Introduction

Autism as a specific syndrome was first described in the scientific literature in 1943 by Leo Kanner, a preeminent child psychiatrist at Johns Hopkins University (Kanner, 1943). Drawing from his wealth of experience about early psychiatric and developmental disorders, he identified a set of common features among 11 children seen over a 5-year period that set them apart, and “... whose condition differed so markedly and uniquely from anything reported so far” (p. 217). His first paper described the presenting “fascinating peculiarities” of these 11 children, and his later papers followed their development over time.

Kanner described a range of individual differences in the language ability among the children, but also a set of core features, the most important of which was “the children’s inability to relate themselves in an ordinary way to people and situations from the beginning of life” (p. 242). The parental phrases that he quoted — “happiest when left alone, acting as if people weren’t there, oblivious to everything around him” — are phrases that parents today still use to describe their children during diagnostic evaluations.

Kanner (1971) followed 9 of these 11 children into adulthood. There was some improvement in all symptoms during the school-aged period. Yet all of the individuals continued to lack normal social relations and only two adults were eventually employed, although still single and living with their parents.

Hans Asperger, a German pediatrician, wrote a paper in 1944 (Asperger, 1944) that echoed many of Kanner’s descriptions, although it was not available to readers of English for a number of years. Asperger also used the term “autistic” to refer to his patients and also emphasized that impairment in social integration was primary to the disorder and lifelong, affecting the child’s relations to his or her whole environment. Like Kanner, Asperger emphasized that this difference was present from early in life, and not a progressive event as seen in schizophrenia. He underscored the pervasive nature of the condition: “it totally colours affect, intellect, will, and action” (p. 39). However, Asperger described a degree of loquaciousness, intellectual ability in math and reading, and aggression and conduct problems. The latter do not figure prominently in Kanner’s patients, perhaps due to differences in age and functioning levels of the two groups of patients. Unlike Kanner, Asperger also described an abnormal relation to objects, involving abnormal fixations, collections, and lengthy monologues about these special interests.

Both Kanner and Asperger commented on the individual differences and range of levels and outcomes seen in their patients and attributed this to biological variation in the condition. Both were also of the view that there was a strong genetic contribution. Kanner, in particular, foresaw that the prevalence of autism would increase as the field learned how to differentiate it from other developmental and childhood psychiatric conditions.

Epidemiology of Autism

The current rate of autism in the population has been a cause for marked concern and focused research from many different perspectives, including brain science, toxicology, education, and social policy. Prevalence estimates have increased in the past 15–20 years from a widely accepted figure of 5 cases per 10,000 to current estimates of 1 in 50 for autism spectrum disorders (Chakrabarti & Fombonne, 2005; Blumberg et al., 2013) (Figure 23–1).

While some reasons for the change are understood, others are not, fueling both concern within the parent community and scientific interest in the biologies of autism. Some of
the change is clearly artifactual, due to increased sensitivities in diagnosis (Fombonne, 2005; Newschaffer et al., 2007) and the widening of diagnostic definitions. While definitions of autism 20 years ago reflected the more classic and severe presentation of the disorder, the DSM-IV-TR classification system (American Psychiatric Association, 2000) used until May 2013 included a set of Pervasive Developmental Disorders with classifications for both children who met full criteria for autistic disorder (AD) and those who did not meet these stringent criteria and were classified instead with Asperger disorder, and the even less specified diagnosis of pervasive developmental disorder – not otherwise specified (PDD-NOS). At present the DSM-5 uses the umbrella term of autism spectrum disorders and the aforementioned individual diagnoses (i.e., Asperger and PDD-NOS) are no longer retained (American Psychiatric Association, 2013).

A number of epidemiological studies have examined the prevalence of children diagnosed with PDD-NOS and found it to be higher than those with AD (Baker, 2002; Yeargin-Allsopp et al., 2003; Chakrabarti & Fombonne, 2005). Thus, including both of these diagnostic groups would more than double prevalence rates. Therefore, subjects counted in more recent prevalence studies include many who would not have been counted based on earlier diagnostic definitions of autism.

