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An Overall View

During the past century "mental retardation" was broadly used to label a variety of cognitive impairments that were linked to prenatal or early postnatal brain abnormalities. Some subgroups with easily identifiable physical features, such as Down syndrome, were recognized early on. In recent years syndromes that result from genetic anomalies but do not express obvious physical features, such as fragile X syndrome, have also been delineated.

Common to all of these disorders are mental impairments that persist throughout life, hampering development and learning, hence the terms "neurodevelopmental disorder" and "learning disability." Generally speaking, even if all mental functions seem to be affected, some tend to be more affected than others. This differential vulnerability gives interesting clues about the different origins and developmental time course of specific mental functions in normal development.

In this chapter we focus on autism and briefly consider Down syndrome, fragile X, and other neurodevelopmental disorders with a known genetic basis. Autism is especially interesting because it impairs brain functions that are highly sophisticated in human beings: social awareness and communication. Autism is also an exemplar of many psychiatric disorders: there is a striking range in severity of symptoms, an impressive heterogeneity of comorbid conditions, and no clear cut neuropathology. It is likely that autism will ultimately be viewed as a class of disorders each with different etiologies that include genetic and environmental factors and their interaction.

Autism Has Characteristic Behavioral Features

Autism has probably always been with us, but it was identified and labeled only in 1943 by Leo Kanner and by Hans Asperger in 1944. Where were the autistic people in the past? Rare historical documents suggest that some may have been valued as eccentrics or holy fools, but the majority were probably considered to suffer constitutional mental deficiency.

Today clinicians and researchers think of autism as a spectrum of disorders with three common diagnostic features, each showing a great deal of

variability among individuals: impaired social interaction, impaired verbal and nonverbal communication, and restricted or circumscribed interests with stereotyped behaviors. The label "Asperger syndrome" is often used for individuals who exhibit the typical features of autism but have high verbal ability and no delay in language acquisition.

Autism and related disorders affect approximately 1% of the population, a far higher frequency than was previously recognized. Whether this reflects a better understanding and recognition of the range of disorders that actually belongs in this category or an actual increase in incidence is not entirely clear. The possibility that this increase is due to immunization or any simple environmental factor has been largely eliminated. Some studies indicate that the sperm of older fathers increases the incidence of autism as it does for schizophrenia. Risk also goes up with the age of the mother. As we shall see below, up to 10% of children with autism carry a genetic defect that results from a copy number variation, a mutation that arises in the germline.

Classification today is based on the three diagnostic criteria described above, which are more inclusive than those used in the earliest descriptions of the disease. Boys outnumber girls by 4 to 1, and by approximately 8 to 1 in cases of autism without intellectual disability. Although autism can occur in people with a high IQ, more than half the individuals with autism suffer from intellectual disability (defined as an IQ below 70). By definition, autism should be detectable before the child is 3 years old. Autism occurs in all countries and cultures and in every socioeconomic group.

Although autism is clearly a disorder that affects the brain, there are as yet no diagnostic biological markers and therefore diagnosis is based on behavioral criteria. Because behavior is highly changeable during development and depends on a number of factors, such as age, environment, social context, and availability and duration of remedial help, no single behavior could ever be diagnostic.

Some parents of an autistic child are aware that something is not quite right with their child from an early age. Other parents report that their babies first developed typically and then regressed in their development during the second year of life. A prospective study of siblings at genetic risk for autism showed that at age 6 months infants at genetic risk and later diagnosed autistic did not differ from those who were typically developing on measures of social interaction, such as gaze to faces, social smile, and vocalizations to others. However, differences from typically developing children increasingly emerged and were significant by 1 year of age. One of the earliest signs, near the end of the first year, is that the baby does not turn when called by name. Other early signs include the lack of preference for people over objects, and repetitive use of objects, such as spinning, and unusual visual exploration.

Beginning at approximately 18 months of age several other signs become clear. Most children with autism do not automatically direct their attention to the person or object that is the focus of other people's attention. Children with autism often fail to use pointing or other gestures to direct the attention of other people. They also fail to engage in ordinary make-believe play. Later, signs of delayed and abnormal language development are evident, with echoing of other people's speech (echolalia) and the use of idiosyncratic expressions. By the age of 3, typical cases of autism can be diagnosed reliably on the basis of this constellation of social and communication impairments, and rigid and repetitive behavior and interests. In cases where there is neither intellectual disability nor language delay (Asperger syndrome), diagnosis is typically not made until school age.

Like other neurodevelopmental disorders, autism is a lifelong disorder. Autism is not progressive, however. On the contrary, special educational programs and professional support often lead to marked improvements in behavior with age. The understanding and use of language by people with autism is quite variable. Even in individuals of high ability, language remains literal and conversational skills are lacking, as evident in poor turn-taking and poor understanding of irony. Most people with autism continue to find social situations difficult and are hampered in their ability to make friends or sustain lasting relationships.

A preference for routines and restricted behavior patterns remains throughout life, although the nature of obsessions and interests often undergo marked changes. In early childhood an individual may be drawn to shiny pieces of metal, in later childhood collect light bulbs, and in adulthood obsessively construct a novel dictionary. Hypersensitivity to touch, taste, sound, or vision is frequently mentioned in personal accounts and appears to play a role in restricting behavior by creating strong avoidances or preferences. Unfortunately, no neurobiological insight into these alterations in sensory function has yet emerged. People with autism are commonly susceptible to a variety of co-morbid psychiatric problems, particularly anxiety and depression. Nevertheless, reasonably good

adaptation is possible when the environment is stable and highly structured.

There Is a Strong Genetic Component in Autism

Convincing data that autism has a strong genetic component come from studies of monozygotic twin pairs, who have identical genes. These studies show anywhere from 60% to 91% concordance of autism. The range is broad in part because some studies consider only the most serious forms of autism, whereas others consider the full spectrum of autism-like disorders. Dizygotic twins, in contrast, have been estimated to have 10–30% concordance when the full autism spectrum is considered. If a woman has one child with autism, the risk that a second child will have autism increases approximately 20-fold. Approximately 20% of siblings of a child with autism may also have autism. The risk increases if the second child is a male or if two prior children have disorders on the autism spectrum.

These family studies indicate that autism is not generally the result of mutations in a single gene but rather variation in many genes, giving rise to a complex pattern of inheritance. As in other polygenic disorders, it is likely that the genes responsible are not the same genes in all individuals but that different combinations are drawn from a larger pool of predisposing genes. This heterogeneity has made the identification of specific genes difficult.

Despite the difficulties, genomic regions have been implicated on several chromosomes. Of particular interest are mutations in two genes on the X chromosome in two sibling pairs with either autism or Asperger syndrome. These genes encode neuroligins, postsynaptic cell adhesion proteins important in synapse formation. These observations are intriguing because they are X-linked genes and may explain the male preponderance. The neuroligin discovery has recently been supported by a study of mice harboring mutations similar to the human mutations. These mice show impaired social interactions and, as a neural correlate, increased inhibitory synaptic transmission.

