CHAPTER 2

Historical Perspectives and Etiology of Autism Spectrum Disorders

KEY TERMS

Autistic Psychopathy
Cross-modal Associative Memory
Etiology
Feral Children
Habit Memory
Lesion
Low-incidence Disability
Multiplex Family
Neural Plasticity
Neurotransmitters
Neurotypical
Organic Disorder
Prevalence
Psychopharmacological
Representational Memory

❖ LEARNING WITH MS. HARRIS: The Need to Learn More

Ms. Harris is amassing a great deal of information about ASD. She treasures the insight into family life provided by Ms. Owens and accompanied her to a parent support meeting where Ms. Harris continued to be amazed at the parents' resilience in facing the daily challenges their children present. Although Ms. Harris laughed about becoming as pedantic as some individuals on the spectrum, she talked about ASD to anyone who would sit still. At dinner with a group of her friends one evening, however, Ms. Harris's sense of superior knowledge vanished as her friends started asking questions.

"OK, so some kids have autism and some kids have Asbergers," stated Leia.

"AsPERgers," corrected Ms. Harris.

"Yeah, right," replied Leia, "Anyway, so why do they call them that?"

"Oh, I know," said Franklin. "They got the name autism from that kid on St. Elsewhere *on TV."*

"No way," shouted Twyla. "Dustin Hoffman did Rain Man *before that. The name came from him."*

"That's right," responded Franklin. "And I remember when Dustin Hoffman said he interviewed some guy named Joseph Sullivan in order to prepare for the part. Wonder where Joseph came up with the name?"

"I think 'AsPERgers'", said Leia, pronouncing carefully, "sounds like some kind of detergent."

"Oh, and I heard that kids get autism from their parents," interjected Twyla.

Ms. Harris, dizzy from all the banter, realizes she has no idea where the terms came from or when they were first applied. She vaguely recalls one of her professors saying the term had something to do with the Greeks, which would certainly predate the kid on St. Elsewhere *as well as Dustin Hoffman. Could there be any truth to the idea that parents cause autism? For the first time in weeks, Ms. Harris changes the subject to something other than ASD and eats the rest of her meal very quietly.*

AUTISM THROUGH HISTORY

Autism is not a new disability. Individuals have demonstrated the characteristics associated with Autism Spectrum Disorders (ASD) for thousands of years. Long ago, children born with autism probably suffered the same fate experienced by babies born with any disability. Infants and children seen as defective were abandoned in remote areas and left to die (Kirk, Gallagher, & Anastasiow, 1993). Indeed, in 1799, Jean Marc Gaspard Itard made history in special education when a child named Victor, who had been found living in the woods among wolves, was brought to him. Itard determined to demonstrate that he could socialize the boy (Itard, 1806/1962; Lane, 1976). Victor's ability to survive alone in the wilderness indicates that he was not an infant when abandoned but older, yet his behavior was viewed as uncontrollable. This would be consistent with the presence of autism. Although most instances of autism are present at birth, many children, particularly those born centuries ago, might not have been perceived as markedly different until they were 3 or 4 years old or even older. Itard wanted to prove that appropriate instructional techniques could teach a boy as wild as Victor. Unfortunately, Victor proved to be resistant to Itard's efforts, and Itard deemed his experiment a failure. Given his abandonment and his resistance to Itard's efforts, it is highly likely that Victor had autism.

Victor is not an isolated example of the historical presence of ASD. A number of **feral children** (children growing up isolated from humans, said to be

raised by animals) have been described in the literature, including Kaspar Hauser and the "wolf-girls" of India (Candland, 1993; MacLean, 1977; Newton, 2003). Frith (2003) marvelously recounts the story of Peter, the Wild Boy of Hanover, who was discovered in Germany when he was about 12 years of age. Peter, who captured the interest of King George I and Queen Caroline, never learned to speak even though he was given every advantage. However, Peter loved music and would hum tunes he heard.

Although ASD, like many other disabilities, has been present in humans for centuries, efforts to educate individuals with disabilities have been a relatively recent phenomenon. Specialized instructional techniques and schools for students with disabilities did not appear in the United States until after the 1820s, and then they focused primarily on individuals with peripheral sensory disabilities, such as the blind or deaf (Hallahan & Kauffman, 2003). Even with the legislation of compulsory education toward the end of the nineteenth century in the United States, it was still not compulsory for children with disabilities to attend school. This did not keep interested individuals from providing training and education to persons with disabilities, but it was more often with private than public services.

Kanner's Use of the Term *Autism*

Toward the middle of the twentieth century, a psychiatrist at Johns Hopkins University named Leo Kanner began to notice similarities among a group of children who had been brought to him for diagnoses and treatment. Kanner published an article in which he described these 11 children (Kanner, 1943) as having marked differences in their ability to socialize with others and extreme rigidity in their behaviors. Although the term had been used in the early 1900s by Bleuler to describe socialization deficits and a singular focus on personal interests in persons with schizophrenia (Bleuler as cited in Frith, 1991), Kanner was the first to apply the term *autism* to a group of children who were demonstrating remarkably similar behavioral features.

The Greek root of the term *autism* is *autos* which roughly translates as *self*. *Autos* is also the root for the word *automatic* which is equated with independent functioning without the need for external input (like an automatic transmission or an automatic dishwasher). Kanner viewed the children as demonstrating little need for interaction with others and viewed them as being self-absorbed and self-satisfied. Therefore, he used the term *autism* to characterize the children's behaviors (Volkmar, Carter, Grossman, & Klin, 1997).

Much of what Kanner described about those children's characteristics form the basic description of individuals who have what is now termed *classic* or *Kannerian* autism. However, Kanner made a few assertions that have proved inaccurate. First, Kanner noted that the children lacked any obvious physical differences, so the condition could not have been organic (i.e., not a congenital condition or some type of birth defect) and therefore would have no associated medical conditions. Today it is recognized that autism is an **organic disorder** (present at birth) and may be associated with

other medical conditions such as seizure disorders, Cornelia de Lange syndrome, Fragile X, William's syndrome, tuberous sclerosis, and Landau-Kleffner syndrome (Canitano, Luchetti, & Zappella, 2005; Rutter, Bailey, Bolton & Le Couteur, 1994).

Second, Kanner noted that the children he examined all had intelligence quotients (IQs) in the normal range, and stated that children with autism would have normal intelligence. Researchers today document that the majority of individuals with autism demonstrate some level of mental retardation (i.e., IQ < 70; Fombonne, 1999; Rutter et al., 1994). Kanner used the term *functionally retarded* to refer to the children's dysfunction in the presence of what he thought was normal intelligence. Kanner's position that the children with autism had a normal or brilliant innate capacity which was not being exhibited continues to be believed by many people today, even in the face of evidence to the contrary.

Finally, Kanner certainly saw a skewed population. In the 1940s, the parents who brought their children to his office at Johns Hopkins University were university professors and other professionals who probably earned enviable salaries. This led Kanner to conclude that autism would occur only in families of higher socioeconomic status. Today it is recognized that autism occurs in families at any and all income levels and is not unique to the wealthy. Because of a presumed focus on their career rather than their children, Kanner also postulated that the parents played a role in the development of autism. Today it is recognized that the only role parents play might be via genetics (Szatmari, Jones, Zwaigenbaum, & MacLean, 1998).

In 1908, even before Kanner began to study this group of children, a special educator in Vienna, Theodor Heller, was describing children who apparently had typical early development but then regressed severely as exhibited by their lack of language, interest in others, and relatedness. In addition to social withdrawal, children with "Heller's dementia infantilis" engaged in bizarre and perseverative, or repetitious, motor behaviors as well as sensory avoidance (Yakovlev, Weinberger, & Chipman, 1948). Today, Heller's syndrome is synonymous with what some view as a type of autism called childhood disintegrative disorder (CDD) (Malhotra & Gupta, 1999), described in Chapter 1.

Asperger Describes a Similar Profile

About the same time that Leo Kanner was studying the similarities in children who had been brought to his clinic, Hans Asperger, a doctor in Vienna during World War II, wrote about four young boys (6 to 11 years old) who were seen at the University Paediatric Clinic at which he worked. In what would become his second doctoral thesis, Asperger wrote that the boys all seemed to have "clever-sounding language" (Frith, 1991, p. 10) with obvious differences in nonverbal communication, including unusual eye gaze, prosody, voice tone, and gestures. Asperger described the boys as having typical intellectual abilities but inept social skills. He reported being concerned about how frequently the boys were bullied and teased by their peers

at school. They also experienced motor problems and were clumsy, and they had severely restricted interests, including obsessively collecting unusual objects. Asperger described the boys' egocentrism and pursuit of circumscribed interests as leading to aggression, noncompliance, and negativism (Asperger, 1944/1991). These differences in behavior seemed to emerge in the second year of the children's lives, and the boys had family histories of such differences. **Autistic psychopathy** is the term Asperger used to designate the boys' condition. Although this term is unusual by today's standards, it simply reflects that Asperger believed the boys' condition to be stable as opposed to progressive (Frith, 2004).

Asperger's work was relatively unknown in English-speaking countries until Wing (1981) wrote a series of case studies profiling the syndrome. It is from Wing's writing that the term **Asperger syndrome** (and more recently, simply Aspergers) began to be used rather than autistic psychopathy. With the translation of Asperger's work into English (Frith, 1991), more people became aware of the syndrome that was eventually associated with similar pervasive developmental disorders in the *DSM-IV*. Currently there is great disagreement regarding the similarities and differences between high-functioning autism and Aspergers, with some arguing a lack of distinction (Howlin, 2003) and others claiming the presence of clinical and neurobiological uniqueness (Rinehart, Bradshaw, Brereton, & Tonge, 2002). Asperger (1977) believed the syndrome he defined was different from Kanner's autism.

As with Kanner's observations, many of the characteristics described by Asperger and associated with Asperger syndrome continue to be accurate today. And like Kanner, Asperger made several assertions that have now been proved incorrect (Frith, 2004). First, since he had met only males with the characteristics, Asperger indicated that this condition would occur only in males. In reality, although at a smaller percentage, Asperger syndrome is also observed in females. Second, in the late 1940s, Asperger suggested that individuals with this syndrome would demonstrate unusual intellectual abilities. The *DSM-IV-TR* contains normal intelligence as a criterion for Asperger syndrome, although some individuals with Asperger syndrome may test in the range of mild intellectual disabilities. Finally, Asperger described the males he studied as having good language skills. Today, it is recognized that individuals with Asperger syndrome may have excellent vocabularies and possess the ability to talk incessantly (Ghaziuddin & Gerstein, 1996), but there may be delays in the emergence of language, difficulties with the pragmatics (use) of language, and an inability to understand nonliteral language (Ghaziuddin & Gerstein, 1996; Mayes, Calhoun, & Crites, 2001; Minshew, Goldstein, Muenz, & Payton, 1992; Young, Diehl, Morris, Hyman, & Bennetto, 2005).

ETIOLOGY OF AUTISM SPECTRUM DISORDERS

The **etiology** is the assignment of cause or source for a disorder. As researchers began to describe and define the conditions that now fall under the broader category of ASD, there was speculation about what causes such

dramatic differences in behavior and learning. From the 1940s until the late 1960s, the predominant theory was that psychological factors caused autism. According to this theory, a healthy child was born into an environment where she or he did not feel loved and accepted (Rank, 1955). Because of the extreme psychological stress related to this absence of affection, the child would turn inward and become isolated from, and unresponsive to, the outside world. This theory held the parents responsible for the child's condition, placing specific blame on the mother for being cold and unloving and for not being more emotionally available to the child. Indeed, Bruno Bettelheim (1967) used the term "Refrigerator Mother" to refer to the root cause of a child's autism. Treatment for children with autism during this time was solely directed at the parents, with mothers being subjected to hours of psychoanalysis to determine why they failed to love their children enough. Blame was extended to the fathers, who were also made to endure psychoanalysis to identify their shortcomings and their contribution to their child's condition.

As it became apparent that the parents were operating from love and for the best interests of their children, the perception that autism was caused by "Refrigerator Parents" gradually lost favor. The etiology of autism continued to exist in the psychological realm, however. The emphasis shifted from the actions and inactions of the parents to the children's environments. The "deprived" environment theory gained in popularity and suggested that the children had to turn inward to escape from external environments that they found deplorable. Children with autism were still believed to be born healthy and capable of typical development, but were then forced to retreat into their own worlds due to inadequate home environments. Because of glaring contradictions based on the presence of stimulating and favorable environments, the deprived environment theory was soon replaced by a more reasonable theory for the etiology of autism. However, it would be years before the originally held etiological misconceptions that psychological factors caused autism would be totally discredited. Although there have always been those who maintain that autism is present at birth and caused by something intrinsic to the child, an impressive body of research now demonstrates that ASDs are related to neurological dysfunctions of unknown origins.

NEUROLOGICAL DIFFERENCES

There is consensus that ASD are neurodevelopmental disorders of prenatal origin (Bailey, Phillips, & Rutter, 1996). This fact is received as both good and bad news. The good news is that attributing the etiology to the individual's neurological system eliminates useless exploration of psychological determinants. The news is also good because of the brain's ability to compensate for some defects or **lesions** (injuries). The bad news is that science knows relatively little about the brain in typically developing populations, much less in populations where the brain is known to be different (Lord & Bailey, 2002). For individuals with ASD, the heterogeneity of the population further

complicates the study of neurological development and functioning (Lord, Cook, Leventhal, & Amaral, 2000).

The majority of what is known about the brains of individuals with ASD comes from three branches of investigation (Lord et al., 2000; Pickett, 2001). Researchers evaluate the brains of individuals with ASD by examining them after death or through neuroimaging procedures while the person is alive (the most common procedures being EEG, CT, PET, MRI, and fMRI). Researchers also study brains of typically developing people and make inferences regarding differences. Finally, researchers create animal models, in which the neural systems of the animals are altered to see how behavior is affected (e.g., removing part of the animal's brain). The use of animal models can be suggestive but caution is warranted because it is likely that differences exist between species (Lane, 2002). What becomes confusing across these types of analyses is that there is great variety in the neurological differences exhibited by individuals with ASD.