Social practices have also affected autistic spectrum disorder (ASD) screening and diagnosis. Due to public policies involving educational practices for children with ASD, more special education services and other types of supportive and habilitative services have become available. Such interventions often have diagnostic criteria for inclusion and thus have led to greatly increased use of differential assessments that identify autism, particularly in school-aged and younger children, when the symptoms are clearest. Greater diagnostic attention has likely identified many more cases (Gurney et al., 2003; Chakrabarti & Fombonne, 2005).

A variety of biological causes have also been suggested to account for some of the increasing prevalence rates of autism spectrum disorders. Increased use of fertility treatments; interactions between immune abnormalities in mother or child and exposure to immune challenges in the uterine or postuterine environments; and air and environmental pollutants such as heavy metals and PCBs (Newschaffer et al., 2007) have increased significantly in the past decade. Most important, understanding the changing prevalence rates is frustratingly limited at this time by our lack of knowledge of the underlying biologies of autism.

**Diagnosis and Behavioral Features**

**Core Behavioral Features of Autism**

The first key features Kanner described were that his patients were oblivious to the social world, not unaware but uninterested. They ignored speech to such an extent that some were considered to be deaf, although none had a hearing impairment. The children ignored the comings and goings of their parents, the presence of strangers, and the presence of other children (Kanner, 1943). Kanner described what is now considered to be the most severe form of a continuum of impairment in reciprocal social relatedness. Wing (1981) has suggested three main types of relatedness impairments in ASD: aloof (as Kanner described), passive (responsive to others’ interactions but not initiating interactions themselves), and active but odd (clearly interested in social interaction but very unusual in the way they go about it).

Children demonstrate social reciprocity in a variety of ways, including patterns of eye gaze, shared emotional expressions, social body postures, and gestures. This capacity is present in human development from the first few months
DSM-5 overlapping symptoms were combined into one category: communication and social problems. There are three subdomains of social and communication problems that a person needs to have in order to qualify for an ASD diagnosis: social-emotional reciprocity, nonverbal communication used for social interaction, and deficits in developing and maintaining relationships, appropriate to developmental level. These criteria along with those for restrictive and repetitive behaviors (in at least two of four subdomains) include a “sliding scale” to gauge the personal severity of symptoms from mild to severe. Restrictive and repetitive behaviors also include hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of environment. Symptoms must be present in early childhood but may not become fully manifested until social demands exceed the limited capacities of the individual.

Rett syndrome is generally not currently considered part of the autism spectrum disorder group. Rett syndrome is a single gene mutation involving the MECP2 gene. It affects mostly girls, is progressive in its course, and results in very severe intellectual impairment and profound disability in all areas of functioning over time. While the surface features of Rett syndrome may resemble AD at its early stages, it differs in many symptoms, in onset patterns, in course, and in response to treatment.

Despite differences to other autism spectrum disorders (e.g., acuity and severity of regression) the condition of childhood disintegrative disorder is still considered part of the autistic continuum under DSM-5. Childhood disintegrative disorder is a very rare condition in which a fairly rapid regression occurs, generally between the third and fifth years, in children previously developing typically. The regression is marked by a dramatic loss of language abilities, onset of motor abnormalities, severe anxiety, and profound changes in social engagement and activities. After an initial regression, the functioning level stabilizes, and after that point children appear indistinguishable from other children with fairly severe AD and intellectual deficits (Volkmar & Klin, 2005).

Diagnostic Practices, Tools, and Problems
The diagnosis of autism spectrum disorders is made from three types of diagnostic procedures: a detailed history from parental interviews; parental description of current functioning in typical situations; and clinical observation and assessment of the child’s behavior. Recent developments in assessment tools have made the diagnosis of autism much more reliable. In fact, the diagnosis of AD among experienced clinicians has the highest rate of Interrater agreement and the most stability of any of the psychiatric diagnoses. However, as with any behavioral disorder, diagnostic agreement is strongest in the moderate range of symptoms. There is less Interrater agreement at the mildest end of the autism spectrum disorders, and in the end where very severe intellectual deficits are also present (Lord, 2005).