In addition to conventional mutations in specific genes, copy number variation has emerged as a potentially important genetic mechanism in autism. Copy number variation describes genomic deletions and duplications of pieces of a chromosome involving up to 100 consecutive genes on a chromosome. These deletions and duplications have recently been appreciated as a significant source of genetic variation in humans. Although copy number variants are almost always inherited, recent studies suggest that 10% of autistic patients carry a de novo gene copy number that neither parent carries. These are caused not by more common conventional mutations of discrete genes but by sporadic mutations of genomic structure in the germline in the cells that give rise to sperm and ova. Thus copy number variations may play an important role in autism (and other disorders) and perhaps explain the difficulties encountered in identifying autism-susceptibility genes.

Even though heritability, or the proportion of the phenotypic variance due to genetic factors, is very high for autism, environmental factors likely also play an important role, although no specific environmental factors have been conclusively identified. Infections by viruses (such as rubella, measles, influenza, herpes simplex, and cytomegalovirus) may contribute to the etiology of autism and perhaps represent environmental cues. The possibility that a genetic defect alters features of brain development by affecting the immune system is receiving greater attention. There is substantial evidence that mediators of immune functions such as cytokines and chemokines also play a role in brain development including synaptogenesis. Given the complexity of autism and its various forms, it is likely that a variety of etiologies will ultimately be discovered, some purely genetic, others that depend on genetic risk factors coupled with environmental factors, and some purely environmental causes.

Autism Has Characteristic Neurological Abnormalities

If autism is a developmental disorder of the brain, what parts of the nervous system are most severely affected? Research in this area is still in its infancy and no comprehensive picture of the neuropathology of autism is yet available. In fact, for a disorder with such a profound impact on the life of an individual, the brain, at least at a superficial level, looks relatively normal. However, more detailed quantitative analyses have begun to demonstrate consistent alterations in the size and time course of development of particular brain regions.

The first magnetic resonance imaging (MRI) studies of autism in the mid-1980s focused on the cerebellum and suggested that hypoplasia of the cerebellar vermis was characteristic of autism. These findings,

however, have generally not been replicated. Other brain regions that have been found to be abnormal in autism include the cerebral cortex (although the salient portion of the cerebral cortex varies from study to study), medial temporal lobe structures such as the amygdala and hippocampus, and the corpus callosum (Figure 64–1).

The notion that cortical development may be altered in autism arose from clinical observations that before age 2 the head circumference of children with autism is often larger than typically developing controls. Approximately 20% of individuals with autism have unusually large heads (macrocephaly). These data would suggest that a large head and thus increased brain size might be a common, although by no means universal, feature of autism. There is, however, increasing evidence that an abnormal time course in development, not the outcome of brain development, is diagnostic of autism.

Several research groups have gathered provocative evidence for precocious growth of the brain, and particularly of the frontal lobe, during the first few

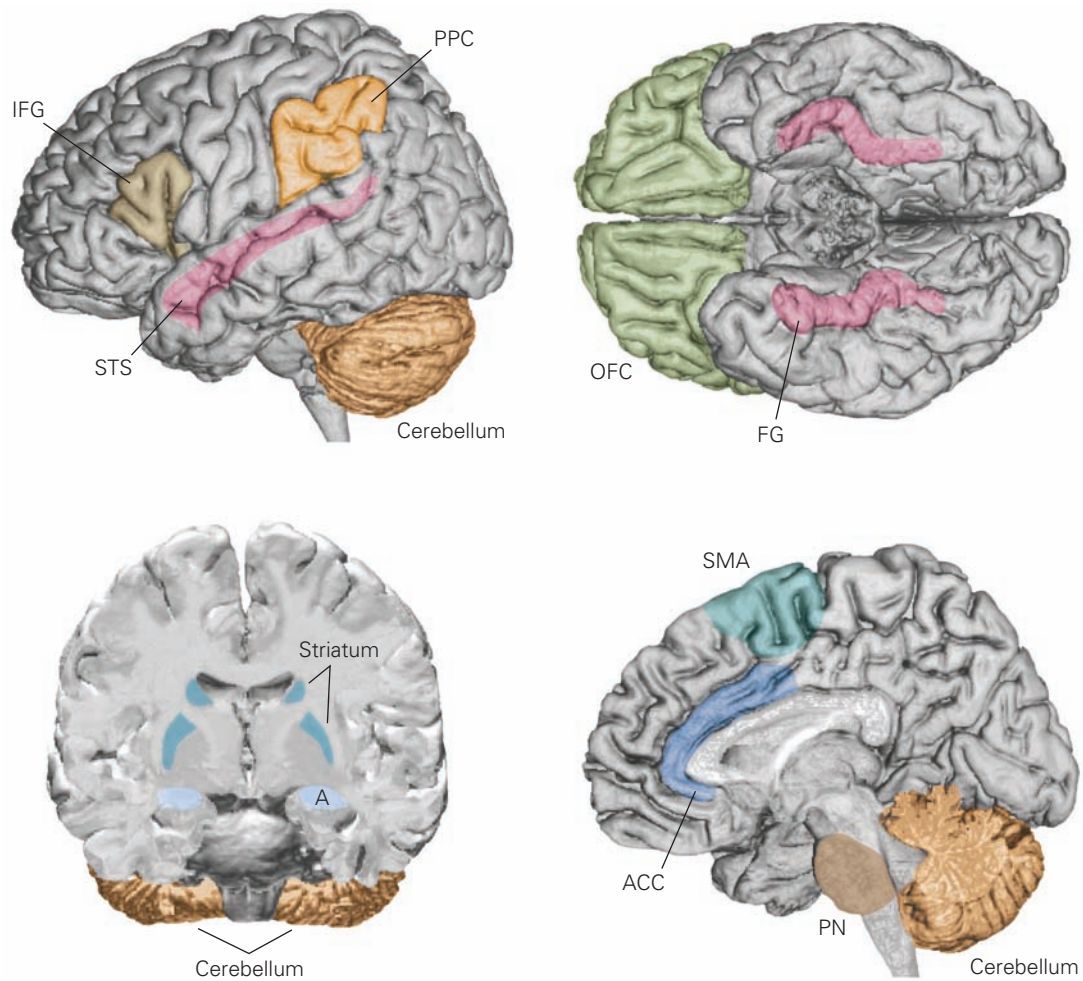

Figure 64–1 Brain areas implicated in the three core deficits characteristic of autism: impaired social interaction, impaired language and communication, and severely restricted interests with repetitive and stereotyped behaviors. Areas implicated in social deficits include the orbitofrontal cortex (**OFC**), 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. A number of imaging and postmortem studies have indicated that the cerebellum may also be pathological in autism.

years of life of autistic children. Most studies show that at birth the brains of children with autism are either of normal size or perhaps slightly smaller than typically developing children and this is true again in adulthood. Clearly, the development of the brain is a precisely orchestrated process; if one or more brain regions develop out of sequence, patterns of brain connectivity and thus brain function could be seriously disturbed.

