more impaired than others. And indeed, these differences are reified in diagnostic schemes that draw distinctions between developmental abnormalities that affect primarily general cognition, social cognition, or perception. These differential cognitive and behavioral vulnerabilities may provide useful clues about the origin and developmental time course of specific mental functions in normal development.

In this chapter, we focus principally on neurodevelopmental disorders that include abnormalities in social functioning, including ASD, fragile X syndrome, Williams syndrome, Rett syndrome, and Angelman and Prader-Willi syndromes. These conditions all impair highly sophisticated brain functions including social awareness and communication. ASD is a prime focus for several reasons: the high prevalence in the population; the overlap in genetic risks with other common neuropsychiatric conditions, including schizophrenia; and the absence of a defining neuropathology. They are also exemplars of the etiological and phenotypic heterogeneity common to many psychiatric syndromes. In this respect, ASD is a paradigmatic neuropsychiatric syndrome.

Autism Spectrum Disorder Phenotypes Share Characteristic Behavioral Features

Profound social disability has probably always been with us, but the characterization of autism as a medical syndrome was first described in the literature in 1943 by Leo Kanner and in 1944 by Hans Asperger. Today, clinicians and researchers think of autism as a spectrum of disorders with two defining but highly variable diagnostic features: impaired social communication and stereotyped behaviors with highly restricted interests.

Until recently, the term "Asperger syndrome" was used to describe individuals who met these two diagnostic criteria, but in whom language acquisition was not delayed and IQ was in the normal range. In the most recent edition of the standard psychiatric diagnostic manual, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), Asperger syndrome along with a distinct disorder known as pervasive developmental disorder not otherwise specified—designed to capture individuals with deficits in social communication who did not meet full criteria in other areas—were eliminated in favor of including variations within a single spectrum construct.

Autism spectrum disorder is present in at least 1.5% of the population. Rigorous epidemiological studies estimate prevalence as high as 2.6% for the full spectrum of social disability, far higher than estimated only decades ago. The reasons for the increase in the prevalence over a relatively short time frame are of considerable interest and active debate, particularly among the lay public. Within the scientific community, a consensus has emerged that this increase reflects a combination of changing diagnostic criteria, increased awareness among families and health care professionals, "diagnostic substitution" (in which individuals who formerly would have been diagnosed with intellectual disability are now more likely to be identified as socially disabled), and some true increase in incidence. These issues will be discussed below with regard to genetic risks.

Autism spectrum disorders occur predominantly in males, although the typically cited 4:1 male-to-female ratio has recently been called into question based on concerns about male bias in the approaches used to ascertain the diagnosis, including the diagnostic instruments. Even accounting for these challenges, however, the cumulative evidence suggests a ratio bias of at least 2:1 to 3:1 male excess. Individuals across the IQ spectrum are affected, and based on current diagnostic practices, about half of all individuals with ASD also have intellectual disability. By definition, ASD must be detectable before 3 years of age, but recent studies have shown that it is possible to identify affected children in high-risk families well within the first year of life. ASD occurs in all countries and cultures and in every socioeconomic group.

Although ASD clearly affects the brain, no definitive biological markers have yet been identified; thus, diagnosis is based on behavioral criteria. This does not mean that there are not strong biological correlates, including specific gene mutations and neuroimaging findings, but none of these are sufficiently specific or predictive to be useful as an alternative to the gold standard of clinical assessment. Moreover, because behavior is variable during development and depends on a number of factors—age, environment, social context, and availability and duration of remedial help—no single behavior is likely ever to be conclusively diagnostic.

Like other neurodevelopmental syndromes, ASD typically endures throughout life. However, in recent longitudinal studies, approximately 10% of clearly affected children showed improvement, with little or no evidence of social disability later in life. Autism is not progressive. On the contrary, special educational programs and professional support often lead to improvements in behavior and adaptive functioning with age.

Autism Spectrum Disorder Phenotypes Also Share Distinctive Cognitive Abnormalities

Social Communication Is Impaired in Autism Spectrum Disorder: The Mind Blindness Hypothesis

One cognitive theory of social communication postulates that humans have a particularly well-developed ability to understand the mental states of others in an intuitive and fully automatic fashion. Watching a young person surreptitiously trying to open a car door without a key, you instantly understand that she believes she can break in while being unobserved, and you expect her to run away as soon as she realizes someone is watching. Thus, you explain and predict her behavior by inferring her mental states (desires, intentions, beliefs, knowledge) from her overt behavior. This so-called mentalizing ability, termed a *theory of mind*, is thought to depend on specific brain mechanisms and circuits underlying social cognition (Figure 62–1). Further, it is postulated that mentalizing is impaired in ASD, with profound effects on social development.