Although the brain is labeled with separate and distinct terms, it functions only because of the interdependence of the components. For example, the amygdala can be labeled on the diagram of the brain. Serotonin, a neurochemical, can be measured. Neuroimaging can reveal brain structures and activity. However, the brain functions as a result of the structural, chemical, and functional components working together; they would be useless in isolation. This is an important consideration to keep in mind when reading the results of research conducted on individual components in order to guard against simplistic conclusions drawn from limited data on isolated neurological aspects (Goodman, 2002). For example, finding chemical differences may indicate that there are also structural and functional differences that have not been detected (Santangelo & Tsatsanis, 2005).

Even with the caution against overgeneralizing research results, research is critical for enhancing an understanding of the neurological differences in individuals with ASD for the purposes of developing genetic, pharmacological, and behavioral interventions (Pickett, 2001). The summary of research provided here of the structural, chemical, and functional aspects of the neurological system are intended to lay a foundation for understanding why individuals with ASD might behave the way they do and how their neurological systems may predispose them to interact with the world differently.

STRUCTURAL DIFFERENCES

The inconvenience, expense, and reluctance on the part of participants who are involved in studying the brain results in only small samples of a population being studied. Historically, the studies of the human brain in persons with autism were limited to those conducted during autopsy or done using unwieldy and expensive equipment. Kanner (1943) noted that the heads of his 11 subjects were larger than normal, suggesting differences in brain size. Kanner's suspicions were confirmed when it was found that the brains of autistic children who were younger than 12 years of age were found to be

slightly heavier and with more volume than those of their matched controls (Bailey, Palferman, Heavey, & Le Couteur, 1998), whereas conclusions about the brain structure of autistic adults were inconsistent (Dekaban & Sadowsky, 1978; Rakic, 1971; Rakic & Sidman, 1970). These differences could be attributed to one or a combination of factors including an interruption of normal maturation in the limbic system, a change in prenatal neural development in the first 30 weeks of gestation, or initial swelling of the brain followed by atrophy and cell loss (Kemper & Bauman, 1998).

Courchesne, Redcay, and Kennedy, (2004) found evidence to support the third of the possible factors influencing the size difference. He noted that children with autism have small head circumferences at birth but experience a period of rapid head growth between 6 and 14 months of age. The rapid period of growth appears to affect a disproportionate increase in the volume of the white matter relative to the gray matter, which connects the cerebral cortex to other areas of the brain (Filipek et al., 1992). The theory is that this rapid period of growth that selectively affects only certain parts of the brain may impede interhemispheric connectivity, making it difficult for the infant to interact with the environment. The overgrowth could result from inflammation of the brain based on innate immunologic problems (Vargas, Nascimbene, Krishnan, Zimmerman, & Pardo, 2004) influenced by genetics or exposure to neurotoxins. Whatever the cause, these defects in neural maturation affect cortical organization and the brain's capacity for learning. The overgrowth could lead to fewer neural connections and decreased brain size (Akshoomoff, Pierce, & Courchesne, 2002). Dementieva et al. (2005) reported that 35% of their 364 participants experienced accelerated head growth during the first 2 months of life. However, they correlated this finding to higher levels of adaptive functioning and less social impairment.

In addition to considering the brain as a whole, various substructures of the brain have been examined to determine whether differences exist in individuals with ASD. A number of structures in the brain have been examined with the majority of the research being conducted on the brainstem, limbic system, cerebrum, and cerebellum. As mentioned, these findings are merely suggestive since they attempt to isolate individual parts of a complex whole. However, even rudimentary knowledge of a simplified approach to understanding the brain provides educators with excellent insight regarding the implications of neurological differences found in some individuals with ASD. Figure 2.1 contains a diagram of the major brain structures that will be discussed.

Brainstem

The brainstem controls basic functions such as breathing, eating, balance, reflexes, and motor coordination. The brainstem also influences waking, sleeping, arousal, and focus of attention, and it helps regulate sensory input and motor output. In individuals with ASD, a fondness for twirling and other self-stimulatory behavior was seen as indicative that the brainstem needed more stimulation (Wong & Wong, 1991). Researchers noted that children

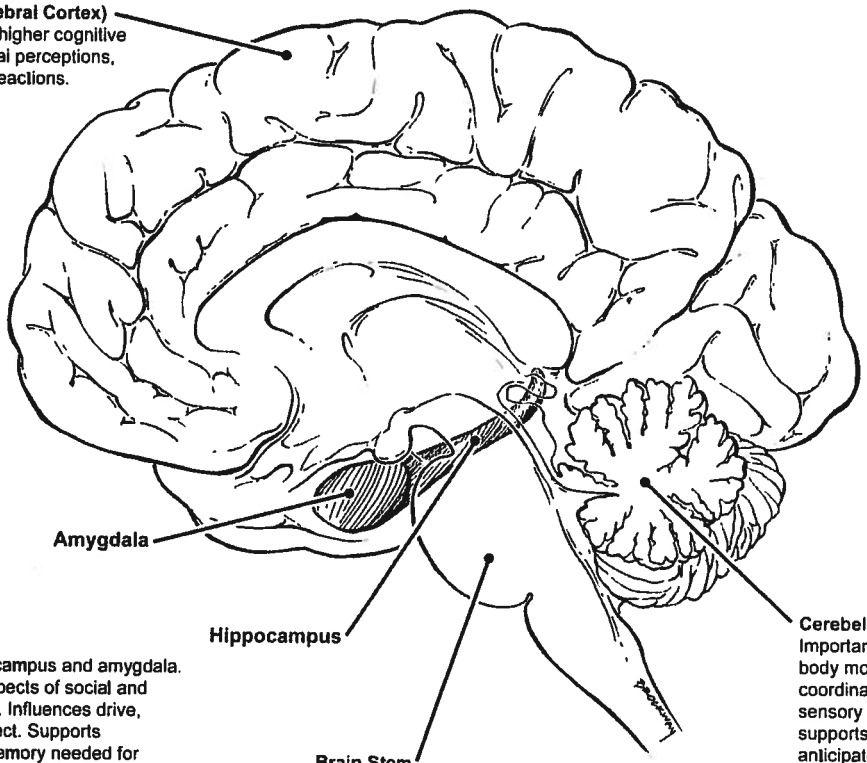

FIGURE 2.1
Major Brain Structures Researched in ASDs
Source: Provided by Brian Brockway, Brockway Biomedical Studios.

with ASD moved differently. Attempts to turn the head resulted in the whole body turning. Additionally, researchers noted that children with ASD retained their primitive reflexes longer than typically developing children and experienced more sleep disturbances (Limoges, Mottron, Bolduc, Berthiaume, & Godbout, 2005; Schreck, Mulick, & Smith, 2004; Tani et al., 2004). Likewise, individuals with ASD react differently to sensory stimuli, with some being overly responsive to sounds or touch and others being noticeably less responsive (Rogers, Hepburn, & Wehner, 2003).

Early nystagmus studies suggested differences in the brainstem. These studies evaluated the eyes of individuals who were subjected to rapid spinning and then stopped suddenly. In most typical individuals, the rapid spinning produced side-to-side bouncing of the eyes. But this was not so for subjects with autism; their eyes did not bounce in response to the spinning.

Differences have also been shown in tissue samples from the brainstem of a woman with autism (Rodier, 2000). In the analysis, the scientists discovered that the brainstem was shorter, had a smaller facial nucleus (400 v. 9,000 cells), and was missing the superior olive. The facial nucleus is responsible for controlling the muscles for facial expressions, and the superior olive acts as a relay station for auditory information. This preliminary study demonstrated that the brainstem of this woman with autism was different, and the mechanisms for controlling facial expressions and processing auditory information were missing or diminished. Rodier's research corroborated the work by Tanguay and Edwards (1982), who suggested that brainstem differences could distort auditory input, negatively affecting language and cognitive development. Individuals functioning on the lower end of the spectrum may experience more of an auditory delay (Wong & Wong, 1991) than individuals functioning on the higher end of the spectrum (Courchesne, Courchesne, Hicks, & Lincoln, 1985). However, for those individuals functioning on the higher end of the spectrum, problems comprehending spoken language may be as detrimental as the problems perceiving auditory input (Mayes et al., 2001).

Limbic System

The limbic system has received considerably more attention than the brainstem, primarily due to the demonstration of autistic-like behaviors in animals that have had their limbic systems altered. The limbic system, which includes the hippocampus and amygdala, provides the foundation for all aspects of social and emotional behavior. It allows people to gather psychological meaning from events and influences drive, motivation, and affect. The limbic system is also credited with creating a desire for social and emotional contact (Joseph, 1999). In research on adult rats, those who are inflicted with lesions to the hippocampus complex become hyperactive, demonstrate stereotypic motor behaviors, and respond unusually to novel stimuli (Kimble, 1963; Roberts, Dember, & Brodwick, 1962). Some animals with limbic system lesions become overresponsive to touch, temperature changes, lights, and sounds (Green & Schwartzbaum, 1968). When lesions are made to the amygdala in adult monkeys, they demonstrate a loss of fear, withdrawal, compulsive indiscriminate examination of objects, and a reduced ability to attach meaning to events (Mishkin & Aggleton, 1981; Vergnes, 1981). In addition to these outcomes, the animals experience severely impaired **cross-modal associative memory** (Murray & Mishkin, 1985), which means they have problems recognizing by sight something previously touched or tasted and therefore demonstrate an impaired ability to generalize.

The inability to generalize affects the development of representational memory (Mishkin & Appenzeller, 1987; Murray, 1990; Squire & Zola-Morgan, 1991). **Representational memory** involves all sensory modalities and mediates the processing of facts, experiences, and events. Representational memory develops over time as neuronal circuitry matures, but appears to be abnormal in persons with ASD (Bauman, 1997). What appears to be

deterioration in some young children identified as having ASD may just be the emergence of the abnormality in representational memory (Kemper & Bauman, 1998). Another type of memory, habit memory, which resides in systems within the cerebral hemisphere, does not appear to be abnormal in individuals with ASD.

Habit memory occurs with the repeated presentation of the same stimulus and allows for automatic connections between those stimuli and the expected responses. Because of repeated pairings, habit memory is not a conscious process. For example, when the phone rings, the automatic response is to answer it. When driving, it is automatic to slam on the brakes if the car in front stops suddenly. Habit memory appears to be intact in individuals with ASD and repetitive pairings of stimulus-response, such as what occurs in discrete trial training, capitalizes on that fact. Unfortunately, as an unconscious process and specific to the repeated trials, habit memory does not usually lead to the reliable or functional use of the skills learned in this method; however, habit memory can allow individuals to memorize facts or acquire specialized skills in areas of their fixation (e.g., playing the piano and drawing). In addition to good rote memorization, reliance on habit memory without representational memory can lead to preoccupations with a narrow range of activities and interests as well as a need for sameness (Kemper & Bauman, 1998).

The limbic system matures across time, requiring social, emotional, and environmental stimulation during the first years of life to function properly (Joseph, 1999). For example, the limbic system supports the preference young infants have for any human face. Infants later identified as having ASD do not show a preference for faces (Pascalis, de Schonen, Morton, Deruelle, & Fabre-Grent, 1995), instead orienting more frequently to objects (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998). By about 8 months of age, typically developing infants show a preference for their mother's face over other faces, and shortly after that will discriminate between faces of people they know and faces of strangers. Some young children with ASD fail to show a differentiated response to their mother's face over a stranger's (Dawson et al., 2002), which may diminish the subsequent development of emotion and attachment. Although typically developing infants form attachments early in life, some children with ASD have been found to show preference for and attachment to their caregivers between 3 to 5 years of age (Sigman, Dijamco, Gratier, & Rozga, 2004). The development of attachment, which appears to be influenced by the limbic system, may be affected by mental age (Rutgers, Bakermans-Kranenburg, van Uzendoorn, & van Berckelaer-Onnes, 2004). Individuals with ASD may demonstrate unusual attachments (Rogers, Ozonoff, & Maslin-Cole, 1993), with strong attachments to objects (Volkmar et al., 1994).

Given that the limbic system matures over time, researchers wondered if early damage to the limbic system would produce the same effects as damage inflicted to the limbic systems of adult animals. Researchers found that when the amygdala is altered or removed in very young animals, differences in behavior do not occur immediately as they had with the adult animals, but

emerge over time (Bachevalier & Vargha-Khadem, 2005). After about 8 months, the animals withdrew socially and did not interact well with other animals. At 3 years of age, the animals were not only socially deficit, but also hyperactive (Thompson, 1981). When both the hippocampus and amygdala were altered in neonatal nonhuman primates, a period of typical development was followed by the emergence of behavioral abnormalities that included stereotypies (rocking, crouching, doing somersaults); tantrums in novel situations; blank, expressionless faces; unusual posturing; and poor eye contact (Bachevalier, 1991, 1994). Unlike the adult animals, the animals with early insults did not demonstrate a loss of fear (Bachevalier, Málková, & Mishkin, 2001). The behavioral manifestations were slightly different among animals even though lesions were inflicted on the same areas of the brain. The implications of this research suggest that limbic system problems, present at birth, may not manifest noticeably until about 2 or 3 years of age. Some postmortem studies on the brain have found structural abnormalities within the limbic system (Kemper & Bauman, 1998).

Cerebrum

Unusual findings on computerized tomography suggest the presence of left hemisphere processing deficits that interfere with integration of various systems of the brain. Behaviorally, researchers have noted that some individuals with ASD fail to develop a right ear advantage, as is commonly seen in the population of persons without autism. While not conclusive (Rinehart, Bradshaw, Brereton, & Tonge, 2002), some behavioral observations would suggest that individuals with autism (as opposed to Asperger syndrome) have left hemisphere deficits because of their greater problems with spoken language (Dawson, 1983; Rumsey, 1992), whereas individuals with Asperger syndrome may have more right hemisphere difficulties because their language is relatively intact (when compared to individuals with autism). Additionally, the differences in the white matter of the brain among individuals with Asperger syndrome may be similar to differences seen in those with nonverbal learning disabilities (Rourke, 1989; Tsai, 1992).