Beyond the cerebral cortex, other brain regions also show abnormal development. Perhaps most striking is the amygdala, a region of the temporal lobe that is involved in the detection of dangers in the environment and in modulating some forms of social interaction (see Chapter 48). Interestingly, in typically developing boys the amygdala develops over an unusually long period, increasing in size by nearly 40% between the ages of 8 and 18 years. The rest of the brain actually decreases in size during this same time period by approximately 10% because of refinement of connectivity and function. For boys with autism the amygdala reaches adult size by eight years of age. Thus whatever refinement of connectivity takes place in typically developing preadolescent and adolescent children may not occur in boys with autism.

Many studies have gone beyond simply evaluating the volume of the brain or brain regions and have analytically broken down a region of the brain into compartments representing grey matter and white matter. Alterations in white matter volume may actually be a more sensitive indicator of pathology in autism than grey matter differences. In fact, some researchers have proposed that the enlarged brain volume that has been reported in young children with autism can be accounted for, in large part, by disproportionate increases in white matter volume. Thus some studies have found a larger volume of white matter in boys with autism aged 2 to 3 years compared to controls. Interestingly, this difference was not found in adolescence, further evidence of an abnormality of early development.

As these studies illustrate, autism is not a disorder that affects a single brain region. The amount and kind of brain pathology in a particular individual may depend on whether the etiology is more genetic or environmental. Finally, the pathology of autism may not be apparent in the mature size and shape of the brain but in the time course of development of both the structure and connections of the brain.

The picture of the neuropathology of autism at a microscopic level is also not clear. This is in part because of the paucity of brains available for analysis. To date fewer than 200 brains have been subjected to microscopic analysis, and only a small fraction of these have undergone quantitative analysis. Another problem is the co-morbid occurrence of epilepsy. Approximately 30% of individuals with autism also have seizure disorders, and seizures damage the amygdala and many of the other brain regions that have been implicated in autism.

One reasonably consistent finding in autism has been the lower number of Purkinje cells in the cerebellum. Gaps in the orderly arrays of Purkinje cells are noticeable when using neural stains that mark cell bodies. Whether this reduction in cell number is because of autism, epilepsy, or the co-occurrence of both disorders is not clear. It is also not clear whether reduced numbers of Purkinje cells are characteristic of autism or a more general finding in neurodevelopmental disorders. Cerebellar alterations have been found in cases of idiopathic intellectual disability, Williams syndrome, and many other childhood disorders. A few cases of alterations of brain stem nuclei that are connected to the cerebellum, such as the olivary complex, have also been reported.

Microscopic abnormalities have also been observed in the autistic cerebral cortex, including defects in the migration of cells into the cortex, such as ectopias, nests of cells in white matter that failed to enter the cortex. It has also been proposed that the columnar organization of the autistic cortex is abnormal. These provocative findings are awaiting confirmation in larger studies using quantitative strategies. Finally, one study found fewer neurons in the mature amygdala of people with autism. Because this study was carried out with individuals that did not have co-morbid epilepsy, the change in the amygdala looks to be a real component of autistic neuropathology. It raises the possibility that autism may have a neurodegenerative component to its pathology.

There Are Distinctive Cognitive Abnormalities in Autism

Social Communication Is Impaired: The Mind Blindness Hypothesis

One cognitive theory of social communication, termed *theory of mind*, postulates that humans have a particularly well-developed ability to attribute mental states to others in an intuitive and fully automatic fashion. Watching a young man surreptitiously trying to open a car door without a key, you instantly understand that he believes he can break in while being unobserved, and expect him to run away as soon as he realizes someone is watching. Thus you explain and predict his

behavior by inferring his mental states (desires, intentions, beliefs, knowledge). This so-called mentalizing ability is thought to have an identifiable biological basis and to depend on a dedicated brain mechanism. Further, it is postulated that this mentalizing mechanism is faulty in autism, with profound effects on social development.

It is now generally agreed that certain social insights typical of humans depend on the capacity to mentalize spontaneously. Spontaneous mentalizing allows us to appreciate that different people have different thoughts and that thoughts represent internal functions of the mind that are different from external reality. From an evolutionary point of view, the capacity to mentalize is extremely advantageous. It enables us to predict what other people are going to do next by "reading" their minds. It helps us to deceive and outsmart others, but also to teach and persuade, thus facilitating social and cultural learning.

The inability to mentalize, or "mind blindness," was first tested in autism with a simple puppet game, the Sally-Anne test. Young children with autism, unlike those with Down syndrome and unlike typically developing four-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 64–2). Many autistic children 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 autism show excellent appreciation of physical causes and events. For instance, the child who is incapable of deceiving a character (by falsely telling him that a box is locked), is quite capable of locking the same box to prevent the thief from stealing its contents.

Variations of the Sally-Anne test and other mentalizing tasks have been used with children and adults with autism and Asperger syndrome since the mid 1980s (Figure 64–3). Compared to people with low-functioning autism, people with Asperger syndrome do much better when tested on mentalizing tasks, but they still show subtle difficulties. Whereas they solve many of these tests through effortful mentalizing, they show a lack of automatic mentalizing. This can be assessed by eye gaze anticipation. In contrast, there is some evidence that typically developing infants as young as 7 months show spontaneous mentalizing, and there is wide agreement that this automatic ability is well established from the second year of life.

Functional neuroimaging studies have scanned the brains 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. The results indicate that mentalizing is associated with the activation of a network of specific brain regions.

In one positron emission tomography (PET) study healthy adults viewed silent animations of geometric shapes. In some of the animations the triangles move in scripted scenarios designed to evoke mentalizing (for example, triangles tricking each other). In other animations the triangles move randomly and do not evoke mentalizing. Comparison of the scans made while subjects viewed the two types of animations reveals a specific network of four brain centers involved in mentalizing (Figure 64–4). Confirming the earlier PET study, more recent fMRI studies using the same animations also showed that in autism this network has reduced activation and weaker connectivity between its components.

One component of this network, 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 involves the amygdala, which is involved in the evaluation of social and nonsocial information for indications of danger in the environment. The fourth region involves the inferior temporal region, which is known to be involved in the perception of faces. All these components have been implicated in brain abnormalities in autistic individuals.

Other Social Mechanisms Contribute to Autism

The mind blindness hypothesis attributes all impairments in social communication to an inability to imagine the mental states of others. It has thus been influential as an example of how a specific cognitive deficit that explains a range of behavioral symptoms can arise from a neurophysiological or anatomical abnormality in specific networks of the brain.