It is now generally agreed that insight into the mental state of others depends on the capacity to mentalize spontaneously. Spontaneous mentalizing allows us to appreciate that different people have different

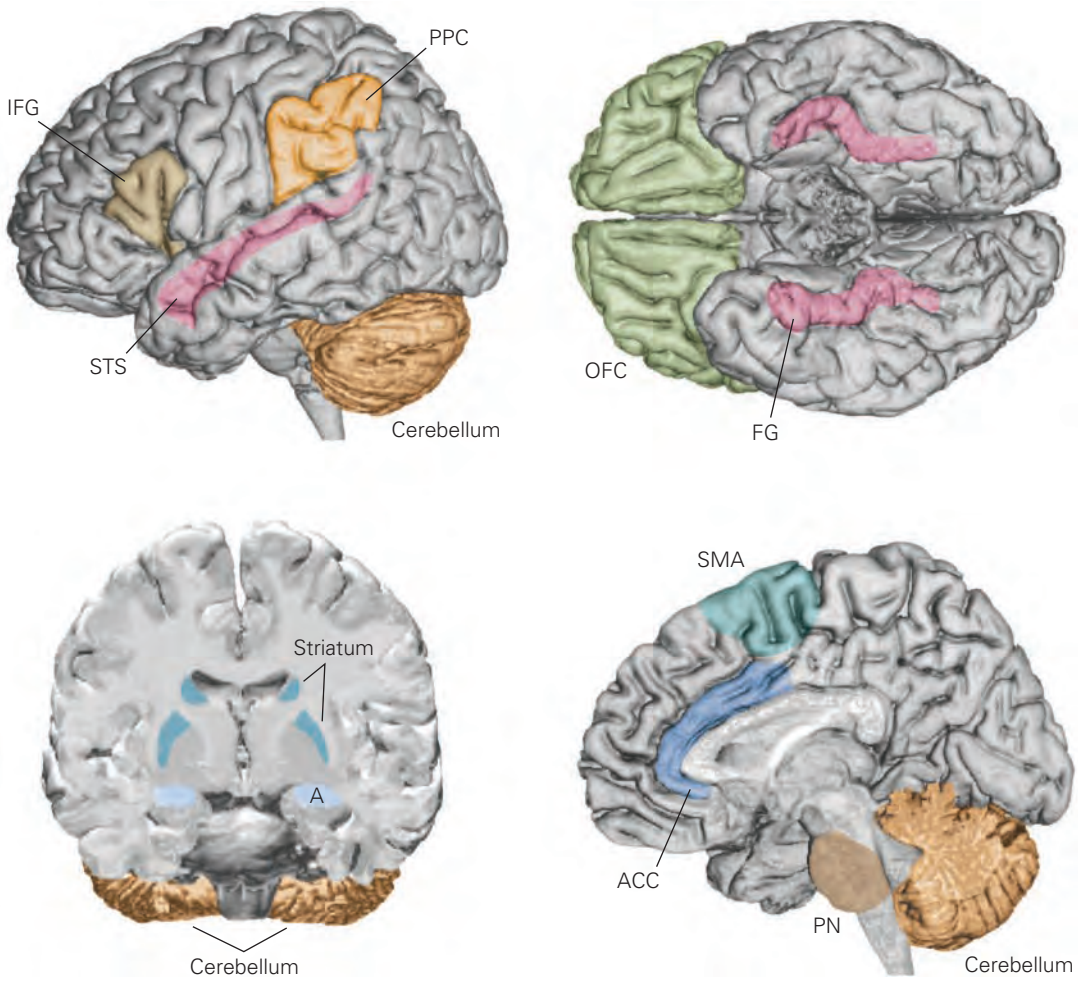

Figure 62–1 Brain areas implicated in the three core deficits characteristic of autism: impaired social interaction, impaired language and communication, and severely restricted interests with repetitive and stereotyped behaviors. Areas implicated in social deficits include the orbitofrontal cortex (**OFC**), the anterior cingulate cortex (**ACC**), and the amygdala (**A**). Cortex bordering the superior temporal sulcus (**STS**) has been implicated in mediating the perception that a living thing is moving and gaze perception. Face processing involves a region of the inferior temporal cortex within the fusiform gyrus (**FG**). Comprehension and expression of language involve a number of regions including the inferior frontal region, the striatum, and subcortical areas such as the pontine nuclei (**PN**). The striatum has also been implicated in the mediation of repetitive behaviors. (Abbreviations: **IFG**, inferior frontal gyrus; **PPC**, posterior parietal cortex; **SMA**, supplementary motor area.)

thoughts and that thoughts are internal and different from external reality.

The inability to mentalize, or "mind blindness," was first tested in children with autism using a simple puppet game, the Sally-Anne test. Young children with ASD, unlike those with Down syndrome or typically developing 4-year-olds, cannot predict where a puppet will first look for an object that was moved while the puppet was out of the room. They are not able to imagine that the puppet will "think" that the object will be where the puppet had left it (Figure 62–2). Many children with ASD eventually do learn to pass this task, but on average with a 5-year delay. Mentalizing acquired so slowly remains effortful and error-prone even in adulthood.

At the same time, young children with ASD show excellent appreciation of physical causes and events. For instance, a child who is incapable of falsely telling another that a box is locked is quite capable of locking the same box to prevent its contents from being stolen.