Unlike most other psychiatric and developmental diagnoses, autism is diagnosed from infancy through adulthood, and in people who range from intellectual impairment to normal and gifted intellects. This large range of functioning within autism results in very few tools that can discriminate autism at all ages and all functioning levels. Clinicians need to choose diagnostic instruments accurately that will best differentiate autism from other diagnostic conditions (Lord, 2005). The most common tools for ascertaining autism spectrum disorder participants in research...
studies include the autism diagnostic inventory (ADI-R), an experimenter-administered interview; the social communication questionnaire, a parent questionnaire with key questions from the ADI-R; the autism diagnostic observational scale (ADOS), an interactive semistructured interview with the child or adult being diagnosed; and the childhood autism rating scales (CARSs), an examiner behavior rating system completed after a developmental evaluation.

Medical and Other Comorbid Features
As the prevalence of autism spectrum disorders has increased over the past two decades, parents, clinicians, and researchers have attended to a variety of common comorbid symptoms. Some of these were already described, at least in some form, by Kanner and Asperger.

Seizures
While epilepsy has long been associated with autism spectrum disorders, the proportion of patients reported to demonstrate comorbid seizure disorder varies from 5% to 44% (Tuchman & Rapin, 2002). A recent study (Hara, 2007) carried out a follow-up of 135 patients with idiopathic autism. Of these, 33 (25%) exhibited epileptic seizures, which had an onset between 8 and 26 years of age. Two types of seizures were observed: partial seizures with secondary generalization (in 61%) and generalized seizures. While 18% of the non-epileptic group exhibited epileptic discharges on EEG, 68% of the epileptic group revealed epileptiform EEG findings before the onset of epilepsy. Some studies have found an association between low IQ and the occurrence of epilepsy (Pavone et al., 2004) or low IQ and motor deficit and epilepsy (Tuchman et al., 1991). As in the Hara (2007) study, abnormal or epileptiform EEG is also observed in substantial numbers of individuals with autism who do not have seizures (Tuchman et al., 1991; Tuchman & Rapin, 1997). While the presence of seizure disorder and its association with other aspects of autism may provide interesting clues to the underlying pathophysiology, it remains unclear to what extent epileptiform activity is a core attribute of autism spectrum disorders.

Anxiety
In Kanner’s (1943) original description of autism, he noted unusual fear or anxiety in several of his young patients. One child, Herbert, was “tremendously frightened by running water, gas burners, and many other things.” He became upset by any change of an accustomed pattern. “If he notices change, he is very fussy and cries.” Another child did a “good deal of worrying.” He was upset because the moon did not always appear in the sky at night. He preferred to play alone and would get down from a play apparatus as soon as another child approached. Insistence on sameness leads children with autism to become greatly distressed when anything is broken or incomplete, and they demand consistency in the sequence of daily events. Kanner noted that although many individuals with autism learn to tolerate changes in routine and interactions with other people in their environment as adults, these interruptions cause a great deal of anxiety in young children with autism. Social interactions with other people are an unwelcome intrusion to the child with autism. When social interaction is forced upon the child, Kanner observed that the child, with a great deal of anxiety, will either ignore the person attempting to interact or quickly answer to end the intrusion. This aspect of autism, although consistently described by parents (Gurney et al., 2006) and included as a feature in the DSM-5, has not been extensively studied.

Muris and colleagues (1998) examined the presence of co-occurring anxiety symptoms in 44 children diagnosed with autism or pervasive developmental disorder. Using parental reports, they found that 84.1% of the children met criteria for at least one anxiety disorder. Gillott et al. (2001) compared high-functioning children with autism to two control groups including children with specific language impairment and normally developing children on measures of anxiety and social worry. Children with autism were found to be significantly more anxious on both indices.