Cerebellum

Researchers have found differences in the size of the cerebellum in individuals with ASD (Courchesne, Yeung-Courchesne, Press, Hesselink, & Jernigan, 1988; Miles & Hillman, 2000; Saitoh & Courchesne, 1998). In addition to assisting in the regulation of emotion and higher level thinking (Kemper & Bauman, 1998), the cerebellum plays an important role in learning associations that allow individuals to anticipate and prepare for upcoming events (Grafman et al., 1992; Leiner, Leiner, & Dow, 1987). Individuals with ASD do not lack associative learning, but often their associations are considered unusual. For example, the teacher of a child with autism introduced a daily puppet activity by gently bopping the child on the head with the puppet and

saying "hello." During an assessment in a clinic, the child picked up an available puppet and bopped himself on the head, much to the dismay of the evaluators, who thought he was being self-abusive. Fortunately, the teacher was watching from behind a one-way mirror and was able to explain the association the child had acquired.

Without the development of appropriate associations, it is difficult to predict what will happen next. That makes it hard to prepare for upcoming events because a majority of cerebellar activity goes toward figuring out what is happening. As an individual develops associations and increases predictability, he can focus attention elsewhere. If, however, his routines are disrupted, it may be difficult for him to predict what will happen next and he must concentrate on trying to determine that. For example, most people drive the same route to go home from school or work. Since the trip is predictable, the driver can think of many other things while driving and even engage in nondriving activities like eating and talking on a phone. However, if there is a wreck and traffic is being diverted, the driver must pay attention and devise an alternate route to get to the destination. She may discontinue the call, stop eating, and even turn off the radio. As predictability decreases, the need to concentrate increases. Imagine what it must be like for students whose cerebellar differences make associations and predictions difficult. They must spend a great deal of energy trying to figure out what is going on. This goal will be much easier if everything stays the same and there is little variability in schedules, routines, or even furniture arrangements (Volkmar, Carter, Grossman, & Klin, 1997; Steingard, Zimnitzky, DeMaso, Bauman, & Bucci, 1997). Indeed, students functioning on the higher end of the spectrum have been found to have typical motor execution but were unable to anticipate which motor movements were needed for an activity (Rinehart, Bradshaw, Brereton, & Tonge, 2001), interfering with their ability to participate in sports.

In addition to the important role the cerebellum plays in prediction and preparation (Courchesne & Allen, 1997), the cerebellum also contains the brain's filtering system by way of the Purkinje cells. The cerebellum in some individuals with autism is 20–30% smaller than in those without autism, and they have fewer Purkinje cells (Arin, Bauman, & Kemper, 1991; Bailey et al., 1998; Kemper & Bauman, 1998; Ritvo et al., 1986). Without a filtering system, all sensory information assaults the brain with the same intensity and importance. Irrelevant noises such as fans, airplanes, and distant noises are perceived by the brain to be as important as the voice of a teacher (Teder-Sälejärvi, Pierce, Courchesne, & Hillyard, 2005). The lack of adequate sensory filtering can also make certain fabrics or tags in clothing feel very uncomfortable. The impact of a deficient filtering system is described more completely in Chapter 5. Purkinje cell loss has also been found among individuals with seizure disorders (Dam, 1992) raising an interesting question about the correlation between Purkinje cell loss and seizure disorders, which can affect a substantial minority of individuals with ASD (Canitano et al., 2005; Volkmar & Nelson, 1990).

The cerebellum also plays a critical role in the capture, maintenance, and shift of attention between visual and auditory stimuli (Courchesne, Akshoomoff & Townsend, 1992). Some individuals with ASD have been noted to have difficulty disengaging from one stimuli in order to attend to a new stimuli (Townsend, Courchesne, & Egaas, 1996), much like the behavior seen in a typically developing 2-month-old (Landry & Bryson, 2004). In studies using alternating stimuli, individuals with autism and without autism show that they can shift attention from one stimulus to another, but it takes longer for the shift to occur (Wainwright-Sharp & Bryson, 1993). Shifting attention is easier if there is a cue (e.g., adult pointing) that stays in place (Bryson & Landry, 1994; Townsend, Harris, & Courchesne, 1996) and sufficient time for the shift to occur (Townsend & Courchesne, 1994). Klin, Jones, Schultz, Volkmar, and Cohen, (2002a) noted that individuals with ASD who are watching a movie tend to focus on nonsocial stimuli, like a picture on the wall or a lamp, instead of the human characters' faces. Likewise, individuals with autism may be more interested in details or the component parts, rather than the comprehensive entity (Boucher & Lewis, 1992; Hobson, Ouston, & Lee, 1988; Langdell, 1978; Tantam, Monaghan, Nicholson, & Stirling, 1989). This awareness of details is documented by the finding that some individuals with ASD are able to locate figures hidden in pictures better than individuals without ASD (Mottron, Burack, Iarocci, Belleville, & Enns, 2003). Indeed, the tendency to focus on component parts may lead to differences in processing facial information because they look at others' mouths rather than eyes to try to understand communicative content (Klin, Jones, Schultz, Volkmar, & Cohen, 2002b; Langdell, 1978).

Abnormal development of the cerebellum interferes with the development of other neurological systems. Indeed, differences in any area of neuroanatomical development affect development of other areas of the brain (Kemper & Bauman, 1998). Although some of the more researched neural systems were described separately, the subsystems of the brain are highly interrelated, and it is important to consider the intricate functioning of the brain as a whole with many unexplained variances (Bailey, Phillips, & Rutter, 1996).

NEURAL PLASTICITY

The brain changes due to maturation and experience, modifying existing neural circuitry and creating novel circuitry. The functions of an area of the brain that is deficient or damaged may be taken over by another area of the brain, particularly in terms of one hemisphere taking over responsibility for specialized functions usually associated with the other damaged hemisphere (e.g., language; Rutter, 2002). The term **neural plasticity** describes this compensatory ability in the brain (Lenn, 1991; Nass, 2002). For people who have had strokes or head injuries, rehabilitation techniques begun as soon as possible following the trauma take advantage of the brain's plasticity by compensating for areas of the brain that have been damaged. Neural plasticity may provide some of the explanation for why individuals with the same initial neurological pathology can have different functional outcomes. Much

of the emphasis on early intervention for children with ASD is based on the hope that the strategies can facilitate the development of compensatory brain activity and mitigate the effects of the neurological differences. However, researchers are beginning to realize that the behavioral manifestations in ASD are the result of systems failures or lesions in both hemispheres of the brain, not just pinpointed lesions to one hemisphere (Rutter, 2002), overwhelming the capacity of neural plasticity. Intervention may certainly promote skill acquisition and improved performance, but may not result in neural changes sufficient to compensate for deficits.

There is also emerging speculation that neural plasticity may actually contribute to the development of ASD (Courchesne et al., 1992). The brain develops through an individual's experiences. For individuals with ASD, their neurological differences tend to interfere with their experiences. For example, differences in the limbic system may result in infants being more interested in objects than people (Dawson et al., 1998), which then does not support the neural development of a preference for faces (Pascalis et al., 1995; Werner, Dawson, Osterling, & Dinno, 2000). The neurological differences that are probably present at the time of birth (although they may not manifest until later) set the stage for experiencing the world differently, which then causes further changes in the brain (Kemper & Bauman, 1998). Therefore, the neural reorganization that occurs because of the brain's plasticity may be more harmful than beneficial because of the extension of disrupted functioning to other neural systems (Bachevalier et al., 2001). Although there is a clear genetic and biologic component for some neuroanatomical differences, an interesting question is whether subsequent neurological differences that are evident in postmortem and neuroimaging studies cause ASD or are the result of the individual having an ASD (Akshoomoff et al., 2002; Bauman & Kemper, 2005).

CHEMICAL DIFFERENCES AND PSYCHOPHARMACOLOGICAL TREATMENTS

In addition to structural differences that have been suspected or detected among individuals with ASD, researchers have found chemical differences in the neurology. Indeed, all of the major **neurotransmitters** (chemicals that transport signals and messages in the brain) have been implicated in ASD, but many of the research conclusions lack replication (Lord & Bailey, 2002). As with the study of the structure of the brain, research on neurotransmitters relies on the use of animal models and comparisons between individuals with ASD and those with other clinical conditions, as well as inferences made about neurochemistry by monitoring **psychopharmacological** (use of medications to cause an effect on the mind) interventions. Medications cannot be used to cure ASD; however, they can be used to address some of the behavioral symptoms (Palermo & Curatolo, 2004). For example, a number of stimulant medications have been used to treat overactivity in individuals with ASD (Nicolson & Castellanos, 2000).

Many individuals with ASD may be prescribed medications as a primary form of intervention (Aman, Van Bourgondien, Wolford, & Sarphare, 1995). The challenge in using medications is to balance the benefit against the risk, since all medications have side effects. For example, some medications carry the risk of causing seizures. Those may not be the first choice for use with a population already at high risk for experiencing seizures (Canitano et al., 2005). Some of the stimulant medications may increase anxiety and stereotypies (Aman et al., 1995), which already exist at high levels in a number of individuals with ASD (Bellini, 2004; Tani et al., 2004). Many of the medications used with individuals on the spectrum have a sedative side effect. Although the sedation may reduce problem behaviors, it may also decrease social interaction and reduce the student's attention to learning tasks (Lord & Bailey, 2002). However, without a medication, the student's behavior may preclude the opportunity for instruction. Additional medication may be given to counteract the side effects of the primary medication, resulting in the need for the student to take several medications each day. Medications should be used in combination with other interventions that teach students important skills.

Given the copious amount of research conducted on the neurochemistry of individuals with ASD, it is disappointing that there are so few conclusive answers. The lack of conclusive answers relates both to methodological issues with some of the studies as well as to the unique responses of individuals to various medications. Serotonin has been the most consistently implicated neurotransmitter in ASD and is of interest because of its role in language production (Chandana et al., 2005) and sensory responses. A number of researchers have verified that about one-third of individuals with ASD have elevated levels of serotonin (Anderson et al., 1987; Cook, 1990, 1996; Hollander et al., 1998), as do their close relatives. Chugani, Muzik, and Rothermel (1997) found elevated serotonin synthesis in seven boys with autism but not the one girl.

The elevated levels of serotonin in some individuals but not others suggest unusual brain synthesis of serotonin in the brain, but the reasons are not clear (Palermo & Curatolo, 2004). Elevation in serotonin is evident in typically developing children, but the levels slowly decline by 5 years of age. This decline does not appear to occur in some individuals with ASD (Chugani et al., 1999). About half of individuals with mental retardation also have increased levels of serotonin (Martineu, Barthelemy & LeLord, 1992). Elevated serotonin levels have been suggested as a possible familial marker signaling a genetic risk for ASD (Piven et al., 1991).

Fenfluramine (Pondimin) was one of the first medications to be systematically studied for reducing elevated levels of serotonin. After initially promising results, researchers and families became frustrated by the negative side effects, which included increased irritability and aggression (Ekman, Miranda-Linné, Gillberg, Garle, & Wetterberg, 1989). Subsequently, fenfluramine (a common ingredient in some medications for losing weight) was found to be associated with heart problems (Connolly & Crary, 1997) and is no longer recommended for use in modifying serotonin levels.

Other researchers have used selective serotonin reuptake inhibitors (SSRIs) to modify serotonin levels in individuals with ASD. The SSRIs (fluoxetine [Prozac], sertraline [Zoloft], fluvoxamine [Luvox], and paroxetine [Paxil]) may reduce anxiety, obsessive and repetitive behaviors, and self-injury (McDougle et al., 1996). Hollander et al. (2005) found that liquid fluoxetine was more effective than a placebo in reducing repetitious behavior in 45 children and adolescents with ASD. A review of studies using SSRIs as well as a nonselective serotonin reuptake inhibitor (Potenza & McDougle, 1997) concluded that the medications promoted improvement in some symptoms (including reductions in repetitive and aggressive behavior and increased eye contact) in some participants, but was also associated with behavioral deterioration and unwanted side effects (e.g., seizures) in other participants. The SSRIs may hold more potential for individuals with family members who have histories of anxiety and depression (DeLong, Teague, & McSwain-Kamran, 1998; Lord & Bailey, 2002), and the presence of compulsive behaviors may also predict a positive response (Hollander et al., 1998).

In addition to elevated levels of serotonin, some individuals with ASD have been found to have a higher production and turnover of dopamine, which is associated with hyperactivity, stereotypies, attention differences, and cognitive deficits (Campbell, Small, Anderson, Malone, & Locascio, 1992). Others have suggested that dopamine deficiency is common in children with ASD because of similarities in performance with children with poorly controlled phenylketonuria (PKU) (Dennis et al., 1999). Dopamine may also be important for modulating the brain's ability to plan behavior. Treatment with medications that serve as dopamine antagonists (e.g., haloperidol, risperidone) have shown some promise for use with individuals with ASD but present some cautions. Research regarding the effectiveness of haloperidol [Haldol] has shown some benefit for decreasing hyperactivity while increasing verbal production and attention. However, haloperidol has also been shown to increase aggressive behaviors and exacerbate stereotypies. Early suggestions that haloperidol could be useful in conjunction with structured teaching have not been verified (Anderson et al., 1989). The long-term use of haloperidol is associated with the development of involuntary movements that continue after withdrawal, resulting in the need for caution with the use of this medication (Lord & Bailey, 2002; Palermo & Curatolo, 2004).

Risperidone [Risperdal], classified as an atypical neuroleptic, also inhibits dopamine production and turnover. Risperidone has been used effectively to treat the symptoms of schizophrenia. A small number of controlled studies with individuals with ASD demonstrate its effectiveness in reducing interfering behaviors (repetitious movements, self-injury, aggression) while improving social awareness, with few side effects (McDougle et al., 1998).