Variations of the Sally-Anne test and other mentalizing tasks have been used with children and adults with ASD since the mid-1980s (Figure 62–3).

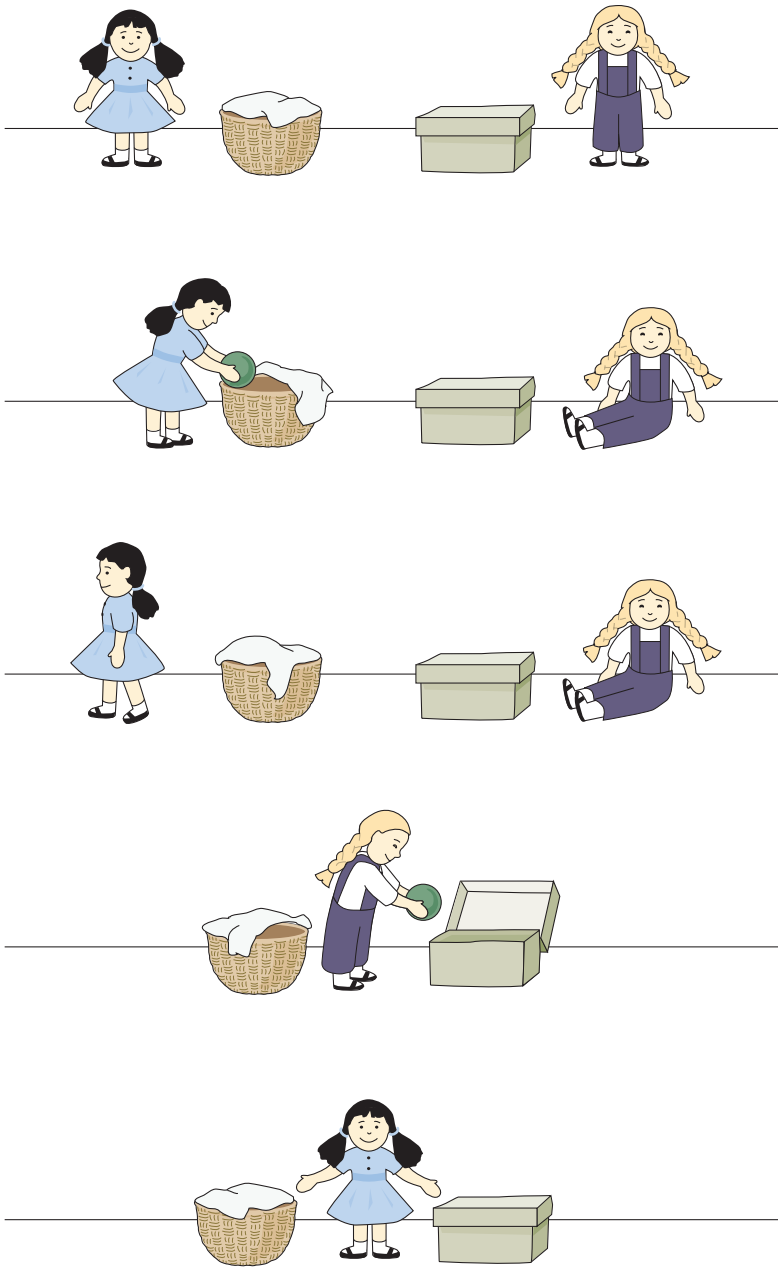

Figure 62–2 The Sally-Anne test. This first test of the "theory of mind" begins with a scripted performance using two dolls. Sally has a basket; Anne has a box. Sally puts a ball into her basket. She goes for a walk and leaves the room. While Sally is outside, naughty Anne takes the ball out of the basket and puts it into her box. Now Sally comes back from her walk and wants to play with her ball. Where will she look for the ball, the basket or the box? The answer, the basket, is obvious to most typically developing 4-year-olds but not to autistic children of the same or even higher mental age. (Adapted from original artwork by Axel Scheffler.)