The absence of preferential attention to social stimuli and mutual attention are widely acknowledged as early signs of autism. However, these may be distinct problems independent of mentalizing, given that mutual attention normally appears toward the end of the first year when signs of mentalizing are still sparse. Researchers have been considering the possibility

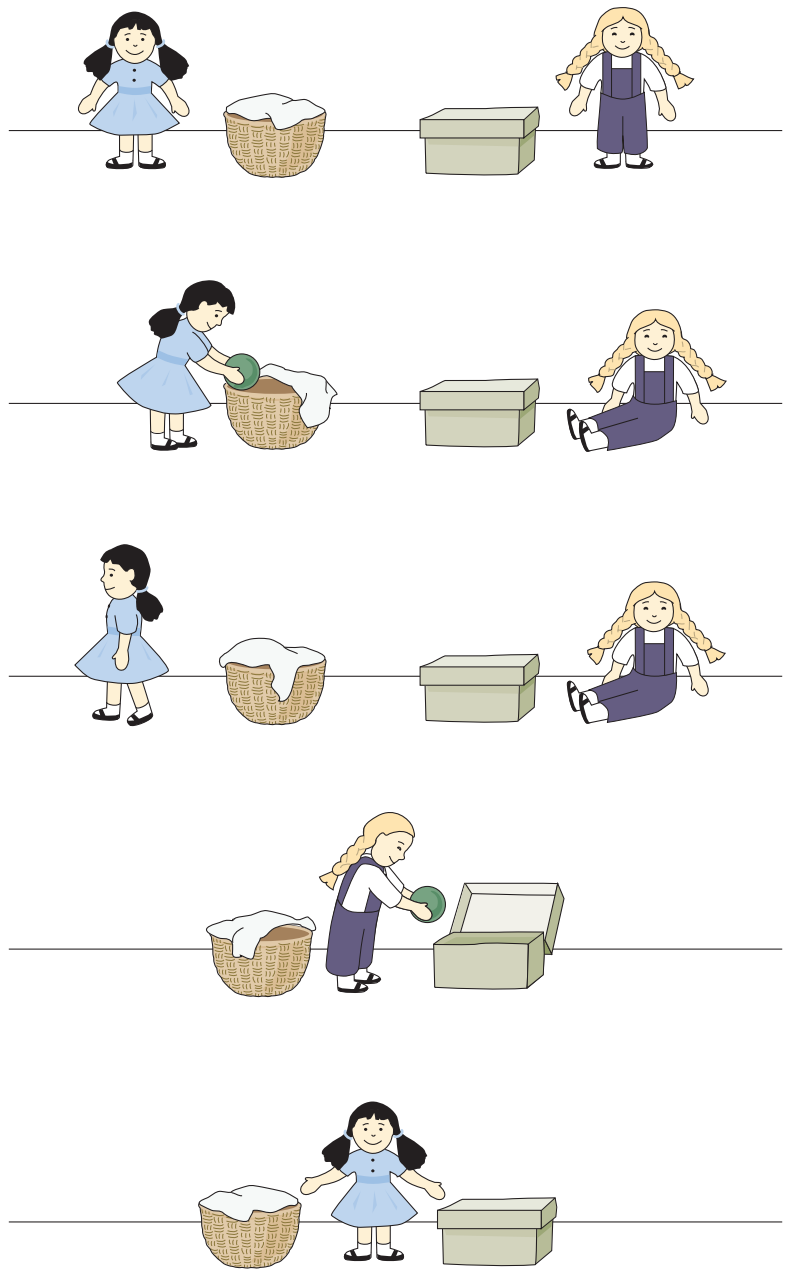

Figure 64–2 The Sally-Anne test. This first test of the "theory of mind" begins with a scripted performance using two dolls. Sally has a basket; Anne has a box. Sally puts a ball into her basket. She goes for a walk and leaves the room. While Sally is outside, naughty Anne takes the ball out of the basket 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 with permission, from Axel Scheffler.)

that a specific neural mechanism underlies attention to social stimuli, such as faces, voices, and biological motion. From birth normal infants prefer to attend to agents rather than other stimuli. An absence of this preference could lead to an inability to understand and interact with others. In favor of this hypothesis, researchers found that the gaze of individuals with autism is markedly abnormal when watching social scenes. One study found that autistic individuals fixate on people's mouths instead of the normal preference for eyes (Figure 64–5).

Imaging experiments have compared brain activity in autistic and normal subjects while they watch agents, their movements, their faces or voices. In these studies evidence has been accumulating in support of the idea that autistic individuals show atypical perception of eye movements, facial expressions, body gestures, and actions. This evidence implicates

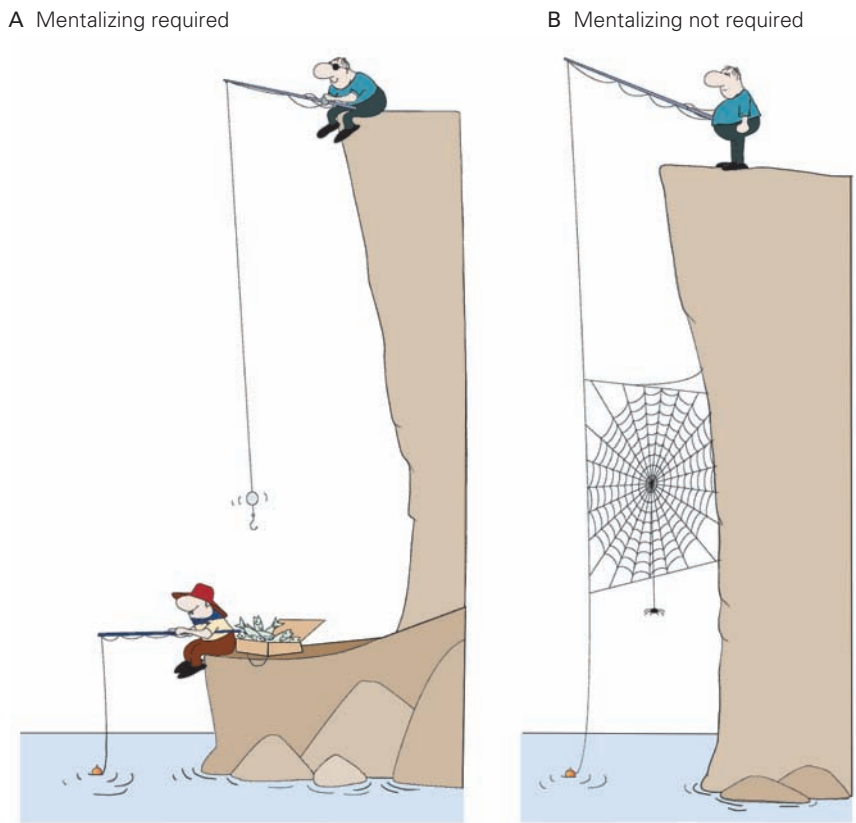

Figure 64–3 Examples of cartoons used in imaging studies of "mentalizing." Participants were asked to consider the meaning of each picture (silently) and then to explain them. In a functional magnetic resonance imaging (fMRI) study normal adults passively viewed cartoons that require mentalizing versus those that do not. A characteristic network of brain regions is activated in each subject (see Figure 64–4). (Reproduced, with permission, from Gallagher et al. 2000.)

the superior temporal sulcus region, a region of the brain that is known to have a role in the perception of intention of actions. In addition, frontal and parietal attentional brain systems that facilitate orientation to social stimuli appear to exert less top-down control in autism.