Some individuals with autism have also been found to have elevated levels of endogenous opioids (Panksepp & Sahley, 1987) that not only influence attachment and motor activity, but also leave the individual in a high state of self-satisfaction with an increased pain threshold. High levels of opioids appear to diminish responsiveness to social stimuli and may lead to social withdrawal. As with serotonin, typically developing infants have an excess of

opioids that become weaker and shorter acting in the months after birth (Panksepp, 1979). Some children with ASD continue to experience an excess of opioids, interfering with their responsiveness to social stimuli. Self-injurious behaviors may actually increase the opioid levels in the brain (Barrett, Feinstein, & Hole, 1989). Treatment using opioid antagonists (e.g., naltrexone, naloxone) is typically provided only in cases of severe self-injurious behavior. Contradictory findings (Gillberg, 1995) have interfered with the ability to draw definitive conclusions regarding the positive impact of the medication on reductions in self-injury and overactivity (Campbell et al., 1993).

Oxytocin is a neuropeptide critical for the development of attachment, bonding, and social behavior. In animal models, mice without oxytocin exhibit severe deficits in socialization (Lim, Bielsky, & Young, 2005). The similarities in social deficits between the mice without oxytocin and individuals with ASD have led to an exploration of this chemical. Waterhouse, Fein, and Modahl (1996) found that the social impairments in 30 children with ASD correlated significantly with their levels of oxytocin. Because of concerns that the oxytocin levels of individuals with ASD might be precipitated by the use of pitocin (containing oxytocin) during labor and delivery (Wahl, 2004), Gale, Ozonoff, and Lainhart (2003) studied 41 boys with ASD compared to a matched control group containing typically developing boys and boys with mental retardation. They found no link between the use of pitocin during labor and the subsequent development of ASD. At this point, direct manipulation of oxytocin is occurring only in animal models (Welch et al., 2005).

A considerable amount of research has been and continues to be conducted to identify the neurochemical differences that may influence the development and maintenance of ASD. Again, the interconnectivity of the brain requires that the chemical differences found in some individuals with ASD, although described and studied separately, suggest structural and functional differences (Santangelo & Tsatsanis, 2005).

FUNCTIONAL DIFFERENCES

Study of the functional differences in the brains of individuals with ASD brings together the structural and chemical components. Advances in the technology used to analyze living brains have led to remarkable discoveries about the neurological functioning of individuals with ASD. The earliest studies involved electroencephalogram (EEG) technology. Using EEGs, abnormalities were noted in 50% of the participants with ASD (Minshew, 1991). Although the findings have not been verified, some suggested that the abnormalities shown on EEGs may have been the reason why typically developing children appeared to regress into ASD (Lewine et al., 1999). Event-related potentials (ERPs) have been used to demonstrate that some children with autism show an absence of electrophysiological activity when looking at pictures of their mothers and increased activity when looking at pictures of their favorite toys (Dawson, Osterling, Meltzoff, & Kuhl, 2000). For many years, event-related potentials were the only method for examining the

functioning of the brain during active engagement. Problems with the technology made it difficult to interpret readings and may have contributed to contradictory findings (Lord & Bailey, 2002).

The functioning of the brain was also inferred through observations taken during the performance of activities commonly associated with intelligence and achievement tests. For example, individuals with ASD have been compared to individuals who are typically developing or who have other disabilities on tasks that required recall, imitation, visual-spatial processing, problem solving, and so forth. Using this approach, Minshew et al. (1992) found that individuals with ASD appeared to lack organizing strategies, such as categorization, and flexibility of thinking that would enable them to perform better on tasks involving higher order processing. Other individuals with ASD were found to have problems with immediate and delayed recall of faces and family scenes (Williams, Goldstein, & Minshew, 2005). A large number of studies have documented deficits in higher order thinking (executive functioning) in individuals with ASD of various ages and different cognitive levels (Ozonoff, 1997) using the observation of performance. However, evidence for the use of compensatory strategies among individuals with ASD has been well documented in empirical literature (Klin et al., 2002a), and the question that couldn't be answered through behavioral observation was: Which of the neurological systems were being used in the performance of tasks?

The advent of functional magnetic resonance imaging (fMRI) technology opened a window for direct observation of how the brain functions during activities. An impressive quantity of research is being conducted that identifies differences in brain functioning in individuals with ASD. A number of studies have demonstrated that the areas of the brain used by individuals without ASD to recognize and process faces as well as identify emotions (areas in the amygdala) are not used by individuals with ASD (Ashwin, Wheelwright, Baron-Cohen, 2005; Baron-Cohen et al., 2000; Pierce, Muller, Ambrose, Allen, & Courchesne, 2001). Those with ASD tend to use a part of the brain that is usually reserved for nonface object recognition (Schultz et al., 2000; Schultz, 2005). However, when one boy with an ASD was shown a picture of his favorite cartoon character (Digimon), he used the same parts of the brain that others use to recognize human faces (Grelotti et al., 2005).

Using fMRIs, researchers can also see how various parts of the brain work together. For some individuals with ASD, the parts of the brain that should be working together to process photographs of fearful faces were not working together (Welchew et al., 2005). Luna et al. (2002) compared the brain functioning of 11 individuals with ASD and 6 typically developing controls to determine which parts of the brain were connected for accomplishing specific mental tasks. They found that both groups performed the tasks, but that the individuals with ASD relied on lower regions of the brain while the individuals without ASD used higher functioning regions of the brain. Probably due to structural and chemical differences affected by maturation, the higher order neural systems had not developed in the participants with ASD. A similar

finding was reported for sentence comprehension tasks (Just, Cherkassky, Keller, & Minshew, 2004). In contrast to a typically developing control group, 17 participants with ASD showed less integrated brain patterns, less activity in the area of the brain that processes connected speech, and more activity in the part of the brain that processes individual words.

Further evidence of differences in brain functioning among individuals with ASD is the unusually high percentage that develop seizure disorders (Canitano et al., 2005), particularly in adolescence and young adulthood (Volkmar & Nelson, 1990). Abnormal brain activity, such as seizures, can further inhibit brain functioning (Vargha-Khadem, Issacs, van der Werf, Robb, & Wilson, 1992).

Evidence clearly links behavioral differences among individuals with ASD to differences in the functioning of the brain, which is influenced by the interconnected structural and chemical aspects. Ironically, individuals functioning on the high end of the spectrum have actually used the term **neurotypical** (having a normally functioning brain) to describe people who do not have ASD, even developing a Web site with an assessment for diagnosing and suggestions for treating "neurotypical syndrome" (*www.autistics.org/isnt/*).

Although new knowledge is continuously being discovered, a basic understanding of how neuralgic differences could manifest in behavior can be helpful for putting the behaviors and needs of students with ASD in perspective. Clearly, some of the neurological differences found in individuals with ASD are shared by individuals who are neurotypical as well as by those with other disabilities. To summarize, some of the neurological differences associated with ASD can lead to behavioral differences. These may include:

- Sensory input and motor output regulation problems
- Need for greater levels of sensory stimulation
- Sleep disturbances
- Retention of primitive reflexes
- Stereotypic behaviors
- Compulsive behaviors
- Inability to recognize with one sense something experienced by another sense (failure to watch and then do)
- Difficulty with novel situations
- Poor eye contact
- Inability to predict upcoming events; preference for status quo
- Equal and potent response to sensory stimuli (magnified sensation); may compensate by shutting out and becoming intensely preoccupied with something else
- Attention to irrelevant details
- Difficulty shifting attention quickly
- Good fact memorization (habit memory)
- Good rote motor acquisition
- Poor generalization
- Difficulty with higher level information processing

ROLE OF GENETICS

The behavioral and learning differences that are demonstrated by individuals with ASD are clearly a result of differences in neurology. The next logical question is to ask: What causes those differences? Palermo and Curatolo (2004, p. 155) sum up the prevailing belief succinctly when they state that ASD are a "genetically heterogeneous polygenic neurodevelopmental disorder." ASD are "genetically heterogeneous" because there is no simple dominant/recessive or X-linked pattern of transmission (Szatmari et al., 1998). The spectrum is "polygenic" because there appear to be 10 or more genes interacting to produce ASD (Pickles et al., 1995; Piven & Folstein, 1994; Wassink, Brzustowicz, Bartlett, & Szatmari, 2004; Risch et al., 1999). "Neurodevelopmental" refers back to the fact that the genetic foundation leads to changes in the brain and the way it develops.

Several factors together provide fairly conclusive evidence that ASD are genetically based. Some of the structural and chemical differences in the brain support the idea that ASD evolve from genetic or biologic causes that affect the fetus early in development. Research suggests that neural development is different as early as 20–24 days after conception (Rodier, Ingram, Tisdale, Nelson, & Romano, 1996). Differences in the cerebellum can be traced to fetal development during the fifth week of gestation (Courchesne, 1997). Other critical neurological differences occur prior to 12 weeks of gestation (Bailey et al., 1998; Rodier et al., 1996) and still others before 28–30 weeks' gestation (Bauman, 1997). Behavioral manifestations that occur during the first several years of life, such as the emergence of "regressive" autism (occurring at about 2 years of age), may reflect a latent effect of genetic inheritance (Lawler, Croen, Grether, & Van de Water, 2004). Clearly, the potential exists that neurological differences are based on events that occur prior to birth, which suggests that genetics play a crucial role.

Analyses of multiplex families provide the most compelling evidence that ASDs are genetically based. A **multiplex family** is one in which more than one family member has an ASD. Two percent to 8% of the siblings of individuals with ASD also have an ASD, a percentage that is significantly greater than what is found in the general population (Chudley, Gutierrez, Jocelyn, & Chodirker, 1998). The genetic predisposition is further supported by research done with twins. With identical (monozygotic) twins, if one child has autism, there is a 60% chance that the twin will also have autism (Bailey et al., 1995). However, there is a 92% chance that if one of them has autism, the other will have associated communication and social disorders. In contrast, if the twins are fraternal (dizygotic) and one is diagnosed with autism, there is a 0–10% chance that the other will have associated communication disorders. The genetic similarities between identical twins provide strong substantiation for the genetic basis of ASD. Since the chance of both identical twins demonstrating autism is not 100%, other factors must have some influence over the genetic predisposition.

In addition to the higher rates of associated conditions in siblings and twins, immediate and extended biological families of children with ASD often report histories of language, learning, or social problems (Bolton et al., 1994; Dawson et al., 2002; Folstein & Rutter, 1977; Piven et al., 1994), including psychiatric issues such as obsessive compulsive disorders, depression, schizophrenia, social phobia, and bipolar disorder (DeLong, 1999; Ghaziuddin, 2005; Hollander, King, & Delaney, 2003). Asperger (1944) wrote that he was concerned about the parents of the boys he studied because of their social isolation and problems with un- and underemployment. Extended family members also report increased rates of other health issues such as rheumatoid arthritis, lupus, otitis media (ear infections), and other autoimmune disorders. The presence of numerous health issues in families of children on the spectrum suggests that susceptibility to common infections may indicate unusual immune responses based in genetic makeup. Szatmari et al. (1998) concluded that 90% of the cases of autism are related to the genetic contributions of heredity.

The question then becomes: How does genetics precipitate or influence the development of ASD? A number of options are possible. Recent speculation suggests that individuals with some of the characteristics of ASD are mating and producing children who then demonstrate enough of the characteristics to be diagnosed, a phenomenon known as *assortative mating* (Constantino & Todd, 2005). Holden (2005) cites as evidence for this concept that the fathers and grandfathers of a number of individuals with ASD tend to work in very technical professions such as engineering and demonstrate weak social skills. Another option is that genetic inheritance may result in disabilities with known genetic causes. A very small percentage of individuals with single gene defects, such as those that lead to phenylketonuria (PKU), Cornelia de Lange syndrome, tuberous sclerosis, Angelman syndrome, and Fragile X syndrome, are also diagnosed as having an ASD (Gillberg, Gillberg, & Ahlsen, 1994; Hunt & Shepherd, 1993; Muhle, Trentacoste, & Rapin, 2004; Rapin, 1999). Rett syndrome, currently considered akin to autism, is linked to a single gene (Ellaway & Christodoulou, 1999). Another option is that multiple genes may contribute to the situation in which the individual is more susceptible to experiencing neurological damage or disruption because the system has lost protective factors, as in the case of a weakened immune system.

IMMUNE SYSTEM INVOLVEMENT

Genetic predispositions may lead to compromises in the immune system that make the individual susceptible to autoimmune disorders and a dysfunctional immune system, a predisposition that may occur in populations in addition to those with ASD (Lawler et al., 2004). These may anatomically change the brain or result in behavioral changes. The genetic predisposition toward a suppressed immune system can also make an individual more sensitive to toxins in the environment, affecting the neurology of the developing

fetus or even of the developing child (Arndt, Stodgell, & Rodier, 2005). The link between certain toxins and development of ASD has been speculated for years. In-utero exposure to rubella was shown to increase the chance that a child would develop autism (Chess, Korn, & Fernandez, 1971). Maternal use of antiseizure medication (valporic acid (VPA) as in Depakote) during pregnancy has been linked to the development of ASD (Moore et al., 2000). Vaccines, and more specifically some of the compounds in the vaccines (i.e., ethylmercury, thimerosal), have been linked to the emergence of ASD. For some, the link has been refuted (Barbaresi, Katusic, Colligan, Weaver, & Jacobsen, 2005; DeStefano, Bhasin, Thompson, Yeargin-Allsopp, & Boyle, 2004; Hviid, Stellfeld, Wohlfahrt, & Melbye, 2003; Kaye, del Mar Melero-Montes, & Jick, 2001), but for others the possibility still exists (c.f., Rimland, 2004). Although rare complications from a vaccine cannot be ruled out (Chen, Landau, Sham, & Fombonne, 2004), scientists suggest that the likelihood of a child contracting a fatal childhood disease if not vaccinated is much greater than the likelihood that the child will develop autism if given vaccinations.

Some have speculated that the genetic predisposition that underlies the immune system suppression or even alteration might lead to heightened sensitivity to food products. Advocates of this theory suggest that the main culprits for individuals with ASD are gluten (wheat products) and casein (amino acid found in milk products). Some believe that eliminating these ingredients from the diet may result in improvements in communication, socialization, and independent functioning (Knivsberg, Reichelt, Noland, & Hoien, 1995). Although there is a great deal of popular support for these claims, research does not demonstrate that eliminating specific foods can help a child recover from an ASD.