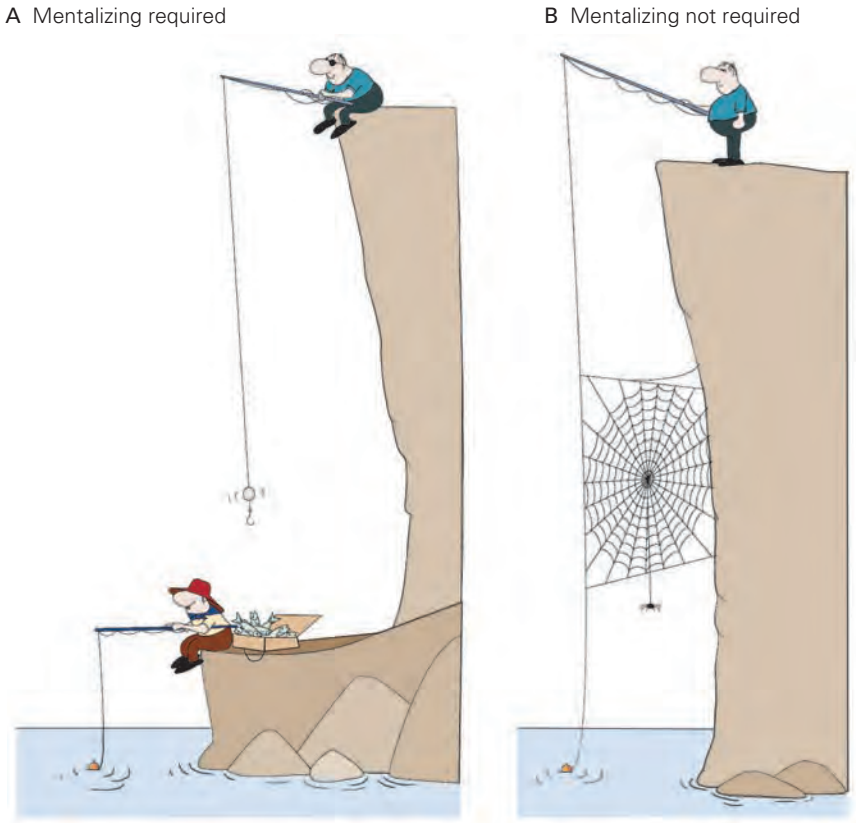

Figure 62–3 Examples of cartoons used in imaging studies of "mentalizing." Participants were asked to consider the meaning of each picture (silently) and then to explain them. In a functional magnetic resonance imaging study, normal adults passively viewed cartoons that require mentalizing versus those that do not. A characteristic network of brain regions is activated in each subject (see Figure 62–4). (Adapted from Gallagher et al. 2000.)

Functional neuroimaging has been used to examine activity in the brain of healthy subjects while they are engaged in tasks that necessitate thinking about mental states. A wide range of tasks using visual and verbal stimuli has been used in these studies. In an early positron emission tomography study, adults in a control cohort viewed silent animations of geometric shapes. In some of the animations, the triangles move in scripted scenarios designed to evoke mentalizing (eg, triangles tricking each other). In other animations, the triangles move randomly in a manner that does not evoke mentalizing. Comparison of the scans made while subjects viewed each type of animation reveals a specific network of four brain centers involved in mentalizing (Figure 62–4). Functional magnetic resonance imaging (MRI) studies using the same animations have shown that activity in this network is reduced in subjects with ASD.

This network has four components. The first, in the medial prefrontal cortex, is a region thought to be involved in monitoring one's own thoughts. A second component, in the temporoparietal region of the superior temporal lobe, is known to be activated by eye gaze and biological motion. Patients with lesions in this area in the left hemisphere are unable to pass the Sally-Anne test. The third region is the amygdala, which is involved in the evaluation of social and nonsocial information for indications of danger in the environment. The fourth region is an inferior temporal region involved in the perception of faces.

Recent studies have used stimuli intended to capture more nuanced and naturalistic social content, for example, using movies of actual social encounters as opposed to static pictures of facial expressions. These studies have identified, among other things, the role of the orbital frontal cortex in social cognition.

Other Social Mechanisms Contribute to Autism Spectrum Disorder

From birth, normal infants prefer to attend to people rather than other stimuli. An absence of this preference could lead to an inability to understand and interact with others. Indeed, the absence of preferential attention to social stimuli and mutual attention are widely acknowledged as early signs of ASD. These deficits may not involve problems with mentalizing, given that mutual attention normally appears toward the end of the first year when signs of mentalizing are still sparse.