Gastrointestinal Disorders
Children with autism have a higher incidence of gastrointestinal (GI) problems than typically developing children or children with developmental delays (Valicenti-McDermott et al., 2006). GI problems are a common complaint of parents of children with autism and have been one of the factors that have prompted the use of complementary and alternative medicines (Harrington et al., 2006). Autistic individuals seem prone to gastrointestinal complaints as a result of behaviors leading to constipation and feeding issues/food selectivity (Ibrahim et al., 2009). A number of clinicians have emphasized the need to investigate GI problems, particularly in low-functioning children who are unable to communicate their distress and for whom alleviation of the GI condition may appreciably improve the quality of life.

Autoimmune Disorders
Immune dysfunction may play an important role in a subset of autism spectrum disorder cases (van Gent et al., 1997). Some patients with autism spectrum disorder demonstrate abnormalities and/or deficits of immune system function leading to inappropriate or ineffective immune response to pathogen challenge (Ashwood & Van de Water, 2004b). For example, children with autism spectrum disorders often have recurrent infections (Stern et al., 2005), peripheral immune abnormalities (Singh, 1996; Croonenberghs et al., 2002; Ashwood et al., 2003), or neuroinflammatory responses in the central nervous system (CNS) (Vargas et al., 2005). In addition to general immune system dysfunction, recent evidence suggests that certain forms of autism are associated with an autoimmune condition (Ashwood & Van de Water, 2004a,b). Autoimmunity occurs when the immune system inappropriately identifies and reacts to “self” components. Antibodies produced during an autoimmune response play a critical role in the pathogenesis of several peripheral neurological diseases, including myasthenia gravis, Lambert–Eaton myasthenic syndrome, and neuromyotonia (Lang & Vincent, 2003; Lang et al., 2003a,b; Newsom-Davis et al., 2003; Scoppetta et al., 2003). Autoimmunity may also play a role in CNS diseases, notably psychological and neural disorders associated with streptococcus (PANDAS), which accounts for a subgroup of childhood-onset obsessive–compulsive disorders (OCD) and tic disorders (Snider & Swedo, 2003). Several studies have also reported that autoimmune disorders
are more common in family members of ASD patients compared to typically developing controls. Mothers and first-degree relatives of children with autism are more likely to have an autoimmune disorder (16% and 21%) than controls (2% and 4%) (Comi et al., 1999). Similar results were obtained in a study of autoimmune disorder frequency in families that have children with pervasive developmental disorders, including autism (Sweeten et al., 2003). A recent study of 308 children with ASD reported that regression in autism was significantly associated with a family history of autoimmune disorders (Richler et al., 2006). In this section of the chapter, we address developmental and genetic mechanisms that are likely to participate in autism.

Implicated in the Etiology of Autism

There is growing consensus that autism is caused by multiple mechanisms that derail development of the brain (Belmonte & Bourgeron, 2006; Happe et al., 2006; Moldin & Rubenstein, 2006; Moldin et al., 2006; Freitag, 2007; Gupta & State, 2007). In this section of the chapter, we address developmental and genetic mechanisms that are likely to participate in susceptibility to autism.

Autism affects boys roughly fourfold more often than girls, a key observation whose mechanism remains a mystery. Based on the concordance rates from early studies in monozygotic twins (∼2% of multiplex cases and 1% of controls (Sebat et al., 2007). The mechanisms that cause these copy number variations are unknown, but paternal age contributes to autism risk (Reichenberg et al., 2006); perhaps increasing age leads to the accumulation of these de novo germline mutations.