IMPACT OF ENVIRONMENTAL TOXINS

If the genetic predisposition leads to suppression of the immune system, an individual may be more susceptible to environmental toxins. Intuitive logic supports this view, because it is recognized that individuals with ASD are not distributed evenly across geographic areas (Rutter et al., 1994). There are two plausible reasons for this phenomenon. The most simple is that families tend to relocate to areas where services are available for their children, resulting in higher concentrations of children with ASD in some geographic locales than others. The second reason goes back to the possibility that environmental toxins negatively affect developing neurology, leading to the manifestation of ASD. However, it would be unusual for an environmental toxin to be the only precipitating agent for the development of ASD. The more likely scenario is that an environmental toxin would only negatively impact children who have an increased genetic susceptibility (Lawler et al., 2004). Although there is no conclusive support in published literature for environmental links to ASD via agents that are toxic to the developing brain, the possibility is intriguing and additional scrutiny is probably justified.

❖ LEARNING WITH MS. HARRIS: Sunday Night in Front of the Television

Ms. Harris, as is her habit, is glued to the television set on a Sunday evening, watching her favorite news exposé program. Tonight, following a discussion on how to protect oneself from identity theft, the program profiles children with ASD and how they are unable to take another person's perspective. The program fascinates Ms. Harris, particularly since she has just read a similar article in one of the news magazines and also because one of her cousin's sons has been diagnosed with autism. "Wow," thinks Ms. Harris, "we were taught in college that autism is a low-incidence disability. Why is it that everywhere I turn, someone is talking about knowing someone who has autism?"

HOW MANY PEOPLE HAVE AN ASD?

Prevalence is an accounting of how often something occurs. For example, the prevalence rate of left-handedness in a classroom depends on the number of people who are left-handed divided by the total number of people in the class. If there are 12 left-handed people in a class of 50 students, the prevalence rate of left-handedness is .24 (12/50) or 24%. Until the end of the twentieth century, prevalence rates for autism (not ASD) were 5–15 out of every 10,000 (Wing & Gould, 1979). This low prevalence rate resulted in autism being referred to as a **low-incidence disability,** meaning that it was relatively rare.

The prevalence rates documented in international studies published between 1966 and 1997 show an increase in the prevalence of autism (not the full spectrum) (Gillberg, 1999). Figure 2.2 provides the results of this analysis.

Fombonne (2003) indicated that a reasonable prevalence rate for autism is 10 of every 10,000 individuals or 1 in 1,000. The full spectrum has a higher prevalence at 27.5 per 10,000 or 1 in 364. To answer Ms. Harris's question, ASD are no longer a low-incidence disability. ASD are the third most commonly diagnosed developmental disability. Only mental retardation and cerebral palsy are more common among children than ASD. ASD occur more often than Down syndrome, childhood cancer, cystic fibrosis, multiple sclerosis, or juvenile diabetes.

Late 1960s/early 1970s	4.4/10,000
Late 1970s	4.9/10,000
1980s (*DSM-III* criteria)	7.7/10,000
1990s	9.6/10,000 (approx. 1/1,000)

FIGURE 2.2
Prevalence Rates for Autism
Source: Gillberg (1999).

Several explanations exist as to why the prevalence of ASD has increased so dramatically. It has been suggested that previously published prevalence rates were too low. Some of the increase is attributable to the increase in knowledge about ASD and the ability to correctly identify the syndromes (Lord et al., 2001). However, this knowledge can also be responsible for overdiagnosis of the disability, and this may be what is actually occurring. As Temple Grandin (2002), a woman with high-functioning autism, has so aptly wondered, at what point does a computer nerd become someone with Asperger syndrome?

Some of the increase in the number of individuals identified with ASD relates to changes in the way autism is defined (Fombonne, 1999). Whereas autism was previously thought of only in the classic or Kannerian sense, the recognition of Asperger syndrome and PDD-NOS have greatly expanded perceptions of what constitutes autism. Indeed, the vernacular used in this chapter supports the idea that autism has expanded to include a spectrum of disorders with some common characteristics. Figure 2.3 gives a side-by-side comparison of definitions provided by the Autism Society of America (ASA) at the end of the 1990s, which clearly illustrates changes in the perspectives of ASD.

At the end of 1996, the definition of autism describes it as a "severely incapacitating" disability that occurred at a prevalence rate of 15/10,000. The criteria used to describe the symptoms are clinical in nature and similar to those used in the *DSM*. The definition concludes that autism is treatable, particularly if identified early.

The next newsletter published by ASA (Jan./Feb. 1997) defines autism differently. It is now a "developmental disability" that is not identified as "severely incapacitating." The prevalence rate continues to be listed as 15/10,000. However, the criteria used to characterize the symptoms are less clinical and more broadly defined. The definition reports that 400,000 individuals in the United States have autism. Gone is the optimistic view of autism as being treatable. This has been replaced by the allegation that few people know how to effectively work with individuals with autism.

The definition published by ASA then changed again. In the Sept./Oct. 1998 issue of their newsletter, ASA adds the qualifier "complex" to the description that autism is a developmental disability. The prevalence rates are reported to be 1 in every 500 individuals with a half-million people in the United States having autism (an increase of 100,000 people in approximately 18 months). The description further softens behavioral symptoms, and aggression and self-injurious behaviors have been removed. The allegation remains that few know how to effectively work with individuals with this complex developmental disability. As is shown in this illustration, prevalence changes are partially attributable to expanded definitions of what constitutes autism, since the spectrum has been broadened to include milder forms of the disorder.

In addition to being influenced by expanded definitions of ASD, better diagnostics, and overidentification, prevalence rates may be influenced by

Definition of Autism

AUTISM is a severely incapacitating lifelong developmental disability that typically appears during the first three years of life. The result of a neurological disorder that affects functioning of the brain, autism and its behavioral symptoms occur in approximately fifteen out of every 10,000 births. Autism is four times more common in boys than girls. It has been found throughout the world in families of all racial, ethnic, and social backgrounds. No known factors in the psychological environment of a child have been shown to cause autism.

Some behavioral symptoms of autism include:

1. Disturbances in the rate of appearance of physical, social, and language skills.
2. Abnormal responses to sensations. Any one or a combination of senses or responses are affected: sight, hearing, touch, balance, smell, taste, reaction to pain, and the way a child holds his or her body.
3. Speech and language are absent or delayed, while specific thinking capabilities may be present.
4. Abnormal ways of relating to people, objects, and events.

Autism occurs by itself or in association with other disorders that affect the function of the brain, such as viral infections, metabolic disturbances, and epilepsy. It is important to distinguish autism from retardation or mental disorders since diagnostic confusion may result in referral to inappropriate and ineffective treatment techniques. The severe form of the syndrome may include extreme self-injurious, repetitive, highly unusual and aggressive behavior. Special educational programs using behavioral methods have proved to be the most helpful treatment for persons with autism.

AUTISM IS TREATABLE—Early diagnosis and intervention are vital to the future development of the child. *(Nov./Dec. 1996)*

What Is Autism?

Autism is a developmental disability that typically appears during the first three years of life. The result of a neurological disorder that affects functioning of the brain, autism and its associated behaviors occur in approximately 15 of every 10,000 individuals.

Autism is four times more prevalent in boys than girls and knows no racial, ethnic, or social boundaries. Family income, life-style and educational levels do not affect the chance of autism's occurrence.

Autism interferes with the normal development of the brain in the areas of reasoning, social interaction and communication skills. Children and adults with autism typically have deficiencies in verbal and non-verbal communication, social interactions, and leisure or play activities. The disorder makes it hard for them to communicate with others and relate to the outside world. They may exhibit repeated body movements (hand flapping, rocking), unusual responses to people or attachments to objects and resist any changes in routines. In some cases, aggressive and/or self-injurious behavior may be present.

It is conservatively estimated that nearly 400,000 people in the U.S. today have some form of autism. Its prevalence rate now places it as the *third* most common developmental disability—more common than Down's syndrome. Yet the majority of the public, including many professionals in the medical, educational, and vocational fields are still unaware of how autism affects people and how to effectively work with individuals with autism. *(Jan./Feb. 1997)*

What Is Autism?

Autism is a complex developmental disability that typically appears during the first three years of life. The result of a neurological disorder that affects the functioning of the brain, autism and its associated behaviors have been estimated to occur in as many as 1 in 500 individuals. Autism is four times more prevalent in boys than girls and knows no racial, ethnic, or social boundaries. Family income, lifestyle, and educational levels do not affect the chance of autism's occurrence.

Autism interferes with the normal development of the brain in the areas of social interaction and communication skills. Children and adults with autism typically have difficulties in verbal and nonverbal communication, social interactions, and leisure or play activities. The disorder makes it hard for them to communicate with others and relate to the outside world. They may exhibit repeated body movements (hand flapping, rocking), unusual responses to people or attachments to objects, and they may resist changes in routines.

Over one half million people in the U.S. today have some form of autism. Its prevalence rate now places it as the *third* most common developmental disability—more common than Down syndrome. Yet most of the public, including many professionals in the medical, educational, and vocational fields, are still unaware of how autism affects people and how to effectively work with individuals with autism. *(Sept./Oct. 1998)*

FIGURE 2.3
Changing Definitions Published by the Autism Society of America

Source: Advocate. Reprinted with permission of the Autism Society of America.

diagnostic substitution (Volkmar, Lord, Bailey, Schultz, & Klin, 2004). Although the need for additional data and further analyses exists, diagnostic substitution was suggested as a factor in changing prevalence rates for autism in California (Croen, Grether, Hoogstrate, & Selvin, 2002). In this study, the researchers noted an inverse relationship between the number of children with autism presenting for services in the Department of Developmental Services' regional centers system versus the number of children with mental retardation. As the number of children with autism increased, the number of children with mental retardation decreased. Of interest is the fact that the California State Department of Developmental Services reported the first decrease in the number of diagnoses of new cases with autism in 2004.

As another example, during the 1992–1993 school year, which is the first year that schools were able to use autism as a distinct eligibility category, the total number of students under that label in the 50 states, District of Columbia, and Puerto Rico was 12,222 (U.S. DOE, 1995). Almost a decade later, the total number of students with autism was 78,717 (U.S. DOE, 2004), reflecting a 544% increase in the number of children identified as eligible for special education because they have an ASD. Although some of this increase has to do with better diagnostics using broader definitions as well as the growing population in the United States, some of this increase probably has to do with the transition from other eligibilities on the spectrum (i.e., Other Health Impaired) to the eligibility of autism. That is, many of those students were already receiving services through the public education system, but not under the label of autism, so the increase in prevalence is attributable to the availability of the more accurate eligibility.

Other conditions affecting children have shown remarkable growth. Prevalence rates for asthma, allergies, Type 1 diabetes, autoimmune disorders, and ADHA have also increased precipitously (Lawler et al., 2004). Prevalence rates are one metric to consider with a disability such as ASD. In contrast to prevalence, which simply describes the current number of people identified with the syndrome, incidence rates can be critical for planning future needs for services. Incidence rates project how many individuals will be born in a given time frame (usually a year) with certain conditions. An accurate figure of the incidence of autism has been elusive, and it is not possible to determine if incidence for ASD is changing (Tidmarsh & Volkmar, 2003).

CONCLUSION

Evidence from the reports of "feral" children suggests that individuals with ASD have a long historical presence. Leo Kanner and Hans Asperger provided systematic descriptions of behavioral characteristics in the respective populations they studied that, with few exceptions, have withstood the test of time and continue to ring relevant. Controversy exists as to whether or not the populations they described are truly distinct or represent opposite ends on a continuous spectrum.

Autism Spectrum Disorders are the result of neurological differences that lead to the unusual constellation of behaviors characteristic of individuals on the spectrum. The etiologies of neurological differences are still being examined. There is compelling evidence that neurological differences emerge from a genetic predisposition. Genetics set in motion a sequence of prenatal development of neurological differences that continue to evolve throughout life. Genetics may provoke brain differences through inherited disorders, new mutations, or chromosomal aberrations, which may result in early manifestation or latent emergence of the spectrum disorders. Research has yet to determine if any one of the neurological differences is primary for the development of the spectrum disorders or if the fundamental problem resides in the connectivity within and between different systems in the brain. Side effects of medications that may be useful for addressing some of the symptoms will need to be evaluated and managed. Improvements in social, communication, and cognitive skills may reflect responsiveness to interventions as well as neurological maturation. ASDs are currently diagnosed based on behavioral manifestations. In the future, it may be possible to use medical technology, such as that used for neuroimaging and genetic screening, to diagnose the presence of the spectrum disorders.

The discrete manner in which the chemical and structural differences of the brain were described fails to adequately portray the complex and interconnected functioning of the brain. However, awareness of the possible neurological differences can lead to the development of appropriate accommodations and interventions. Classroom manifestations of the neurological differences and general suggestions for supporting associated behaviors in students with ASD, as well as those with other disabilities, are provided in Table 2.1. The instructional strategies suggested in the right column will be described more fully in the following chapters. Readers may find the figure useful for helping colleagues understand some of the probable reasons for a few of the behavioral differences seen in students with ASD.

DISCUSSION QUESTIONS AND ACTIVITIES

1. ASD may be based in similar neurological pathologies. However, functional outcomes can be quite varied across individuals because of the impact of experience and learning on the plasticity of the developing brain. Identify two individuals who have the same diagnosis (e.g., both have been diagnosed with autism, Aspergers, or cerebral palsy) but different behaviors and characteristics. Solicit information from them about their lives to identify variations in their experiences that might account for the difference in their outcomes.
2. Generate a list of as many behavioral characteristics as possible that would result from the differences described in the brainstem, limbic system, cerebrum, and cerebellum for individuals with autism.
3. Watch *Rainman* or *Mercury Rising* and speculate which neurological differences might be affecting the lead characters.

