akshoomoff, 2003; Newschaffer et al.,

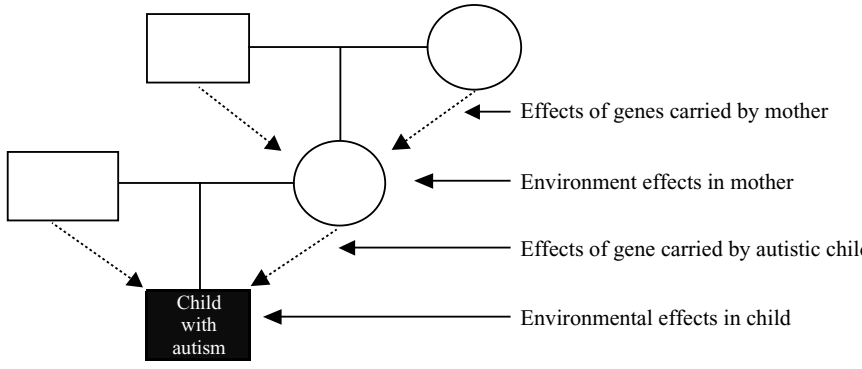

FIGURE 2.3. A model of the potential etiologic role of the environments of the mother and the child, and the genetics of both mother and child. [Reprinted from Newschaffer et al., "Heritable and Nonheritable Risk Factors for Autism Spectrum Disorders, *Epidemiologic Review*, 2002, 24(2), 137–153, by permission of Oxford University Press. Copyright © 2002 Johns Hopkins Bloomberg School of Public Health.]

2002; Nicolson & Szatmari, 2003). No single pathology has been found to account for all cases of autism, rather several different etiologies have been proposed. This fact is consistent with the hypothesis that autism is not a distinct clinical entity. Rather, it is a collection of different disorders with similar behavioral manifestations.

Brain Size

Clinical onset of autism's behavioral manifestations appears to be preceded by slightly reduced head size at birth, followed by a rapid and excessive increase in head circumference measurements (reported to be an accurate index of early brain size) between 1 to 2 and 6 to 14 months. Although seen in 6 percent of healthy developing infants, Courchesne and colleagues (2003) found 59 percent of the 48 children they studied to demonstrate such growth. They report that on average, between 6 to 14 months head size increased from the 25th to the 84th percentile rank (according to CDC norms). These data are illustrated in Figure 2.4. Especially provocative was the finding that the most dramatic early increases in head size were demonstrated among those children with more severe Autistic Disorder. Conversely, those with less severe manifestations of autism (e.g., PDD-NOS) showed smaller increases. This rapid early growth in the first year of life is then followed by a period of two to four years during which the rate of brain growth slows, and then during middle or late childhood through adolescence a plateau in overall head growth occurs.

Given that the first year of life is an important period of brain development and learning, Courchesne and colleagues (2003) speculate that this early period of rapid brain growth is an important causal factor in the emergence of autistic symptoms.

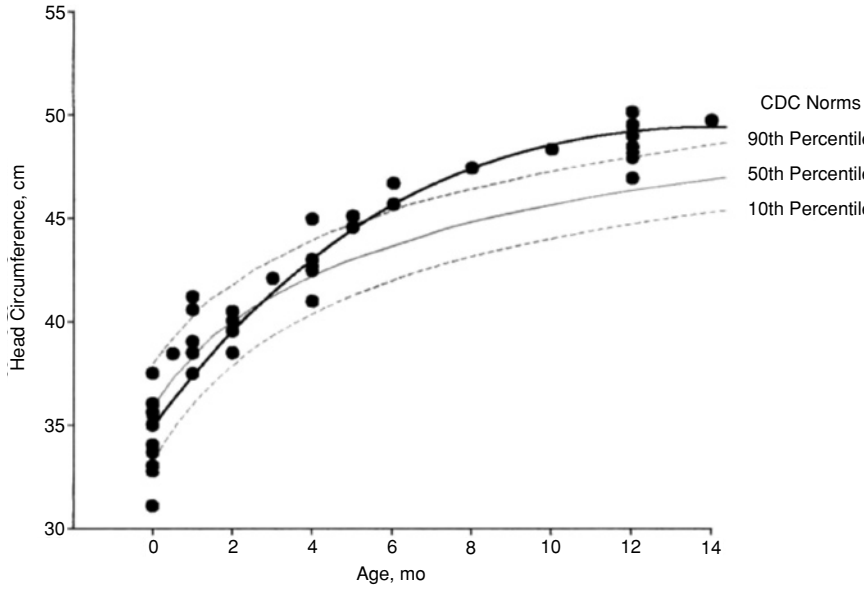

FIGURE 2.4. Courchesne et al. (2003, p. 342) head circumference measurements for a sample of children with autism as compared to CDC norms. [Reprinted from *JAMA* with permission from the American Medical Association. Copyright © 2003 American Medical Association.]