People with Autism Show a Lack of Behavioral Flexibility

Repetitive and inflexible behavior in autism may reflect abnormalities in the executive functions of the frontal lobe, a wide array of higher cognitive processes that includes the ability to disengage from a given task, to inhibit inappropriate responses, to plan and manage sequences of deliberate actions by staying on task, keeping multiple task demands in working memory, monitoring performance, and shifting attention from one task to another.

Even autistic individuals with normal or superior IQ have problems in planning, organizing, and flexibly switching between behaviors. Both low- and high-functioning individuals are stumped when asked to suggest different uses of one 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. In autism lack of flexible thinking appears to relate to a lack of behavioral flexibility in everyday life.

Difficulties in executive functioning are characteristic of other neurodevelopmental disorders: attention-deficit/hyperactive disorder, phenylketonuria, Tourette syndrome, dyslexia, and dyspraxia. For example, attention deficit hyperactive disorder is characterized by poor inhibitory control, whereas autism is characterized by poor flexibility, generativity, and planning. How the neural mechanisms underlying each of these difficulties differ is as yet unclear.

Some People with Autism Have Special Talents

One of the most fascinating features of autism is the existence of so-called "islets of ability", in at least 10% of the cases, in music, art, calculation, or memory.

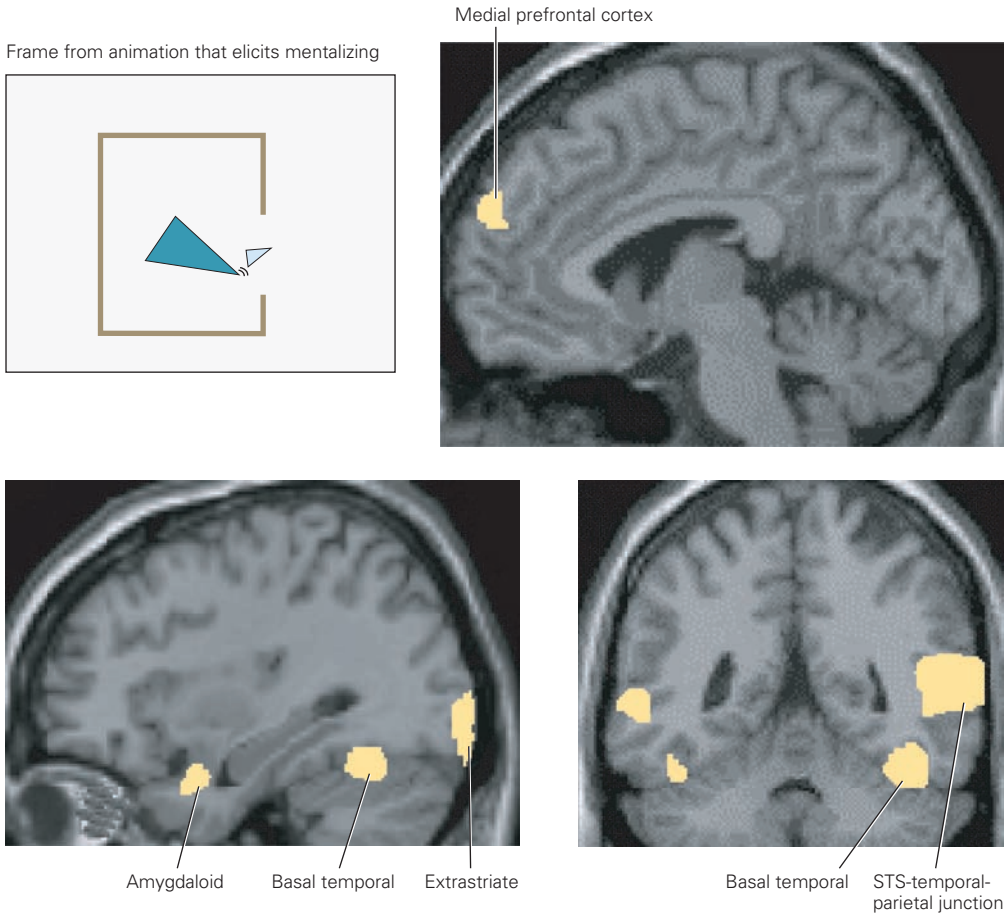

Figure 64–4 The mentalizing system of the brain. Healthy volunteers were presented with animated triangles that moved in such a way that viewers would attribute mental states to them. In the sample frame shown, the larger triangle was seen as encouraging the smaller triangle to leave the enclosure. They 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 (PET) scans of brain activation when these two viewing conditions were compared. (Reproduced, with permission, from Castelli et al. 2002.)

Figure 64–5 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.)

The frequency of superior rote memory for facts related to special interests is higher still. Approximately one-third of individuals with autism have perfect pitch, even when not musically trained. It is unknown what networks in the brain give rise to these phenomena.

One explanation for islets of ability is that information processing is preferentially geared to tiny details at the cost of seeing the bigger picture (the "weak central coherence" account). A similar idea is that brain regions involved in perception are over-functioning (the "enhanced perceptual functioning" account), and another idea is that there is a preference for processing details that suit "systemizing" such as calendar knowledge. Neuropsychological data support both explanations, but decisive experiments still remain to be done. The drawing by the gifted artist with high-functioning autism in Figure 64–6 shows beautifully detailed cityscapes, as well as detailed numerical patterns and dates.

Some Neurodevelopmental Disorders Have a Known Genetic Basis

It is generally accepted that 10% to 15% of individuals with autism have other known genetic diseases. Many of these diseases are developmental disorders leading to other phenotypes of intellectual or learning disability, which may overlap with autism.

Intellectual disability is generally defined as measurable intelligence substantially below the population mean that is associated with significant limitations in adaptive functioning before the age of 18 years. Adaptive functioning is defined as how well one copes, at a given age, with common demands of life and includes such things as communication, social and interpersonal skills, and self-care.