TABLE 2.1
Basic Strategies to Support Neurologic Differences

Neurology	Behavior Related to Differences	Instructional Strategies
Brainstem: Reticular activating system Regulates sensory input/output	Unusual reactions to sensations Stims to increase vestibular input	Environmental analysis Sanctioned movement
Limbic system: Motivation and affect Meaning attached to events	Unmotivated by typical incentives Unusual affect Difficulty understanding cause/effect	Use preferences to motivate Teach reading of social cues and social skills
Cerebrum: Auditory processing and integration	Slow to/fails to respond to directions Fails to orient to verbalizations	Sufficient repetition Give information visually Use telegraphic speech when giving directions
Cerebellum: Purkinje cells (filtering system)	Hypersensitive to sensory input: • Sight • Sound • Smell • Taste • Touch Coping mechanisms to block sensory input: • Overselective attention • Self-stimulatory behavior • Behavioral avoidance	Environmental engineering: • Reduce/eliminate stimuli • Clarify boundaries Teach compensatory strategies: • Moving to a quieter/darker area • Using low-tech devices • "Polite" refusals Highlight important information: • Color/size/bold/marked • Masking template/jig
Cerebellum: Modulate attention (capture, maintain, shift)	Difficult to get attention Easily distracted Shifting is jerky, often shifted to wrong place; takes longer to shift attention	Environmental engineering: • Reduce distractions • Teach clear signals Use visual cues to capture and direct attention Allow a few extra seconds for response
Cerebellum: Preparatory system	Wants a set routine Resists changes Perseverations Self-stimulatory behaviors to cope	Visual schedules/activity logs Precorrect Warn of upcoming transitions Frequent review and reassurance

4. Using Table 2.1, think of a student with an ASD and design environmental modifications that could be helpful in supporting his or her participation in school environments. Identify the neurotypical students in the school environment who would benefit from the same modifications.
5. Create a timeline that depicts the evolution of the understanding of ASD. Trace the changes in identification, etiology, and prevalence for the spectrum disorders.

REFERENCES

Akshoomoff, N., Pierce, K., & Courchesne, E. (2002). The neurobiological basis of autism from a developmental perspective. *Development and Psychopathology, 14,* 613–634.

Aman, M. G., Van Bourgondien, M. E., Wolford, P. L., & Sarphare, G. (1995). Psychotropic and anticonvulsant drugs in subjects with autism: Prevalence and patterns of use. *Journal of the American Academy of Child and Adolescent Psychiatry, 34,* 1672–1681.

Anderson, G. M., Freedman, D. X., Cohen, D. J., Volkmar, F. R., Hoder, E. L., McPhedran, P., et al. (1987). Whole blood serotonin in autistic and normal subjects. *Journal of Child Psychology & Psychiatry & Allied Disciplines, 28,* 885–900.

Anderson, L. T., Campbell, M., Adams, P., Small, A. M., Perry, R., & Shell, J. (1989). The effects of haloperidol on discrimination learning and behavioral symptoms in autistic children. *Journal of Autism and Developmental Disorders, 19,* 227–239.

Arin, D. M., Bauman, M. L., & Kemper, T. L. (1991). The distribution of Purkinje cell loss in the cerebellum in autism. *Neurology, 41,* 307.

Arndt, T. L., Stodgell, C. J., & Rodier, P. M. (2005). The teratology of autism. *International Journal of Developmental Neuroscience, 23,* 189–199.

Ashwin, C., Wheelwright, S., & Baron-Cohen, S. (2005). Laterality biases to chimeric faces in Asperger syndrome: What is right about face-processing? *Journal of Autism and Developmental Disorders, 35,* 183–196.

Asperger, H. (1944/1991). Autistic psychopathy in childhood (Trans). In U. Frith (Ed.), *Autism and Asperger syndrome* (pp. 37–92). Cambridge, UK: Cambridge University Press.

Asperger, H. (1977). Problems of infantile autism. *Communication, 13,* 45–52.

Bachevalier, J. (1991). An animal model for childhood autism: Memory loss and socioemotional disturbances following neonatal damage to the limbic system in monkeys. In C. A. Tamminga & S. C. Schultz (Eds.), *Advances in neuropsychiatry and psychopharmacology: Schizophrenia research* (pp. 129–140). New York: Raven Press.

Bachevalier, J. (1994). The contribution of medial temporal lobe structures in infantile autism: A neurobehavioral study in primates. In M. L. Bauman & T. L. Kemper (Eds.), *The neurobiology of autism* (pp. 146–169). Baltimore: Johns Hopkins University Press.

Bachevalier, J., Malkova, L., & Mishkin, M. (2001). Effects of selective neonatal temporal lobe lesions on socioemotional behavior in infant rhesus monkeys. *Behavioral Neuroscience, 115,* 545–559.

Bachevalier, J., & Vargha-Khadem, F. (2005). The primate hippocampus: Ontogeny, early insult and memory. *Current Opinion in Neurobiology, 15,* 168–174.

Bailey, A., Le Couteur, A., Gottesman, I., Bolton, P., Simonoff, E., Yuzda, E., et al. (1995). Autism as a strongly genetic disorder: Evidence from a British twin study. *Psychological Medicine, 25,* 63–78.

Bailey, A., Luthert, P., Dean, A., Harding, B., Janota, I., Montgomery, M., et al. (1998). A clinicopathological study of autism. *Brain, 121,* 889–905.

Bailey, A., Palferman, S., Heavey, L., & Le Couteur, A. (1998). Autism: The phenotype in relatives. *Journal of Autism and Developmental Disorders, 28,* 369–392.

Bailey, A., Phillips, W., & Rutter, M. (1996). Autism: Towards an integration of clinical, genetic, neuropsychological, and neurobiological perspectives. *Journal of Child Psychology and Psychiatry, 37,* 89–126.

Barbaresi, W. J., Katusic, S. K., Colligan, R. C., Weaver, A. L., & Jacobsen, S. J. (2005). The incidence of autism in Olmsted County, Minnesota, 1976–1997. *Archives of Pediatrics and Adolescent Medicine, 159,* 37–44.

Baron-Cohen, S., Ring, H. A., Bullmore, E. T., Wheelwright, S., Ashwin, C., & Williams, S. C. (2000). The amygdala theory of autism. *Neuroscience and Biobehavioral Reviews, 24,* 355–364.

Barrett, R. P., Feinstein, C. B., & Hole, W. (1989). Effects of naloxone and naltrexone on self-injury: A double-blind, placebo-controlled analysis. *American Journal of Mental Retardation, 93,* 644–651.

Bauman, M. L. (1997). The neuroanatomy of autism: Clinical implications. In P. J. Accardo, B. K. Shapiro, & A. J. Capute (Eds.), *Behavior belongs in the brain: Neurobehavioral syndromes* (pp. 69–95). Baltimore: York Press.

Bauman, M. L., & Kemper, T. L. (2005). Neuroanatomic observations of the brain in autism: A review and future directions. *International Journal of Developmental Neuroscience, 23,* 183–187.

Bellini, S. (2004). Social skill deficits and anxiety in high-functioning adolescents with autism spectrum disorders. *Focus on Autism and Other Developmental Disabilities, 19,* 78–86.

Bettelheim, B. (1967). *The empty fortress: Infantile autism and the birth of the self.* New York: Free Press.

Bolton, P., Macdonald, H., Pickles, A., Rios, P., Goode, S., Crowson, M., et al. (1994). A case-control family history study of autism. *Journal of Child Psychology and Psychiatry, 35,* 877–900.

Boucher, J., & Lewis, V. (1992). Unfamiliar face recognition in relatively able autistic children. *Journal of Child Psychology and Psychiatry, 33,* 843–859.

Bryson, S., & Landry, R. (1994). Brief report: A case study of literacy and socioemotional development in a mute autistic female. *Journal of Autism and Developmental Disorders, 24,* 225–232.

Campbell, M., Anderson, L. T., Small, A. M., Adams, P., Gonzalez, N. M., & Ernst, M. (1993). Naltrexone in autistic children: Behavioral symptoms and attentional learning. *Journal of the Academy of Child and Adolescent Psychiatry, 32,* 1283–1291.

Campbell, M., Small, A. M., Anderson, L. T., Malone, R. P., & Locascio, J. J. (1992). Pharmacotherapy in autism. In H. Naruse & E. M. Ornitz (Eds.), *Neurobiology of Infantile Autism* (pp. 235–243). Amsterdam: Excerpta Medica.

Candland, D. K. (1993). *Feral children and clever animals: Reflections on human nature.* New York: Oxford University Press.

Canitano, R., Luchetti, A., & Zappella, M. (2005). Epilepsy, electroencephalographic abnormalities, and regression in children with autism. *Journal of Child Neurology, 20,* 27–31.

Chandana, S. R., Behen, M. E., Juhasz, C., Muzik, O., Rothermel, R. D., Mangner, T. J., et al. (2005). Significance of abnormalities in developmental trajectory and asymmetry of cortical serotonin synthesis in autism. *International Journal of Developmental Neuroscience, 23,* 171–182.

Chen, W., Landau, S., Sham, P., & Fombonne, E. (2004). No evidence for links between autism, MMR, and measles virus. *Psychological Medicine, 34,* 543–553.

Chess, S., Korn, S. J., & Fernandez, P. B. (1971). *Psychiatric disorders of children with congenital rubella.* New York: Brunner/Mazel.

Chudley, A. E., Gutierrez, E., Jocelyn, L. J., & Chodirker, B. N. (1998). Outcomes of genetic evaluation in children with pervasive developmental disorder. *Journal of Developmental and Behavioral Pediatrics, 19,* 321–325.

Chugani, D. C., Muzik, O., Behen, M., Rothermel, R., Janisse, J. J., Lee, J., et al. (1999). Developmental changes in brain serotonin synthesis capacity in autistic and nonautistic children. *Annals of Neurology, 45,* 287–295.

Chugani, D. C., Muzik, O., & Rothermel, R. (1997). Altered serotonin synthesis in the dentatothalamocortical pathway in autistic boys. *Annals of Neurology, 42,* 666–669.

Connolly, H. M., & Crary, J. L. (1997). Valvular heart disease associated with fenfluramine-phentermine. *New England Journal of Medicine, 337,* 581–588.

Constantino, J. N., & Todd, R. D. (2005). Intergenerational transmission of subthreshold autistic traits in the general population. *Biological Psychiatry, 57,* 655–660.

Cook, E. H. (1990). Autism: Review of neurochemical investigation. *Synapse, 6,* 292–308.

Cook, E. H. (1996). Pathophysiology of autism: Neurochemistry. *Journal of Autism and Developmental Disorders, 26,* 221–225.

Courchesne, E. (1997). Brainstem, cerebellar, and limbic neuroanatomical abnormalities in autism. *Current Opinion in Neurobiology, 7,* 269–278.

Courchesne, E., Akshoomoff, N. A., & Townsend, J. (1992). Recent advances in autism. In H. Naruse & E. M. Ornitz (Eds.), *Neurobiology of infantile autism* (pp. 111–128). Amsterdam: Elsevier Science.

Courchesne, E., & Allen, G. (1997). Prediction and preparation: Fundamental functions of the cerebellum. *Learning & Memory, 4,* 1–35.

Courchesne, E., Courchesne, R. Y., Hicks, G., & Lincoln, A. J. (1985). Functioning of the brainstem auditory pathway in non-retarded autistic individuals. *Electroencephalography and Clinical Neurophysiology, 61,* 491–501.

Courchesne, E., Redcay, E., & Kennedy, D. P. (2004). The autistic brain: Birth through adulthood. *Current Opinion in Neurology, 17,* 489–496.

Courchesne, E., Yeung-Courchesne, R., Press, G. A., Hesselink, J. R., & Jernigan, T. L. (1988). Hypoplasia of cerebellar vermal lobules VI and VII in autism. *New England Journal of Medicine, 26,* 1349–1354.

Croen, L. A., Grether, J. K., Hoogstrate, J., & Selvin, S. (2002). The changing prevalence of autism in California. *Journal of Autism and Developmental Disorders, 32,* 207–215.

Dam, M. (1992). Quantitative neuropathology in epilepsy. *Acta Neurology Scandinavia, 137,* 51–54.

Dawson, G. (1983). Lateralized brain dysfunction in autism: Evidence from the Halstead-Reitan Neuropsychological Battery. *Journal of Autism and Developmental Disorders, 13,* 269–286.

Dawson, G., Carver, L., Meltzoff, A. N., Panagiotides, H., McPartland, J., & Webb, S. J. (2002). Neural correlates of face and object recognition in young children with autism spectrum disorder, developmental delay, and typical development. *Child Development, 73,* 700–717.

Dawson, G., Meltzoff, A. N., Osterling, J., Rinaldi, J., & Brown, E. (1998). Children with autism fail to orient to naturally occurring social stimuli. *Journal of Autism and Developmental Disorders, 28,* 479–485.

Dawson, G., Osterling, J., Meltzoff, A., & Kuhl, P. (2000). Case study of the development of an infant with autism from birth to 2 years of age. *Journal of Applied Developmental Psychology, 21,* 299–313.

Dekaban, A. S., & Sadowsky, D. (1978). Changes in brain weights during the span of human life: Relation of brain weights to body heights and body weights. *Annals of Neurology, 4,* 345–356.

DeLong, G. R. (1999). Autism: New data suggest a new hypothesis. *Neurology, 52,* 911–916.

DeLong, G. R., Teague, L. A., & McSwain-Kamran, M. (1998). Effects of fluoxetine treatment in young children with idiopathic autism. *Developmental Medicine Child Neurology, 40,* 551–562.

Dementieva, Y. A., Vance, D. D., Donnelly, S. L., Elston, L. A., Wolpert, C. M., Ravan, S. A., et al. (2005). Accelerated head growth in early development of individuals with autism. *Pediatric Neurology, 32,* 102–108.

Dennis, M., Lockyer, L., Lazenby, A. L., Donnelly, R. E., Wilkinson, M. & Schoonheyt, W. (1999). Intelligence patterns among children with high-functioning autism, phenylketonuria, and childhood head injury. *Journal of Autism and Developmental Disorders, 29,* 5–17.