The clinical and neuroanatomical features provide boundary conditions for considering the genetic and developmental underpinnings of autism. Autism is probably caused by defects in neural systems that process social information, language, and sensorimotor integration. The components of the neural systems required for these complex behaviors are beginning to be understood, yet much work needs to be done. Neural system lesions can be localized or distributed (Rubenstein, 2006). A localized lesion that weakens or disables one component of a circuit can impede the function of the entire circuit, generating a behavioral phenotype. This phenotype can likewise be generated by defects in another component of the same circuit. Thus, related behavioral syndromes can be generated by a variety of anatomical defects.

Distributed lesions can be caused by defects that are common to many regions of a given neural system, or to multiple neural systems. For instance, mutation of a gene that is broadly expressed, such as that causing fragile X intellectual disability (FRAXA; FMR1), Rett syndrome (MeCP2), and tuberous sclerosis (TSC1&2), will disrupt neural function throughout the nervous system, weakening neural processes such as synaptic transmission or synaptic plasticity. Localized lesions are exemplified by mutation of genes that are expressed in neurons that share common features (such as neurotransmitter type or participation in a common circuit). For instance, members of the Dlx homeobox gene family (which encode transcription factors) are expressed during development of most forebrain GABAergic neurons, and some Dlx genes are expressed in mature forebrain GABAergic neurons (Cobos et al., 2005). Mutations that simultaneously block the function of pairs of mouse Dlx genes disrupt development of most forebrain GABAergic neurons (Anderson et al., 1997). This has the potential to disrupt the cortex–basal ganglia–thalamus–cortex circuit, through defects in cortical GABAergic local circuit neurons, basal ganglia GABAergic projection neurons, and the GABAergic thalamic reticular nucleus. Furthermore, individual Dlx genes (e.g., Dlx1) are required for function and survival of maturing cortical interneurons; loss of Dlx1 function can result in epilepsy (Cobos et al., 2005). Mutations in the Dlx genes have been detected in autistic individuals, although it is unknown whether these alleles contribute to the disorder (Hamilton et al., 2005).

Developmental defects can alter the connectivity between regions or the function within a given region and thereby derail neural systems. Interregional connectivity defects can be caused by alterations in axon pathfinding and
synapse choice. It is not known whether these types of abnormalities are found in autism, although there is evidence for connectivity defects from functional imaging studies (Just et al., 2004; Kana et al., 2006). Below, we briefly review salient information about genes whose functions are linked to autism. We have organized this information according to known functions of these genes, although many of these genes have functions that are not limited to their assigned categories.

Signal Transduction

Tuberous Sclerosis (TSC1&2) and PTEN

Children with TSC (autosomal dominant) have greatly increased rates of autism (25–50%), epilepsy, and intellectual disability (Wizinietzter, 2004). TSC1 (hamartin, 9q34) and TSC2 (tuberin, 16p13) encode GTPase-activating proteins that inhibit the activity of the small G-protein Rheb. TSC1/TSC2 are tumor suppressors by reducing activity of mTOR kinase (Inoki et al., 2005). mTOR promotes protein synthesis and other processes that increase cell growth.

TSC1/TSC2 are integral regulators of signal-transduction cascades downstream of signaling pathways that activate receptor tyrosine kinases (Inoki et al., 2005). These signals activate a family of phosphatidylinositol lipid kinases (phosphatidylinositol-3 kinases, PI3K) that in turn activate the serine-threonine kinase AKT, which then represses TSC1/TSC2 (Inoki et al., 2005). TSC1/TSC2 are also regulated by intracellular amino acid concentration and by the ATP/AMP ratio—the end product of this regulation is to promote appropriate levels of protein synthesis and cell size (Inoki et al., 2005).

While TSC patients develop focal CNS lesions (tubers), it is likely that the general function of TSC1&2 in most neurons underlies the autistic symptoms. For example, reduced TSC dosage in hippocampal pyramidal neurons results in increased size of the cell body and dendritic spines (Tavazoie et al., 2005). This is intriguing given the increased size of the brain in some children with autism.