Intelligence is usually defined by the intelligence quotient (or IQ), as determined by a variety of

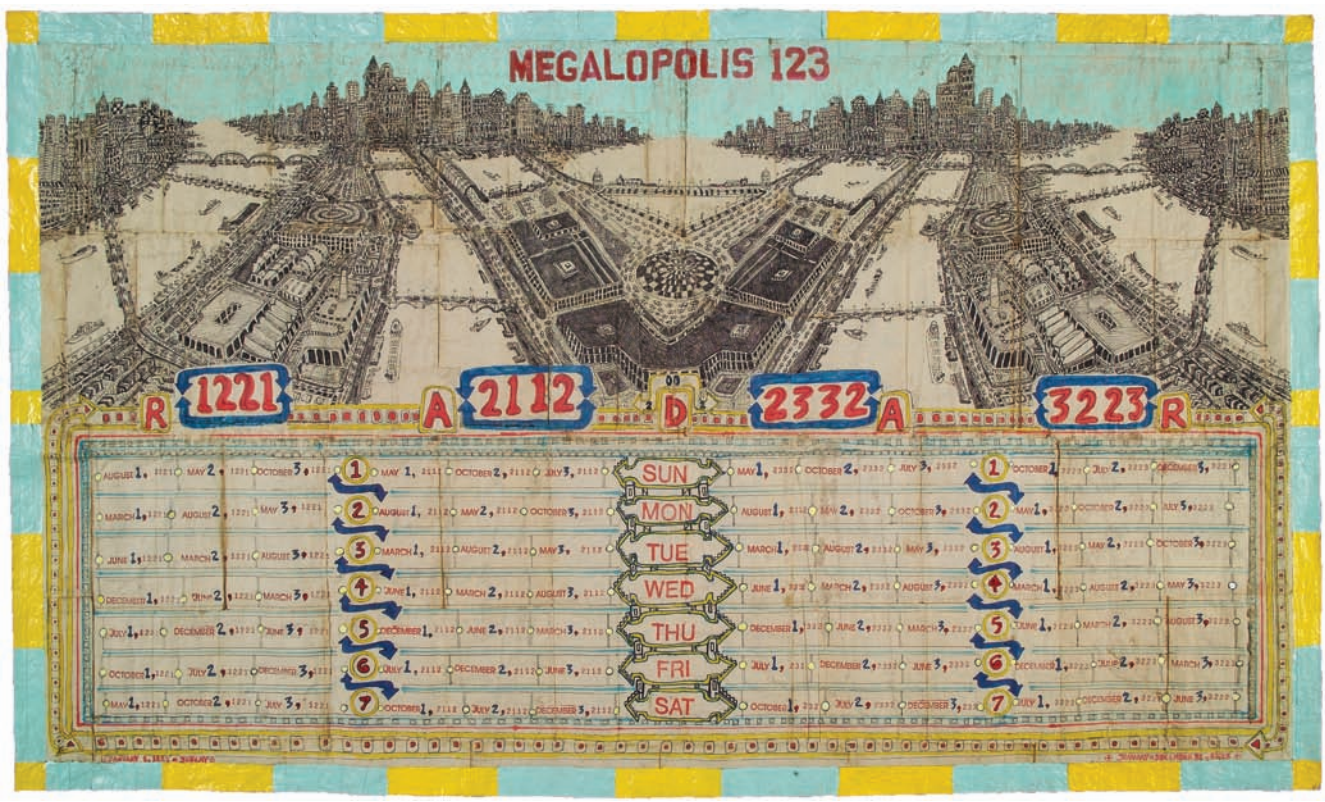

Figure 64–6 Strikingly beautiful art work by George Widener. He is a highly accomplished and much admired outsider artist. In the attention to detail this drawing resembles the drawings of other autistic savant artists. The intricate topographical detail of a symmetrically arranged city, with rivers, 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. www.outsiderart.co.uk.)

standardized tests, such as the Stanford-Binet or Wechsler Scales. These tests, in the general population, produce a range of scores that define a bell curve with the mean at 100 points. By definition an IQ below 2 standard deviations (below 70 points) is considered in the range of intellectual disability. Besides an IQ below 70, a person with intellectual disability also shows deficits in adaptive functioning. Like IQ, adaptive functioning is measured by standardized tests.

Fragile X Syndrome

Fragile X syndrome is a common form of chromosome X-linked intellectual disability. Patients show many similarities to autism, such as poor eye contact, a dislike of being touched, and repetitive behaviors. Its prevalence is approximately one in 4,000 boys and one in 8,000 girls. Estimates of the concurrence of autism and fragile X syndrome vary widely. In some early studies up to 25% of boys with autism were incorrectly diagnosed as having the fragile X syndrome. With the discovery of the gene for fragile X, diagnostic tests based on the genetic abnormality became available, lowering the percentage to approximately 3%. However, among children with fragile X syndrome, nearly 30% meet standard diagnostic criteria for autism.

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. As we have seen in Chapters 3 and 43, this expansion of trinucleotide repeats has since been recognized in other genes leading to neurological diseases, such as Huntington disease. When the number of CGG repeats exceeds 200, the *FMR1* gene becomes heavily methylated, and gene expression is shut off. Consequently, 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 renders messenger RNA dormant by blocking translation until protein synthesis is required. It is found at the base of dendritic spines together with ribosomes, where it regulates local dendritic protein synthesis that is needed both for synaptogenesis and for certain forms of long-lasting synaptic changes associated with learning and memory (see Chapters 66 and 67). Interestingly, a form of long-lasting synaptic change that requires local protein synthesis, the long-term depression of excitatory synaptic transmission, is actually 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 messenger RNAs (mRNAs) important for synaptic plasticity.

Indeed, mice lacking FMRP do not require new protein synthesis for the induction of long-term synaptic depression. An exciting implication of these data is that chemical antagonists of the type 5 metabotropic glutamate receptor, mGluR5, activation of which is required for this form of long-term depression, may lessen the excess protein translation and thus perhaps have a therapeutic benefit.

Rett Syndrome

Another single-gene disorder sometimes confused with autism is Rett syndrome, a devastating disorder that affects girls primarily. Affected children appear normal 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, a loss of motor control, and intellectual retardation. Girls with Rett syndrome can live into adulthood but never regain speech or the ability to use their hands. Its prevalence is approximately one in 15,000 girls.

Rett syndrome is an X-linked inherited disease caused by mutations in the *MeCP2* gene, which normally encodes a transcription factor that binds to methylated cytosine bases in DNA, thus regulating gene expression and chromatin remodeling. Although loss of *MeCP2* alters expression of a wide range of genes, an important contributing factor to the Rett syndrome phenotype may be the result of the reduced expression of the gene that codes for brain-derived neurotropic factor (BDNF). In mice reduced expression of this secreted neurotrophic factor leads to a phenotype much like the mouse model of Rett syndrome; overexpression of BDNF can substantially improve the phenotype in *MeCP2* mutant mice.

One might think that such a global abnormality in gene expression would lead to an even more severe phenotype than that of Rett syndrome. It turns out that one copy of *MeCP2* is essential for survival. Boys who have a single X chromosome and thus a single copy of *MeCP2* die prenatally or soon after birth of encephalopathy if they carry a mutant form of *MeCP2*. Although girls carry two X chromosomes, only one is active in any given cell. Because the choice of which X chromosome is active is random, girls with a *MeCP2* mutation on one X chromosome are mosaics: Some of their cells express the normal protein whereas others express the abnormal form. The cells with the normal protein

compensate and thus the phenotype develops into the Rett syndrome rather than the early lethal disease.

Down Syndrome

Down syndrome is the most common cause of birth defects in the United States and a major cause of intellectual disability. Each year approximately 100,000 infants worldwide are born with Down syndrome—approximately one in 1,000 births. Approximately 7% of children with Down syndrome also have autism.