They suggest that this rapid and disordered growth "produces in too short a time too many [synaptic] connections that may not be adaptive. Faced with the neural noise that would be the result of such rapidly changing aberrant connections, the infant would lose the ability to make sense of its world and withdraw" (p. 343, word in brackets added).

MRI data from a study by Akshoomoff and colleagues (2004) confirm that brain size is a correlate of autism among preschool-age children. In this study, the brains of 52 boys with a provisional diagnosis of autism (aged 1.9 to 5.2 years) and 15 typically developing children (aged 1.7 to 5.2 years) were measured via MRI technology. Subsequently, after the age of 5 years, diagnostic and cognitive testing allowed the autism group to be divided into low functioning ($n = 30$), high functioning (verbal and non-verbal IQs of at least 70, $n = 12$), and PDD-NOS (met *DSM-IV* criteria, but did not meet diagnostic test cutoffs for autism, $n = 10$) groups. This allowed for comparisons of the previously obtained MRI data not only between autism and typically developing children, but also for comparisons among the children with autism spectrum disorders.

Results revealed significant differences in brain size among the groups. For the low-functioning autism group, whole brain, overall cerebral, cerebral gray matter, cerebellar white matter volumes, and the anterior cerebellar vermis area were significantly larger than that found in the control group. For the high-functioning

autism and PDD-NOS groups, cerebellar white matter volumes and the anterior cerebellar vermis area were significantly larger than that found in the control group. In addition, the low-functioning and high-functioning autism groups had significantly different posterior cerebellar vermis areas, with the low-functioning group mean size being significantly smaller than the high-functioning mean. Discriminant function analysis[1] (using cerebellar white and gray matter volumes, area of the anterior and posterior cerebellar vermis, and cerebral white and gray matter volumes as predictors of group membership) correctly classified 84.6 percent of the low-functioning group, 66.7 percent of the high-functioning group, 10 percent of the PDD-NOS group, and all but one (92.3 percent) of the control group. From these data, Akshoomoff and colleagues (2004) conclude that neuroanatomical measures discriminate children with autism from typically developing children. In addition, they suggest that the "results also demonstrate that there are neuroanatomical differences between young children with autism who are higher functioning compared to those who are lower functioning" (p. 355).

Brain Structure

From a review of the literature, Akshoomoff and colleagues (2002) suggest that there is strong evidence for neuroanatomical abnormalities among children with autism (see Figure 2.1). Specifically, they point to postmortem and MRI research that has documented that among individuals with autism, most major brain structures are affected. These areas include the hippocampus and amygdala, cerebellum, cerebral cortex, limbic system, corpus callosum, basal ganglia, and brain stem (Tharp, 2003).

Casanova, Buxhoeveden, Switala, and Roy (2002) have described what may be the most fundamental structural anomalies in the brains of individuals with autism. In a postmortem study, the brains of nine individuals with autism (mean age 12 years) were compared with the brains of nine control subjects (mean age 15 years). Results revealed that individuals with autism differed from normally developing people in the size, number, and arrangement of minicolumns in the prefrontal cortex and in the temporal lobe. Minicolumns are considered to be the basic anatomical and physiological unit of the brain; they take in, process, and then respond to stimuli (Buxhoeveden & Casanova, 2002). Casanova has compared minicolumns to information processing computer chips (McKinney, 2002).

Using computerized imaging software to obtain cell measurements, Casanova and colleagues (2002) found the autistic group's minicolumns to be narrower than those found among the normal control group. Specifically, the autistic group's minicolumns were more numerous, smaller, and less compact in their arrangement (i.e., the cells were more dispersed) than those found among the control group. Figure 2.5 provides images that illustrate these differences.

[1] Discriminant function analysis is a statistical technique that can be used to predict group membership. It uses a combination of variables (in this case specific measures of brain size) to predict group membership.