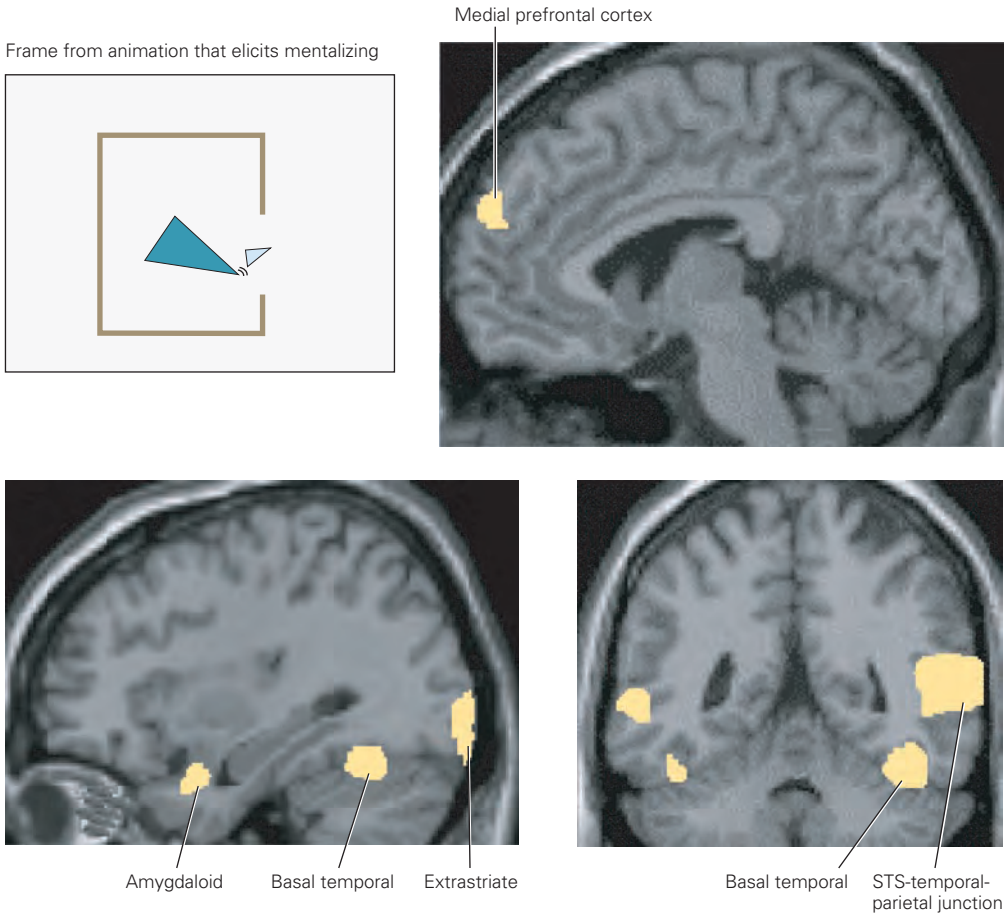

Figure 62–4 The mentalizing system of the brain. Healthy volunteers were presented with animated triangles that moved in such a way that viewers would attribute mental states to them. In the sample frame shown, the larger triangle was seen as encouraging the smaller triangle to leave the enclosure. They were also presented with animated triangles that moved in a more or less random fashion and thus would not elicit mentalizing. The highlighted areas show differences in the positron emission tomography scans of brain activation when these two viewing conditions were compared. (Abbreviation: STS, superior temporal sulcus.) (Reproduced, with permission, from Castelli et al. 2002. Copyright © 2002, Oxford University Press.)

Researchers have long considered the possibility that a specific neural mechanism underlies attention to social stimuli, such as faces, voices, and biological motion. In favor of this hypothesis, researchers found that the gaze of individuals with ASD is abnormal when watching social scenes. For example, multiple studies have found that individuals with ASD fixate on people's mouths instead of showing the normal preference for eyes (Figure 62–5).

People With Autism Show a Lack of Behavioral Flexibility

Repetitive and inflexible behavior in ASD may reflect abnormalities in frontal lobe executive functions, a wide array of higher cognitive processes that include the ability to disengage from a given task, inhibit inappropriate responses, stay on task (plan and manage sequences of deliberate actions), keep multiple task demands in working memory, monitor performance, and shift attention from one task to another.

Even ASD individuals with IQs in the normal range have problems in planning, organizing, and flexibly switching between behaviors. Irrespective of IQ, affected individuals have difficulties suggesting various different uses of a single object such as a handkerchief (used to block a sneeze, to wrap loose objects, etc.). Flexible thinking is also poor in patients with acquired damage to the frontal lobe.

Some Individuals With Autism Have Special Talents

A particularly fascinating feature of ASD in some individuals is "savant syndrome," defined by the presence

Figure 62–5 Individuals with autistic disorder often do not look into the eyes of others. Patterns of eye movements in individuals with autism were studied while the subjects watched clips from the film *Who's Afraid of Virginia Wolf?* When looking at human faces, the subjects tended to look at the mouth rather than the eyes, and in scenes of intense interaction between people, they tended to look at irrelevant places rather than at the faces of the actors. (Reproduced, with permission, from Klin et al. 2002. Copyright © 2002 American Psychiatric Association.)

of one or more exceptional skills that are in marked contrast to the individual's overall disability but also rare in the population at large. The most widely cited estimate is that 10% of individuals with ASD demonstrate such exceptional abilities compared to about 1 in 1,000 individuals with other forms of intellectual disability.

In the largest ASD cohort surveyed by self-reporting to date (about 5,000 families), 531 individuals were reported to have exceptional abilities in the following 10 areas (listed in descending frequency): music, memory, art, hyperlexia, mathematics, mechanical, coordination, directions, calendar calculating, and extrasensory perception. Subsequent small-scale studies have placed the prevalence of savant skills in ASD at between 13% and 28%.

A recently established savant syndrome registry now includes more than 400 people from 33 countries. Among a group of 319 individuals who met some criteria that earned them a savant diagnosis based on family or caregiver reports or self-reporting, 75% who showed savant skills in childhood were diagnosed with ASD. Approximately half reported a single exceptional skill and half reported multiple skills. Music was the most commonly reported exceptional skill, followed by art, memory, and mathematics. Calendar calculating, while present in many savants along with another skill, was the sole skill in only about 5% of the sample. Among this self- or family-selected group, the overall sex distribution mirrored that reported for ASD in general, with a male-to-female ratio of approximately 4:1.