Besides manifesting a characteristic set of facial and physical features, hypotonia, and congenital heart defects, Down syndrome is associated with cognitive defects and with early-onset Alzheimer disease. Among the cognitive deficits are poor spatial memory and difficulties in converting short-term to long-term memory. These memory defects are consistent with the fact that in individuals with Down syndrome the hippocampus is smaller than in typical development. The deficits are also the opposite of the exceptional short-term and long-term memory of many individuals with autism.

What are the specific genes that contribute to the cognitive symptoms of Down syndrome? Down syndrome results from the presence of an extra copy of chromosome 21 (trisomy of chromosome 21). Approximately 88% of these extra chromosomes are maternal in origin, 9% are paternal, and 3% occur at mitosis after fertilization. Studies of rare cases of partial trisomy of chromosome 21 suggest that the entire extra copy of the chromosome does not need to be expressed to have the full-blown syndrome.

A considerable part of the Down syndrome phenotype results from duplication of a 2-Mb region at segment 21q22.2 that contains 50 to 70 genes called *the critical Down region*. Examination of 27 transcripts that cover 80% of this region reveals several genes of potential interest for the cognitive deficit. These include a gene for two inwardly rectifying K^+ channels (*KCNJ6*, Homo sapiens potassium inwardly rectifying channel, subfamily J, member 6, also know as Kir3.2 or GIRK2) that are expressed in the developing and adult central nervous system, the gene for a kainate-type glutamate receptor mGluR5 (*GRM5*) which regulates a form of plasticity implicated in fragile X syndrome, the single-minded gene 2 (*SIM2*), and the gene for a dual-functioning protein kinase called *minibrain kinase* (*Mnbk*).

Prader-Willi and Angelman Syndrome and Other Disorders

Few errors that involve an entire chromosome are compatible with life. Among the autosomes, in addition to Down syndrome, only trisomy 18 and trisomy 13, each leading to severe intellectual disability, occur in an appreciable frequency, with a prevalence of one in 3,000 and one in 20,000 live births, respectively. Various numerical errors of the sex chromosomes occur but usually do not cause a significant degree of delay in cognitive development.

The only exception is Turner syndrome, which occurs in females missing an X chromosome. Girls who carry only the maternal X chromosome display a much higher prevalence of social-interaction difficulties similar to autism than do girls who carry the paternal X chromosome. This suggests genetic imprinting, where maternal and paternal copies of a gene are differentially expressed.

With imprinted genes, which represent only a small fraction (< 1%) of the genome, only one copy of the gene is expressed. In contrast, both the paternal and maternal alleles of nonimprinted genes are expressed. With paternally imprinted genes only the maternal allele is expressed. With maternally imprinted genes the opposite is true; only the paternally inherited allele is active. For example, with a maternally imprinted gene, either of the father's two alleles can be expressed in his children whereas the mother's alleles are silent. However, imprinting is reversible and is erased in the germ cells. Thus the same maternal alleles that are silenced in a mother's offspring can be active when they are transmitted by her son to his children.

Prader-Willi syndrome and Angelman syndrome, two related disorders with intellectual disability and possible connections with autism, are classic examples of imprinting. These two syndromes are usually caused by a specific deletion of the same region of chromosome 15 (Figure 64–7). However, individuals with Prader-Willi syndrome inherit the defective chromosome 15 from their father, whereas individuals with Angelman syndrome inherit the defective gene from their mother (see Chapter 3). Despite involving the same genetic mutation, the two syndromes have different symptoms. Prader-Willi syndrome is associated with mild intellectual disability, hypogonadism, and a hypothalamic abnormality that results in the inability to feel satiated from hunger, leading to morbid obesity. In contrast, Angelman syndrome is characterized by profound intellectual disability and an inappropriately happy demeanor with frequent laughing and smiling.

How can the same genetic deletion produce such different behavioral and physical changes? The answer lies in the differential patterns of imprinting of the paternal and maternal alleles of certain genes in this region of chromosome 15. If the paternal chromosome contains the deletion, as occurs in Prader-Willi syndrome, only

the maternal alleles are present. Thus any maternal alleles that are normally turned off because of imprinting will not be expressed in the offspring. Similarly, if the maternal chromosome contains the deletion, as occurs in Angelman syndrome, those genes that are normally turned off because of paternal imprinting will not be expressed in the offspring. Because different sets of genes are imprinted in males and females, individuals with Prader-Willi syndrome and Angelman syndrome have defects in expression of distinct sets of genes. Therefore, despite having similar deletions of chromosome 15, individuals with Prader-Willi and Angelman syndromes have completely different phenotypes.

Although Prader-Willi syndrome likely involves the loss of more than one imprinted gene on chromosome 15, the cause of Angelman syndrome has been narrowed to a single gene encoding the E3 ubiquitin ligase enzyme. Imprinted genes on chromosome 15 may also predispose for autism, as linkage studies have shown some positive signal from the proximal long arm of chromosome 15. Indeed, a significant number of individuals with autism, perhaps as many as 1%, have maternal duplications of a portion of proximal chromosome 15 immediately adjacent to the Prader-Willi/Angelman syndrome region.

Other chromosome deletions that produce cognitive changes do not involve imprinted genes. Such deletions simply reduce the normal level of that gene's protein product by approximately 50%, because of the loss of one of the two alleles. Half the normal amount of some proteins is insufficient to support normal cellular function (known as *haploinsufficiency*), resulting in a particular behavioral phenotype. Most often these deletions involve varying degrees of intellectual disability and sometimes produce striking neuropsychiatric phenotypes.

One such example is Smith-Magenis syndrome, which results from the deletion of a single band on the short arm of chromosome 17. The syndrome is characterized by mild to moderate intellectual disability and