DeStefano, F., Bhasin, T. K., Thompson, W. W., Yeargin-Allsopp, M., & Boyle, C. (2004). Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: A population-based study in metropolitan Atlanta. *Pediatrics, 113,* 259–266.

Ekman, G., Miranda-Linné, F., Gillberg, C., Garle, M., & Wetterberg, L. (1989). Fenfluramine treatment of twenty children with autism. *Journal of Autism and Developmental Disorders, 19,* 511–532.

Ellaway, C., & Christodoulou, J. (1999). Rett syndrome: Clinical update and review of recent genetic advances. *Journal of Paediatrics & Child Health, 35,* 419–426.

Filipek, P. A., Richelme, C., Kennedy, D. N., Rademacher, J., Pitcher, D. A., Zidel, S., et al. (1992). Morphometric analysis of the brain in developmental language disorders and autism. *Annals of Neurology, 32,* 475.

Folstein, S., & Rutter, M. (1977). Infantile autism: A genetic study of 21 twin pairs. *Journal of Child Psychology and Psychiatry, 18,* 297–321.

Fombonne, E. (1999). The epidemiology of autism: A review. *Psychological Medicine, 29,* 769–786.

Fombonne, E. (2003). Epidemiology of pervasive developmental disorders. *Trends in Evidence-Based Neuropsychiatry, 5,* 29–36.

Frith, U. (Ed.). (1991). *Autism and Asperger Syndrome.* Cambridge, UK: Cambridge University Press.

Frith, U. (2003). *Autism: Explaining the enigma* (2nd ed.). Malden, MA: Blackwell.

Frith, U. (2004). Emanuel Miller lecture; Confusions and controversies about Asperger syndrome. *Journal of Child Psychology and Psychiatry, 4,* 672–686.

Gale, S., Ozonoff, S., & Lainhart, J. (2003) Brief report: Pitocin induction in autistic and nonautistic individuals. *Journal of Autism and Developmental Disorders, 33,* 204–208.

Ghaziuddin, M., & Gerstein, L. (1996). Pedantic speaking style differentiates Asperger syndrome from high-functioning autism. *Journal of Autism and Developmental Disorders, 26,* 585–595.

Gillberg, C. (1995). Endogenous opioids and opiate antagonists in autism: Brief review of empirical finds and implications for clinicians. *Developmental Medicine and Child Neurology, 37,* 239–245.

Gillberg, C. (1999). Prevalence of disorders in the autism spectrum. *Infants and Young Children, 12,* 64–74.

Gillberg, I. C., Gillberg, C., & Ahlsen, G. (1994). Autistic behaviour and attention deficits in tuberous sclerosis: A population-based study. *Developmental Medicine and Child Neurology, 36,* 50–56.

Goodman, R. (2002). Brain disorders. In M. Rutter & E. Taylor (Eds.), *Child and Adolescent Psychiatry* (4th ed., pp. 241–260). Malden, MA: Blackwell.

Grafman, J., Litvan, I., Massaquoi, S., Stewart, M., Sivigu, A., & Hallet, M. (1992). Cognitive planning deficit in patients with cerebellar atrophy. *Neurology, 42,* 1493–1496.

Green, R. H., & Schwartzbaum, J. S. (1968). Effects of unilateral septal lesions on avoidance behavior, discrimination reversal, and hippocampal EEG. *Journal of Comparative and Physiological Psychology, 65,* 388–396.

Grelotti, D. J., Klin, A. J., Gauthier, I., Skudlarksi, P., Cohen, D. J., Gore, J. C., et al. (2005). FMRI activation of the fusiform gyrus and amygdala to cartoon characters but not to faces in a boy with autism. *Neuropsychologia, 43,* 373–385.

Hallahan, D. P., & Kauffman, J. M. (2003). *Exceptional learners: An introduction to special education* (9th ed.). Boston, MA: Allyn & Bacon.

Hobson, R. P., Ouston, J., & Lee, A. (1988). What's in a face? The case of autism. *British Journal of Developmental Psychology, 79,* 441–453.

Holden, C. (2005). Mating for autism? *Science, 308,* 948.

Hollander, E., Cartwright, C., Wong, C. M., DeCaria, C. M., DelGiudice-Asch, E, Buchsbaum, M. S., et al. (1998). A dimensional approach to the autism spectrum. *CNS Spectrums, 3,* 22–26, 33–39.

Hollander, E., King, A., Delaney, K., et al. (2003). Obsessive-compulsive behaviors in parents of multiplex autism families. *Psychiatry Research, 117,* 11–16.

Hollander, E., Phillips, A., Chaplin, W., Zagursky, K., Novotny, S., Wasserman, S., et al. (2005). A placebo controlled crossover trial of liquid fluoxetine on repetitive behaviors in childhood and adolescent autism. *Neuropsychopharmacology, 30,* 582–589.

Howlin, P. (2003). Outcome in high-functioning adults with autism with and without early language delays: Implications for the differentiation between autism and Asperger syndrome. *Journal of Autism & Developmental Disorders, 33,* 3–13.

Hunt, A., & Shepherd, C. (1993). A prevalence study of autism in tuberous sclerosis. *Journal of Autism and Developmental Disorders, 23,* 329–339.

Hviid, A., Stellfeld, M., Wohlfahrt, J., & Melbye, M. (2003). Association between thimerosal-containing vaccine and autism. *Journal of the American Medical Association, 290,* 1763–1766.

Itard, J. M. G. (1806/1962). *The wild boy of Aveyron* (G. Humphrey & M. Humphrey, Trans.). Upper Saddle River, NJ: Prentice Hall.

Joseph, R. (1999). Environmental influences on neural plasticity, the limbic system, emotional development, and attachment: A review. *Child Psychiatry and Human Development, 29,* 189–208.

Just, M. A., Cherkassky, V. L., Keller, T. A., & Minshew, N. J. (2004). Cortical activation and synchronization during sentence comprehension in high-functioning autism: Evidence of underconnectivity. *Brain, 127,* 1811–1821.

Kanner, L. (1943). Autistic disturbances of affective contact. *The Nervous Child, 2,* 217–250.

Kaye, J. A., del Mar Melero-Montes, M., & Jick, H. (2001). Measles, mumps, and rubella vaccine

and the incidence of autism recorded by general practitioners: A time trend analysis. *British Medical Journal, 322,* 460-463.

Kemper, T. L., & Bauman, M. (1998). Neuropathology of infantile autism. *Journal of Neuropathology and Experimental Neurology, 57,* 645-652.

Kimble, D. P. (1963). The effects of bilateral hippocampal lesions in rats. *Journal of Physiological Psychology, 56,* 273-283.

Kirk, S. A., Gallagher, J. J., & Anastasiow, N. J. (1993). *Educating exceptional children* (7th ed.). Boston, MA: Houghton Mifflin.

Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002a). Defining and quantifying the social phenotype in autism. *The American Journal of Psychiatry, 159,* 895-908.

Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002b). Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Archives of General Psychiatry, 59,* 809-816.

Knivsberg, A., Reichelt, K., Noland, M., & Hoien, T. (1995). Autistic syndrome and diet: A follow-up study. *Scandinavian Journal of Education Research, 39,* 223-236.

Lane, H. (1976). *The wild boy of Aveyron.* Cambridge, MA: Harvard University Press.

Lane, S. J. (2002). Structure and function of the sensory systems (pp. 35-70) & Sensory modulation (pp. 101-122). In A. C. Bundy, S. J. Lane, & E. A. Murray (Eds.), *Sensory integration: Theory and practice* (2nd ed.). Philadelphia: F. A. Davis.

Landry, R., & Bryson, S. E. (2004). Impaired disengagement of attention in young children with autism. *Journal of Child Psychology and Psychiatry, 45,* 1115-1122.

Langdell, T. (1978). Recognition of faces: An approach to the study of autism. *Journal of Child Psychology and Psychiatry, 19,* 225-238.

Lawler, C. P., Croen, L. A., Grether, J. K., & Van de Water, J. (2004). Identifying environmental contributions to autism: Provocative clues and false leads. *Mental Retardation and Developmental Disabilities Research Reviews, 10,* 292-302.

Leiner, H. C., Leiner, A. L., & Dow, R. S. (1987). Cerebrocerebellar learning loops in apes and humans. *Italian Journal of Neurological Science, 8,* 425-436.

Lenn, N. J. (1991). Neuroplasticity: The basis for brain development, learning and recovery from injury. *Infants and Young Children, 3,* 39-48.

Lewine, J. D., Andrews, R., Chez, M., Arun Angelo, P., Devinsky, O., Smith, M., et al. (1999). Magnetoencephalographic patterns of epileptiform activity in children with regressive autism spectrum disorders. *Pediatrics, 104,* 405-418.

Lim, M. M., Bielsky, I. F., & Young, L. J. (2005). Neuropeptides and the social brain: Potential rodent models of autism. *International Journal of Developmental Neuroscience, 23,* 235-243.

Limoges, E., Mottron, L., Bolduc, C., Berthiaume, C., & Godbout, R. (2005). Atypical sleep architecture and the autism phenotype. *Brain: A Journal of Neurology, 128,* 1049-1061.

Lord, C., & Bailey, A. (2002). Autism spectrum disorders. In M. Rutter & E. Taylor (Eds.), *Child and Adolescent Psychiatry* (4th ed., pp. 636-663). Malden, MA: Blackwell.

Lord, C., Cook, E. H., Leventhal, B., & Amaral, D. G. (2000). Autism spectrum disorders. *Neuron, 28,* 355-363.

Luna, B., Minshew, N. J., Garver, K. E., Lazar, N. A., Thulborn, K. R., Eddy, W. F., et al. (2002). Neocortical system abnormalities in autism: An fMRI study of spatial working memory. *Neurology, 59,* 834-840.

MacLean, C. (1977). *The wolf children.* New York: Hill and Wang.

Malhotra, S., & Gupta, N. (1999). Childhood disintegrative disorder. *Journal of Autism and Developmental Disorders, 29,* 491-498.

Martineau, J., Barthelemy, C., Muh, J. P., & Lelord, G. (1992). Dopamine, serotonin and their derivatives: Biochemical markers in childhood autism? In H. Naruse & E. M. Ornitz (Eds.), *Neurobiology of Infantile autism* (pp. 251-268). Amsterdam: Excerpta Medica.

Mayes, S. D., Calhoun, S. L., & Crites, D. L. (2001). Does *DSM-IV* Asperger's disorder exist? *Journal of Abnormal Child Psychology, 29,* 263-271.

McDougle, C. J., Holmes, J. P., Carlson, D. C., Pelton, G. H., Cohen, D. J., & Price, L. H. (1998). A double-blind, placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. *Archives of General Psychiatry, 55,* 633-641.

McDougle, C. J., Naylor, S. T., Cohen, D. J., Volkmar, F. R., Heninger, G. R., & Price, L. H.

(1996). A double-blind placebo-controlled study of fluvoxamine in adults with autistic disorder. *Archives of General Psychiatry, 53,* 1001-1008.

Miles, J. H., & Hillman, R. E. (2000). Value of a clinical morphology examination in autism. *American Journal of Medical Genetics, 91,* 245-253.

Minshew, N. (1991). Indices of neural function in autism: Clinical and biological implications. *Pediatrics, 87,* 774-780.

Minshew, N., Goldstein, G., Muenz, L., & Payton, J. (1992). Neuropsychological functioning of non-mentally retarded autistic individuals. *Journal of Clinical and Experimental Neuropsychology, 14,* 749-761.

Mishkin, M., & Aggleton, J. P. (1981). Multiple functional contributors of the amygdala in the monkey from the amygdaloid complex. In Y. Ben-Ari (Ed.), *INSERM Symposium, No. 20.* Amsterdam: Elsevier/North Holland Biomedical Press.

Mishkin, M., & Appenzeller, T. (1987). The anatomy of memory. *Scientific American, 256,* 80-89.

Moore, S. J., Turnpenny, P., Quinn, A., Glover, S., Lloyd, D. J., Montgomery, T., et al. (2000). A clinical study of 57 children with fetal anticonvulsant syndrome. *Journal of Medical Genetics, 37,* 489-497.

Mottron, L., Burack, J. A., Iarocci, G., Belleville, S., & Enns, J. T. (2003). Locally oriented perception with intact global processing among adolescents with high-functioning autism: Evidence from multiple paradigms. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 44,* 904-913.

Muhle, R., Trentacoste, S. V., & Rapin, I. (2004). The genetics of autism. *Pediatrics, 113,* e472-e486.

Murray, E. A. (1990). Representational memory in non-human primates. In R. P. Kesner & D. S. Olton (Eds.), *Neurobiology of comparative cognition* (pp. 127-155). Hillsdale, NJ: Lawrence Erlbaum.

Murray, E. A., & Mishkin, M. (1985). Amygdaloidectomy impairs crossmodal association in monkeys. *Science, 228,* 604-606.

Nass, R. (2002). Plasticity: Mechanisms, extent and limits. In S. J. Segalowitz & I. Rapin (Eds.), *Handbook of neuropsychology* (2nd ed., pp. 29-68). Amsterdam: Elsevier Science.

Newton, M. (2002). *Savage girls and wild boys: A history of feral children.* New York: St. Martin's Press.

Nicolson, R., & Castellanos, F. X. (2000). Considerations on the pharmacotherapy of attention deficits and hyperactivity in children with autism and other pervasive developmental disorders. *Journal of Autism and Developmental Disorders, 30,* 461-462.

Ozonoff, S. (1997). Components of executive function deficits in autism and other disorders. In J. Russell (Ed.), *Autism as an executive disorder* (pp. 179-211). Oxford, UK: Oxford University Press.

Palermo, M. T., & Curatolo, P. (2004). Pharmacologic treatment of autism. *Journal of Child Neurology, 19,* 155-164.

Panksepp, J. (1979). A neurochemical theory of autism. *Trends in Neuroscience, 2,* 174-177.