Further clues that implicate this signaling cascade in autism come from the observation that some patients with mutations in the phosphatidylinositol phosphatase (PTEN; 10q23.31) have autism with macrocephaly (Butler et al., 2005). PTEN reduces activity of the PI3K pathway through dephosphorylation of phosphatidylinositol-tris-phosphate. Mice lacking CNS function of PTEN have increased signaling through the serine-threonine kinase AKT, TSC, and mTOR pathway (Kwon et al., 2006). These mutants have enlarged brains that are associated with increased dendritic and axonal arbors and increased dendritic spines and synapses. PTEN mutant mice also exhibit abnormal social behavior, further implicating this signaling pathway in autism (Kwon et al., 2006).

Met Tyrosine Kinase (MET)

MET encodes a receptor tyrosine kinase (7q31) that is an oncogene which mediates hepatocyte growth factor signaling. MET plays an important role in neuronal migration in the forebrain and cerebellum, as well as in immune and GI function. Mouse knockout mutants have reduced numbers of cortical interneurons and a hypoplastic cerebellum. Campbell et al. (2006) identified a common functional allele in the promoter region of the MET gene that is associated with autism.

Control of Translation

Fragile X (FRAXA; FMR1)

Mutations that reduce expression (usually through CGG triplet expansion) of this X-linked gene (Xq27.3) cause intellectual disability, and about 30% of these boys have autistic symptoms (Belmonte & Bourgeron, 2006). In humans and mice, FMR1 mutants have dendritic spines that have an immature morphology (too long and thin). This may result from the fact that FMR1 encodes an RNA-binding protein whose functions include translation regulation in dendrites. Indeed, activation of metabotropic glutamate receptors leads to FMR1-regulated protein synthesis in dendrites. This includes production of proteins, such as PSD-95, that participate in excitatory synaptic transmission (Todd et al., 2003; Bear et al., 2004). Thus, FMR1 functions at least in part through transducing excitatory synaptic signals into changes in the protein constituents that modify synaptic function and structure.

Synapse Formation and Function

Neuroligins (NLGN3 and NLGN4)

Neuroligins encode plasma membrane proteins that are implicated in regulating synapse development through binding neurexin proteins (Varoqueaux et al., 2006). Specific combinations and splice forms of neuroligin/neurexin proteins can specify whether an excitatory or an inhibitory synapse will form (Chih et al., 2006). In rare cases of autism, mutations in two X-linked neuroligins (NLGN3 and NLGN4; Xq13 and Xp22.33, respectively) have been found (Jamain et al., 2003). Furthermore, a de novo deletion in neurexin1 (NRX1) has recently been identified in a pair of affected siblings.

SHANK3 (ProSAP2)

SHANK3 (22q13.3) encodes a protein associated with the postsynaptic density of excitatory synapses and can promote dendritic spine maturation. Rare missense mutations in SHANK3 have been identified in autistic individuals (Durand et al., 2007). Furthermore, this region of chromosome 22 is a site of recurrent deletions in autism (Sebat et al., 2007).

Neurotransmitters/Neuromodulators

Oxytocin and Vasopressin Receptors (OXTR; AVPR1a)

Oxytocin and vasopressin peptides are neuromodulators expressed by neurons in the hypothalamus and the amygdala. These neuropeptides have been implicated in the mediation of certain social behaviors (Young et al., 2005) and the receptors for oxytocin (OXTR; 3p25–p26) and arginine vasopressin 1a (AVPR1a; 12q14–15) are associated with autism (Wu et al., 2005; Yirmiya et al., 2006).