One explanation for savant syndrome is that information processing is preferentially geared to tiny details at the cost of seeing the bigger picture. (For example, the drawing by the gifted artist with high-functioning autism in Figure 62–6 shows remarkably detailed cityscapes, as well as detailed numerical patterns and dates.) A similar hypothesis is that brain regions involved in perception are overfunctioning; another possibility is that there is a preference for manipulating the bits of information that fit within a strict framework such as calendar knowledge or a bus timetable. Neuropsychological data support both explanations, but decisive experiments to distinguish between them remain to be done.

Genetic Factors Increase Risk for Autism Spectrum Disorder

The earliest evidence that genes contribute to ASD arose from studies of twin pairs as well as familial aggregation. The former show from 60% to 90% concordance among monozygotic twin pairs; this wide range is due in part to previously used diagnostic criteria and classifications. For example, the highest estimates of monozygotic concordance are derived from observations of twins with any of three diagnoses that made up the social disability spectrum prior to the reformulations in the DSM-5. Only approximately 60% of monozygotic twins were found to be concordant for the "full diagnosis" of autism, which was defined at

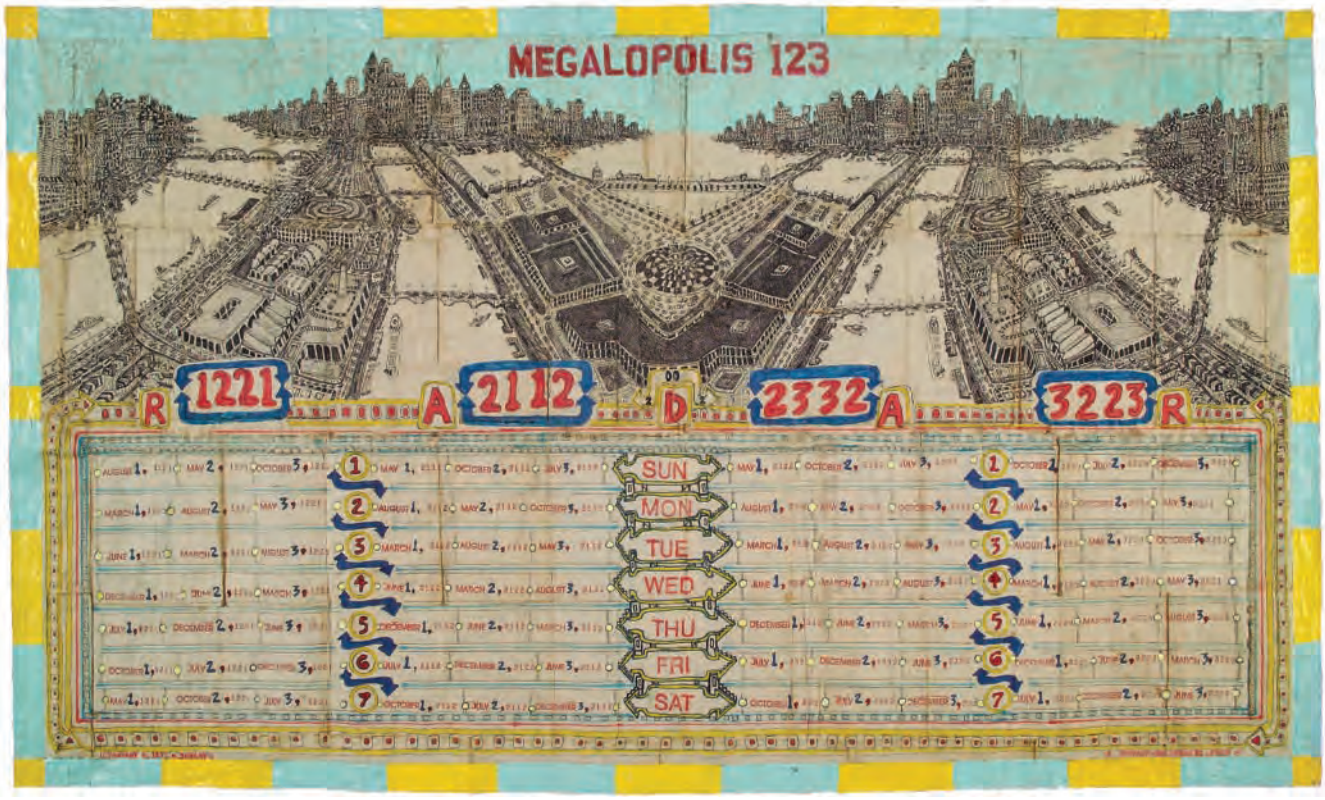

Figure 62–6 Strikingly beautiful art work by George Widener. George is a highly accomplished and much-admired outsider artist. In the attention to detail, this drawing resembles the drawings of other autistic savant artists. The intricate topographical detail of a symmetrically arranged city, with rivers, bridges, and tall buildings, is combined with minutely executed and seemingly abstruse calendar sequences. Mastery of the calendar and the ability to name the day of the week for any given date has often been described for autistic savants. The viewer of this drawing can partake in an otherwise very private world of space and time, numbers, and patterns. (Reproduced, with permission, from the Henry Boxer Gallery, London.)

the time as comprising fundamental impairments in each of three categories: social communication, language development, and restricted interests or repetitive behaviors. In contrast, dizygotic twins show 10% to 30% concordance—again with the lower number estimating concordance for the diagnosis of isolated autism, while the larger number encompasses any of three diagnoses on the autism spectrum.