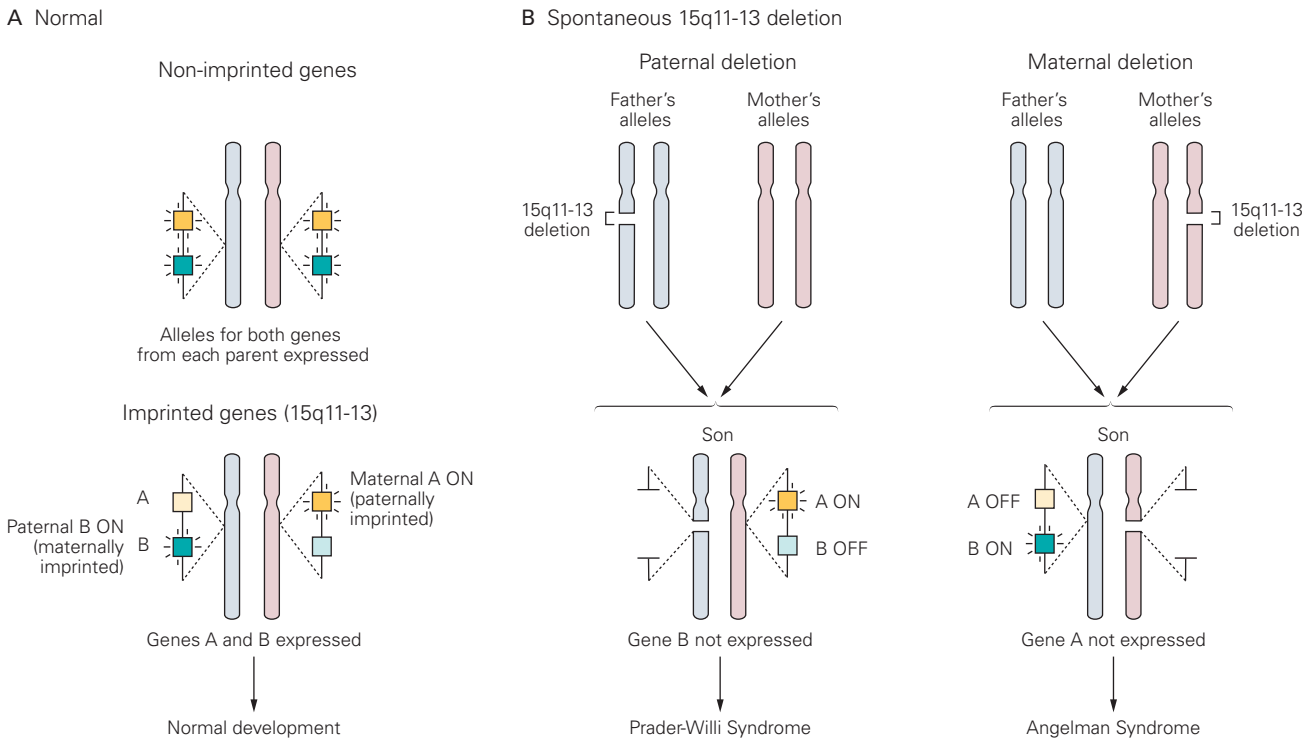

Figure 64–7 **Imprinting in Prader-Willi and Angelman syndrome.** Approximately 70% of Prader-Willi and Angelman syndrome patients inherit chromosome 15 from one parent with spontaneous (noninherited) deletions of the q11–13 interval. This interval contains imprinted genes with alleles that are either expressed or not depending on whether the chromosome was inherited from the father or mother. If the chromosome with the deletion is from the father, Prader-Willi syndrome occurs because maternally imprinted genes on the corresponding interval of the intact maternal chromosome (gene B, for example) are not expressed. If the chromosome with the deletion is from the mother, the gene for ubiquitin ligase (*UBE3A*) will not be expressed in offspring because of its normal inactivation on the paternal chromosome caused by imprinting; loss of expression of this gene leads to Angelman syndrome.

marked hypersomnolence. Smith-Magenis syndrome patients engage in a variety of unusual self-mutilations that they seem unable to resist, such as onychotillomania (self-mutilation of the finger and toe nails) and polyembolokoilomania (insertion of foreign objects into body orifices). They also repeat two stereotypic behaviors, spasmodically squeezing their upper body ("self hug") and hand licking and page flipping ("lick and flip"). What is most remarkable is that although most patients with Smith-Magenis syndrome have a 4-Mb deletion, four patients have been identified recently with a mutation in only one of the genes in this interval, *RAI1,* which is expressed in neurons. Once the function of *RAI1* becomes understood, it will be fascinating to consider how haploinsufficiency leads to the bizarre behaviors of Smith-Magenis syndrome.

Williams syndrome is also a segmental deletion but on the long arm of chromosome 7. Although no specific gene of the 25 to 30 genes within the deletion is singly responsible, the phenotype is nevertheless intriguing. Williams syndrome patients show specific dissociations of cognitive function, such as severe deficits in construction of visuospatial relations, yet have good language capabilities and do well in face recognition tests. However, the cognitive processes underlying these achievements differ from those used by typically developing children. Interestingly, Williams syndrome patients, regardless of family background and ethnicity, share somewhat similar personality traits marked by empathy and overfriendliness, making this syndrome in many ways the opposite of the stereotype of autism.

Probably hundreds of genes can lead to intellectual disability when mutated. Many of them encode proteins whose roles are central to brain development and function. For example, a form of lissencephaly ("smooth brain"), the loss of convolutions and gyri in the cerebral cortex, results from the mutation or deletion of the gene *LIS1,* which encodes a protein that normally participates in the regulation of cytoplasmic dynein heavy chains, which are essential for axonal transport (see Chapters 4 and 53). Intellectual disability also results from mutations of at least three genes with products that interact with Rho GTPases, leading to disruptions in signaling from the cell surface to the actin cytoskeleton that presumably alter neurite outgrowth. Mutations in Rab GTPases, which participate in vesicle fusion, also can lead to severe intellectual disability.

Other gene defects have much more subtle impacts on the nervous system and behavior. For example, Tony Monaco and co-workers studied an extended family, KE, in which a severe speech and language disorder is transmitted as an autosomal dominant condition because of a mutation in the gene *FOXP2*, which codes for a transcription factor. The *FOXP2* mutation causes faulty selection and sequencing of fine orofacial movements necessary for articulation, resulting in deficiencies in language processing and grammatical skills. *FOXP2* mutations have also been found in unrelated individuals with similar language deficits. Interestingly, nucleotide substitution rates in the *FOXP2* gene between species, a measure of evolutionary change, are accelerated in primates, suggesting that this gene had been a target of natural selection, possibly playing a significant role in the evolution of language in humans.

An Overall View

The study of neurodevelopmental disorders via cognitive neuroscience clearly illustrates the power of the synthesis of cognitive psychology and neuroscience and in fact moves this convergence into new directions. In the study of autism, for example, the mind blindness hypothesis has shown how cognitive theory can direct the search for the neural basis of a developmental disorder and how biological studies can open up a new window: the biology of social interactions.

A full understanding of the neurobiological basis of the many neurodevelopmental disorders that lead to intellectual disability will require the convergence of neuroscience, other medical disciplines, and functional genomics. A bottom-up approach—progressing from the identification of genes responsible for cognitive or behavioral disorders to an understanding of their effects on brain development—will clearly be crucial. At the same time, a top-down approach is needed, identifying the specific cognitive profile of each disorder and defining the critical neural circuits involved, using tools such as functional and structural brain imaging.

Autism is an example of a genetically complex disorder with a wide spectrum of manifestations, and the large differences between individual cases are often commented upon. Nevertheless, cognitive neuroscience has made advances in the difficult task of phenotyping patients and has helped pinpoint relevant brain regions and abnormal connections between them. This knowledge should be helpful in identifying the genetic and environmental risk factors that predispose to autism. Other developmental disorders that involve learning disabilities, especially those with much clearer patterns of inheritance than autism, are better suited to a bottom-up approach that begins with gene identification. Regardless of the approach,

the underlying mechanisms that lead to cognitive and behavioral impairment in humans are most likely to be uncovered by research that combines cognitive psychology, neuroscience, and molecular genetics.

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