Panksepp, J., & Sahley, T. L. (1987). Possible brain opioid involvement in disrupted social intent and language development of autism. In E. Schopler & G. B. Mesibov (Eds.), *Neurobiological issues in autism* (pp. 357-372). New York: Plenum.

Pascalis, O., de Schonen, S., Morton, J., Deruelle, C., & Fabre-Grent, M. (1995). Mother's face recognition by neonates: A replication and extension. *Infant Behavior and Development, 18,* 79-95.

Pickett, J. (2001). Current investigations in autism brain tissue research. *Journal of Autism and Developmental Disorders, 31,* 521-527.

Pickles, A., Bolton, P., Macdonald, H., Bailey, A., Le Couteu, A., Sim, C. H., et al. (1995). Latent class analysis of recurrence risks for complex phenotypes with selection and measurement error: A twin and family history study of autism. *American Journal of Human Genetics, 57,* 717-726.

Pierce, K., Muller, R. A., Ambrose, J., Allen, G., & Courchesne, E. (2001). Face processing occurs outside the fusiform "face area" in autism: Evidence from functional MRI. *Brain, 124,* 2059-2073.

Piven, J., & Folstein, S. (1994). The genetics of autism. In M. L. Bauman & T. L. Kemper (Eds.), *The Neurobiology of Autism* (pp. 18-44). Baltimore: Johns Hopkins University Press.

Piven, J., Tsai, G. C., Nehme, E., Coyle, J. T., Chase, G. A., & Folstein, S. E. (1991). Platelet serotonin: A possible marker for familial autism. *Journal of Autism and Developmental Disorders, 21,* 51-59.

Piven, J., Wzorek, M., Landa, R., Lainhart, J., Bolton, P., Chase, G. A., et al. (1994). Personality characteristics of the parents of autistic individuals (preliminary communication). *Psychological Medicine, 24,* 783–795.

Potenza, M. N., & McDougle, C. J. (1997). The role of serotonin in autism spectrum disorders. *CNS Spectrums, 2,* 25–42.

Rakic, P. (1971). Neuron-gila relationship during granule cell migration in developing cerebellar cortex: A Golgi and electron microscopic study in macacus rhesus. *Journal of Comparative Neurology, 141,* 282–312.

Rakic, P., & Sidman, R. L. (1970). Histogenesis of the cortical layers in human cerebellum particularly the lamina dissecans. *Journal of Comparative Neurology, 139,* 473–500.

Rank, B. (1955). Intensive study and treatment of preschool children who show marked personality deviations, or "atypical development" and their parents. In G. Caplan (Ed.,), *Emotional problems of early childhood* (pp. 491–501). New York: Basic Books.

Rapin, I. (1999). Autism in search of a home in the brain. *Neurology, 52,* 902–904.

Rimland, B. (2004). Association between thimerosal-containing vaccine and autism. *Journal of the American Medical Association, 291,* 180.

Rinehart, N. J., Bradshaw, J. L., Brereton, A. V., & Tonge, B. J. (2001). Movement preparation in high-functioning autism and Asperger disorder: A serial choice reaction time task involving motor reprogramming. *Journal of Autism and Developmental Disorders, 31,* 79–88.

Rinehart, N. J., Bradshaw, J. L., Brereton, A. V., & Tonge, B. J. (2002). A clinical and neurobehavioural review of high-functioning autism and Asperger's disorder. *Australian and New Zealand Journal of Psychiatry, 36,* 762–770.

Risch, N., Spiker, D., Lotspeich, L., Nouri, N., Hinds, D., Hallmayer, J., et al. (1999). A genomic screen of autism: Evidence for a multilocus etiology. *American Journal of Human Genetics, 65,* 493–507.

Ritvo, E. R., Freeman, B. J., Scheibel, A. B., Duong, T., Robinson, H., & Guthrie, D. (1986). Lower Purkinje cell counts in the cerebella of four autistic subjects: Initial findings of the UCLA-NSAC autopsy research report. *American Journal of Psychiatry, 143,* 862–866.

Roberts, W. W., Dember, W. N., & Brodwick, H. (1962). Alteration and exploration in rats with hippocampal lesions. *Journal of Comparative Psychiatry, 55,* 695–700.

Rodier, P. M. (2000). The early origins of autism. *Scientific American, 282,* 56–63.

Rodier, P. M., Ingram, J. L., Tisdale, B., Nelson, S., Romano, J. (1996). Embryological origin for autism: Developmental anomalies of the cranial nerve motor nuclei. *Journal of Comparative Neurology, 370,* 247–261.

Rogers, S. J., Hepburn, S., & Wehner, E. (2003). Parent reports of sensory symptoms in toddlers with autism and those with other developmental disorders. *Journal of Autism and Developmental Disorders, 33,* 631–642.

Rogers, S. J., Ozonoff, S., & Maslin-Cole, C. (1993). Developmental aspects of attachment behavior in young children with pervasive developmental disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 32,* 1274–1282.

Rourke, B. (1989). *Nonverbal learning disabilities: The syndrome and the model.* New York: Guilford Press.

Rumsey, J. M. (1992). Neuropsychological studies of high-level autism. In E. Schopler & G. B. Mesibov (Eds.), *High-functioning individuals with autism* (pp. 41–64). New York: Plenum.

Rutgers, A. H., Bakermans-Kranenburg, M. J., van Uzendoorn, M. H., & van Berckelaer-Onnes, I. A. (2004). Autism and attachment: A meta-analytic review. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 45,* 1123–1134.

Rutter, M. (2002). Development and psychopathology. In M. Rutter & E. Taylor (Eds.), *Child and Adolescent Psychiatry* (4th ed., pp. 309–324). Malden, MA: Blackwell.

Rutter, M., Bailey, A., Bolton, P., & Le Couteur, A. (1994). Autism and known medical conditions: Myth and substance. *Journal of Child Psychology and Psychiatry, 35,* 311–322.

Saitoh, O., & Courchesne, E. (1998). Magnetic resonance imaging study of the brain in autism. *Psychiatry and Clinical Neuroscience, 52,* S219–S222.

Santangelo, S. L., & Tsatsanis, K. (2005). What is known about autism: Genes, brain, and behavior. *American Journal of Pharmacogenomics, 5,* 71–92.

Schreck, K. A., Mulick, J. A., & Smith, A. F. (2004). Sleep problems as possible predictors of intensified symptoms of autism. *Research in Developmental Disabilities, 25,* 57–66.

Schultz, R. T. (2005). Developmental deficits in social perception in autism: The role of the amygdala and fusiform face area. *International Journal of Developmental Neuroscience, 23,* 125–141.

Schultz, R. T., Gauthier, I., Klin, A., Fulbright, R., Anderson, A., Volkmar, F. R., et al. (2000). Abnormal ventral temporal cortical activity among individuals with autism and Asperger syndrome during face discrimination. *Archives of General Psychiatry, 57,* 331–340.

Sigman, M., Dijamco, A., Gratier, M., & Rozga, A. (2004). Early detection of core deficits in autism. *Mental Retardation and Developmental Disabilities Research Reviews, 10,* 221–233.

Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science, 253,* 1380–1386.

Steingard, R. J., Zimnitzky, B., DeMaso, D. R., Bauman, M. L., & Bucci, J. P. (1997) Sertraline treatment of transition-associated anxiety and agitation in children with autistic disorder. *Journal of Child and Adolescent Psychopharmacology, 7,* 9–15.

Szatmari, P., Jones, M. B., Zwaigenbaum, L., & MacLean, J. E. (1998). Genetics of autism: Overview and new directions. *Journal of Autism and Developmental Disorders, 28,* 351–368.

Tanguay, P. E., & Edwards, R. (1982). Electrophysiological studies of autism: The whisper of the bang. *Journal of Autism and Developmental Disorders, 12,* 177–184.

Tani, P., Lindberg, N., Nieminen-von Wendt, T., von Wendt, L., Virkkala, J., Appelberg, B., et al. (2004). Sleep in young adults with Asperger syndrome. *Neuropsychobiology, 50,* 147–152.

Tantam, D., Monaghan, L., Nicholson, H., & Stirling, J. (1989). Autistic children's ability to interpret faces: A research note. *Journal of Child Psychology and Psychiatry, 30,* 623–630.

Teder-Salejarvi, W. A., Pierce, K. L., Courchesne, E., & Hillyard, S. A. (2005). Auditory spatial localization and attention deficits in autistic adults. *Brain Research, 23,* 221–234.

Tidmarsh, L. & Volkmar, F. R. (2003). Diagnosis and epidemiology of autism spectrum disorders. *Canadian Journal of Psychiatry, 48,* 517–525.

Townsend, J., & Courchesne, E. (1994). Parietal damage and narrow "spotlight" spatial attention. *Journal of Cognitive Neuroscience, 6,* 220–232.

Townsend, J., Courchesne, E., & Egaas, B. (1996). Slowed orienting of covert visual-spatial attention in autism: Specific deficits associated with cerebellar and parietal abnormality. *Development and Psychopathology, 8,* 563–584.

Townsend, J., Harris, N. S., & Courchesne, E. (1996). Visual attention abnormalities in autism: Delayed orienting to location. *Journal of the International Neuropsychological Society, 2,* 541–550.

Tsai, L. Y. (1992). Diagnostic issues in high-functioning autism. In E. Schopler & G. B. Mesibov (Eds.), High-functioning individuals with autism (pp. 11–40). New York: Plenum Press.

U.S. Department of Education. (1995). *Seventeenth annual report to Congress on the implementation of the Individuals with Disabilities Education Act.* Washington, DC: Author.

U.S. Department of Education. (2004). *Twenty-sixth annual report to Congress on the implementation of the Individuals with Disabilities Education Act.* Washington, DC: Author.

Vargas, D. L., Nascimbene, C., Krishnan, C., Zimmerman, A. W., & Pardo, C. A. (2004). Neurological activation and neuroinflammation in the brain of patients with autism. *Annals of Neurology, 57,* 67–81.

Vargha-Khadem, F., Isaacs, E., van der Werf, S., Robb, S., & Wilson, J. (1992). Development of intelligence and memory in children with hemiplegic cerebral palsy: The deleterious consequences of early seizures. *Brain, 115,* 315–329.

Vergnes, M. (1981). Effect of prior familiarization with mice on elicitation of mouse killings in rats: Role of the amygdala. In Y. Ben-Ari (Ed.), *The amygdaloid complex.* INSERM Symposium, No. 20. Amsterdam: Elsevier/North Holland Biomedical Press.

Volkmar, F. R., Carter, A., Grossman, J., & Klin, A. (1997). Social development in autism. In D. Cohen & F. Volkmar (Eds.), *Handbook of autism and pervasive developmental disorders* (2nd ed., pp. 173–194). New York: Wiley.

Volkmar, F. R., Klin, A., Siegel, B., Szatmari, P., Lord, C., Campbell, M., et al. (1994). Field trial for autistic disorder in *DSM-IV. The American Journal of Psychiatry, 151,* 1361–1367.

Volkmar, F. R., Lord, C., Bailey, A., Schultz, R. T., & Klin, A. (2004). Autism and pervasive developmental disorders. *Journal of Child Psychology and Psychiatry, 45,* 135–170.

Volkmar, F. R., & Nelson, D. S. (1990). Seizure disorders in autism. *Journal of the American Academy of Child and Adolescent Psychiatry, 29,* 127–129.

Wahl, R. U. (2004). Could oxytocin administration during labor contribute to autism and related behavioral disorders? A look at the future. *Medical Hypotheses, 63,* 456–460.

Wainwright-Sharp, J. A., & Bryson, S. E. (1993). Visual orienting deficits in high-functioning people with autism. *Journal of Autism and Developmental Disorders, 23,* 1–13.

Wassink, T. H., Brzustowicz, L. M., Bartlett, C. W., & Szatmari, P. (2004). The search for autism disease genes. *Mental Retardation and Developmental Disabilities Research Reviews, 10,* 272–283.

Waterhouse, L., Fein, D., & Modahl, C. (1996). Neurofunctional mechanisms in autism. *Psychological Review, 103,* 457–489.

Welch, M. G., Welch-Horan, T. B., Anwar, M., Anwar, N., Ludwig, R. J., & Ruggiero, D. A. (2005). Brain effects of chronic IBD in areas abnormal in autism and treatment by single neuropeptides secretin and oxytocin. *Journal of Molecular Neuroscience, 25,* 259–274.

Welchew, D. E., Ashwin, C., Berkouk, K., Salvador, R., Suckling, J., Baron-Cohen, S., et al. (2005). Functional disconnectivity of the medial temporal lobe in Asperger syndrome. *Biological Psychiatry, 57,* 991–998.

Werner, E., Dawson, G., Osterling, J., & Dinno, N. (2000). Brief report: Recognition of autism spectrum disorder before one year of age: A retrospective study based on home videotapes. *Journal of Autism and Other Developmental Disorders, 30,* 157–167.

Williams, D. L., Goldstein, G., & Minshew, N. J. (2005). Impaired memory for faces and social scenes in autism: Clinical implications of memory dysfunction. *Archives of Clinical Neuropsychology, 20,* 1–15.

Wing, L. (1981). Asperger's syndrome: A clinical account. *Psychological Medicine, 11,* 115–129.

Wing, L., & Gould, J. (1979). Severe impairments of social interaction and associated abnormalities in children: Epidemiology and classification. *Journal of Autism and Developmental Disorders, 9,* 11–29.

Wong, V., & Wong, S. N. (1991). Brainstem auditory evoked potential study in children with autistic disorder. *Journal of Autism and Developmental Disorders, 21,* 329–340.

Yakovlev, P. I., Weinberger, M., & Chipman, C. E. (1948). Heller's Syndrome as a pattern of schizophrenic behavior disturbance in early childhood. *American Journal of Mental Deficiency, 53,* 318–337.

Young, E. C., Diehl, J. J., Morris, D., Hyman, S. L., & Bennetto, L. (2005). The use of two language tests to identify pragmatic language problems in children with autism spectrum disorders. *Language, Speech, and Hearing Services in Schools, 36,* 62–72.