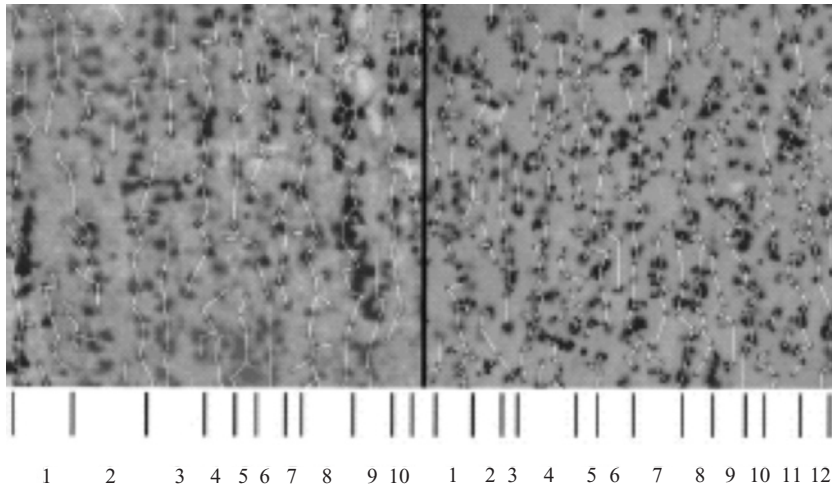

FIGURE 2.5. Casanova et al.'s (2002, p. 431) microscopic fields (original magnification × 100) analysis of layer III of temporoparietal auditory area from the brain of an individual with autism (right) and an age-matched control (left): The superimposed white lines indicate the cell core of the minicolumn. Lines and numbers at the bottom of each figure define the boundaries of each minicolumn. [Reprinted from the American Association of Neurology's journal *Neurology,* with permission from Lippincott Williams & Wilkins. Copyright © 2002 Lippincott Williams & Wilkins.]

The authors speculate that the extra minicolumns may result in cortical "noise" (p. 431). They further suggest that their findings are consistent with the view that autism is a disorder of the brain's arousal-modulating systems and that due to the extra minicolumns "... autistic individuals experience a chronic state of overarousal and exhibit abnormal behaviors to diminish this arousal" (p. 431). If correct, this hypothesis may help to explain some of the behavioral abnormalities observed among individuals with autism. For example, difficulty establishing and maintaining eye contact may be a consequence of being overpowered by the stimuli received when looking someone in the eye (McKinney, 2002).

Brain Chemistry

Through comprehensive literature reviews, Ciaranello and Cirananello (1995) and Rapin and Katzman (1998) identified factors that have been implicated consistently in the development of autism. Their examination of evidence for neurochemical bases for autism reveals a consistent association only with elevated serotonin levels, which are found in the blood of about 25 percent of individuals with autism. Special relevance to autism may be found in the fact that serotonin is involved in the formation of new neurons in the brain ("neurogenesis") and is thought to be important in the regulation of "neuronal differentiation, synaptogenesis,

and neuronal migration during development" (Newschaffer et al., 2002, p. 138). Supporting this hypothesis that abnormal serotonin metabolism is common among individuals with autism is the finding that depletion of tryptophan (a precursor of serotonin) in the diet worsens the behavior of a substantial percentage of children with autism (Joshi, Percy, & Brown, 2004).

It has also been suggested that the inhibition of gamma-aminobutyric acid (GABA) may contribute to the specific functional deficits in autism (e.g., impaired ability to process sensory information and learning tasks). Hussman (2001) proposed a hypothesis of suppressed GABAergic inhibition in autism, which results in excessive stimulation of glutamate-specialized neurons and loss of sensory gating. It is suggested that these hypotheses of impaired neurotransmission in autism are consistent with a broad range of findings from other neurochemical and neuroanatomic research.

Concluding Comments Regarding the Role of Neurobiology

Newschaffer and colleagues (2002) conclude that the variety of different neuropathologies associated with autism implies that these disorders have a variety of different causes. Although these authors argue that these brain differences likely have a prenatal origin, they acknowledge that the plasticity associated with the young brain ". . . may still allow for postnatal factors to affect the disease's natural history" (p. 138).

Concluding Comments

This chapter has illustrated the complexity of the issue of autism's causes. Despite the multitude of research exploring its etiology, definitive conclusions regarding the causes of autism remain elusive. A problem of particular importance relates to the wide range of manifestations of autism symptomatology: two children (even identical twins) diagnosed with autism falling at different points of the autism spectrum may share few characteristics. Consequently, conclusive findings of a single cause for autism are most unlikely. The current consensus regarding the cause of autism is provided in a multifaceted model, which includes genetic, neurobiological, and neuroanatomical mechanisms, as well as environmental influences. In order to successfully integrate findings of several approaches, further research is needed to clarify the nature of the complex interplay between different mechanisms and their unique contribution to the development of autism.