This difference between the rates at which monozygotic and dizygotic twins share an ASD phenotype is attributed to differences in the amount of shared genetic material between the two types of twin pairs. Monozygotic siblings share all their DNA, whereas dizygotic twins share as much DNA as any sibling pair. In addition to these types of data, it has long been observed that ASD runs in families: Current estimates are that if parents have one child with ASD, the risk that a second child will be affected increases approximately 5- to 10-fold over the population base rate.

The most generous estimates of genetic contribution do not explain all risk for ASD in the population. Some contribution from the environment is a certainty. However, given the well-known public debate on the issue of whether immunization is a factor in ASD, it is important to note that there is no credible evidence that the increase in ASD prevalence is due to immunizations. The initial study that raised the issue of the contribution of the trivalent measles-mumps-rubella (MMR) vaccine has been retracted and thoroughly repudiated by the editors of the journal in which the article appeared, as well as by 10 of 12 of the original authors. A wide range of subsequent investigations, both of the MMR vaccine and of vaccines with the mercury-containing preservative thimerosal, has found no evidence for association with ASD risk.

The counter argument that certain rare individuals may be predisposed to a vulnerability to vaccines leading to ASD is nonfalsifiable. However, three lines of evidence suggest that such a contribution, if present, is

likely to be quite small. First, it is important to recall that the basis for the MMR hypothesis has been thoroughly debunked, and consequently, the prior probability that vaccines are major etiological factors is extremely low. Second, even in very large research cohorts, it has so far not been possible to detect a risk signal. Third, although there is a subset of children with ASD who show developmental regression in the second year of life, there is often evidence on careful examination of preexisting delay. In the final analysis, although the current level of understanding of pathophysiological mechanisms makes it impossible to definitively exclude any etiological contributor in a single individual, what is incontrovertible is that the risks to children of not receiving vaccinations are clear, measurable, and far greater overall than the role vaccines might play in ASD risk.

Although the evidence for a predominantly genetic contribution has been consistent, until recently, the search for risk genes contributing to nonsyndromic forms of ASD proved to be extremely challenging. Now, as will be discussed below, technological advances and changes in research culture have transformed the field. Moreover, critically important initial insights into both the genetics and neurobiology of ASD have emerged from the investigation of well-characterized genetic neurodevelopmental disorders, sometimes referred to as Mendelian syndromes (those with a single causative gene or genomic locus to the condition). These disorders typically manifest with intellectual disability, often with evidence of social impairment. Several of these syndromes, including fragile X, Rett, Williams, and Prader-Willi/Angelman syndromes, have been particularly important in beginning to elaborate the biology of ASD.

Rare Genetic Syndromes Have Provided Initial Insights Into the Biology of Autism Spectrum Disorders

Fragile X Syndrome

Fragile X syndrome is a common form of chromosome X–linked intellectual disability. Patients display a range of behavioral abnormalities including poor eye contact, social anxiety, and repetitive behaviors. In addition, approximately 30% of boys with fragile X meet the all diagnostic criteria for ASD. Moreover, in research with multiple cohorts, up to 1% of participants with apparently idiopathic ASD also carried fragile X mutations. The overall prevalence is approximately 1 in 4,000 boys and 1 in 8,000 girls.

The fragile X mutation is quite remarkable. The *FMR1* gene on the X chromosome includes the nucleotide triplet CGG. In normal individuals, this triplet is repeated in approximately 30 copies. In fragile X syndrome patients, the number of repeats is more than 200, with approximately 800 repeats being most common. This expansion of trinucleotide repeats has since been observed in other genes leading to neurological diseases, such as Huntington disease (Chapters 2 and 63). When the number of CGG repeats exceeds 200, the *FMR1* gene regulatory region becomes heavily methylated, and gene expression is shut off. Consequently, in these children, the fragile X mental retardation protein (FMRP) is lacking.

Lack of functional FMRP is considered responsible for fragile X syndrome. FMRP is a selective RNA-binding protein that blocks translation of messenger RNA until protein synthesis is required. It is found with ribosomes at the base of dendritic spines, where it regulates local dendritic protein synthesis that is needed for synaptogenesis and certain forms of long-lasting synaptic changes associated with learning and memory (Chapters 52 and 53). Interestingly, long-term depression of excitatory synaptic transmission, a form of long-lasting synaptic change that requires local protein synthesis, is enhanced in a mouse model of fragile X syndrome in which the gene encoding FMRP has been deleted. Loss of FMRP may enhance long-term depression by allowing excess translation of the messenger RNAs important for synaptic plasticity.

An exciting implication of these data is that antagonists of the type 5 metabotropic glutamate receptor (mGluR5), the activation of which is required for the enhanced protein synthesis underlying long-term depression, may lessen the excess protein translation. In fact, compounds with this activity have been found to rescue the mutant phenotype in mouse and fruit fly models. Thus far, clinical trials of mGluR5 antagonists for individuals with fragile X with ASD have not shown efficacy against the defined clinical end points. However, it is still too early to tell whether these initial forays into rational drug design for neurodevelopmental disorders may or may not be promising in the long run. A range of challenges have confronted these pioneering efforts, including measuring change in individuals with ASD, identifying ideal clinical end points, and determining the best age for evaluating interventions.

Rett Syndrome

Another single-gene disorder showing overlap with ASD is Rett syndrome, a devastating disorder that primarily affects girls. Affected females have normal

development from birth until 6 to 18 months of age, when they regress, losing speech and hand skills that they had acquired. Rett syndrome is progressive, and initial symptoms are followed by repetitive hand movements, loss of motor control, and intellectual disability. Often young girls will display symptoms indistinguishable from ASD early in the course of the syndrome, although social communication frequently improves later in childhood. Its prevalence is approximately 1 in 10,000 live female births.

Rett syndrome is an X-linked inherited disease caused by loss-of-function mutations in the *MECP2* gene, which encodes a transcriptional regulator that binds to methylated cytosine bases in DNA, regulating gene expression and chromatin remodeling. The gene product was initially thought to act predominantly as a transcriptional repressor, but studies of both the mouse model and human induced pluripotent stem cells have shown that overall gene expression is reduced when the gene is knocked out. Among the genes that have reduced expression in neurons is *BDNF*, encoding brain-derived neurotrophic factor. Studies in mouse models of Rett have found that overexpression of *BDNF* improves the knock-out phenotype. Other growth factors that increase gene expression but have more favorable neuropharmacological profiles, including insulin-like growth factor-1 (IGF-1), have also improved aspects of the mouse phenotype, leading to optimism about clinical trials of related compounds. Phase II human trials with both molecules are currently underway.

One might think that such a global abnormality in gene expression would lead to a very severe phenotype, but because females are mosaic, with approximately half of their brain cells expressing one normal copy of *MECP2* (due to random X-inactivation), they are viable but manifest the devastating Rett phenotype. Boys, who have a single X chromosome and thus a single copy of *MECP2*, typically die soon after birth or in infancy if they carry a loss-of-function mutation in *MECP2*.

The role of X-inactivation in the survival of female mutation carriers and the observation that favorable skewing (a shift toward preferential silencing of the mutant X) leads to a less severe clinical course have generated considerable interest in therapeutic strategies aimed at reactivating the normal but silenced X chromosomes in females with Rett syndrome. Although one can imagine considerable challenges resulting from the reactivation of many genes on a normally silenced chromosome, a recent study has reported a mouse mutation that leads to both alleles expressing MeCP2 without wholesale activation of genes on the X chromosome.

Interestingly, in 2005, duplications spanning *MECP2* were identified in males with severe intellectual disability. This condition, called *MECP2* duplication syndrome (MDS), includes autistic features, hypotonia, epilepsy, gait abnormalities, and recurrent infections. Like Rett syndrome, it has also been productively modeled in rodents. However, unlike Rett, the majority of identified cases are familial and not sporadic in nature. In these cases, female carriers are often healthy enough (due to favorable X-inactivation) to reproduce and transmit the duplication to boys with only a single X chromosome.

Williams Syndrome

Williams syndrome is caused by a segmental deletion of about 27 genes on the long arm of chromosome 7 and is characterized by mild to moderate intellectual disability, connective tissue abnormalities, cardiovascular defects, distinctive facies, and a behavioral phenotype characterized by increased sociability, preserved language abilities, affinity for music, and impaired visuospatial capabilities. The disorder occurs in 1 in 10,000 live births. The connective tissue and key cardiovascular symptoms have been attributed to the loss of the gene *ELN* (*elastin*), although no specific genes within the deleted interval have yet been definitively shown to result in the behavioral phenotype. Nonetheless, the social cognitive features of Williams syndrome are particularly intriguing: The degree of interest in social interaction is striking, leading to a nearly universal loss of reticence with strangers in children with the syndrome. In contrast to the almost complete absence of social anxiety, individuals with Williams syndrome have a high degree of general anxiety and isolated phobias. Finally, the affinity for and interest in music among a very large percentage of 7q11.23 deletion carriers, although less well characterized, are striking.

Conversely, duplication of the identical region of chromosome 7, including the same 26 to 28 genes, is a significant risk factor for ASD and other neurodevelopmental syndromes apart from Williams syndrome. The observation of contrasting social phenotypes depending on whether there is loss or gain of a small region of the genome is fascinating. Whether social functioning in William syndrome is truly the opposite of that seen in ASD, as is sometimes argued, seems less interesting than the conclusion that this region of the genome must contain one or more genes that modulate social affiliation. Consequently, the molecular characterization of these deletion and duplication syndromes and intensive investigation of their impact on the development of molecular, cellular, and circuit properties in the central nervous system are particularly important.