Serotonin Transporter (SLC6A4)

Serotonin has potent effects on many behavioral and developmental processes. One of the earliest biochemical indications that serotonin metabolism may be altered in autism was the finding of an increase in serum serotonin levels in approximately 30% of individuals with autism (Cook et al., 1993a). Although this is not a specific diagnostic finding, it increases the potential importance that some alleles of the serotonin transporter gene (SLC6A4, SERT; 17q11.2) might be associated with autism (Sutcliffe et al., 2005; Brune et al., 2006).
Ion Channels

**Calcium and Sodium Ion Channels (CACNA1C, CACNA1H, SCN1A, and SCN2A)**

Missense mutations in the L-type (CACNA1C, Cav1.2; 12p13.3) and the T-type (CACNA1H, Cav3.2) calcium channels have been identified in rare cases of autism (Splawski et al., 2004, 2006). Similarly rare missense mutations have been identified in two sodium channel genes (SCN1A; 2q24; SCN2A; 2q23–q24.3) (Weiss et al., 2003).

**Metabolic Genes**

**Phenylalanine Hydroxylase**

Historically, the finding that autism is highly associated with phenylketonuria (PKU – hyperphenylalaninemia) was one of the turning points in establishing a biological etiology of autism (Cohen et al., 2005). There are several hundred alleles of phenylalanine hydroxylase (12q23.2) (www.pahdb.mcgill.ca), many of which can cause PKU in the homozygous phenotype. Interestingly, relatively little is known concerning the neuropathology of PKU-associated autism; and, the condition is now relatively rare due to neonatal screening and dietary treatment.

**D7-Dehydrocholesterol Reductase**

Smith–Lemli–Opitz Syndrome (SLO)

The Smith–Lemli–Opitz (SLO) gene encodes D7-dehydrocholesterol reductase (DHCR7; 11q12–q13); loss of function mutations cause accumulation of D7-dehydrocholesterol. This recessive disorder has broad developmental affects, including autism (Sikora et al., 2006). While SLO is a rare cause of autism, it demonstrates that the more general disruption of cholesterol metabolism, and related pathways, may be one component of the etiologic mechanisms.

**Regulation of Gene Expression**

**Rett Syndrome (MeCP2)**

Rett syndrome is due to loss of function mutations of the methyl-CpG-binding protein 2 (MeCP2; Xq28) (Moretti & Zoghbi, 2006). Girls with Rett syndrome commonly exhibit autistic symptoms; males generally die prenatally. Some mutations result in milder symptoms that include autism in both boys and girls. MeCP2 is a nuclear protein that binds to methylated CpG dinucleotides. It recruits a corepressor complex that is implicated in transcriptional repression. Mouse MeCP2 mutants show subtle increases and decreases in brain gene expression, including reduced ubiquitin protein ligase E3A (UBE3A) and b3 GABA A receptor (Gabbr3); these are imprinted genes in the Angelman’s disease locus. Inheritance of a maternal duplication of this region (15q11.2–q13) is the most commonly associated chromosomal abnormality found in autism (Schane, 2006). MeCP2 mutants also show increased Dlx5 expression, variable effects on brain-derived neurotrophic factor expression, and RNA splicing defects (Moretti & Zoghbi, 2006). MeCP2’s association with autism highlights the possibility that epigenetic modifications of chromatin (e.g., cytosine methylation and histone methylation/acetylation) and parent of origin effects (imprinting) may have broader roles in the etiology of autism (Shanen, 2006).

**Engrailed2 (EN2)**

Alleles of the En2 homeobox transcription factor (7q36), which regulates cerebellum development, is associated with autism in some studies (Benayed et al., 2005). Mouse mutants exhibit social deficits (Cheh et al., 2005).

**Distal-less 2 and 5 (Dlx2 and Dlx5)**

Missense mutations of the Dlx2 (2q31.1) and Dlx5 (7q21.3) homeobox transcription factors have also been identified in autistic individuals (Hamilton et al., 2005). These genes regulate development of forebrain GABAergic neurons, and Dlx1 mutations lead to epilepsy in mice (Cobos et al., 2005).

**Summary**

The array of genes that either cause or predispose to autism speaks to the diversity of genetic and epigenetic mechanisms that can cause this heterogeneous disorder. It seems likely that autism can be caused by an even larger number of genes – perhaps through combinatorial mechanisms involving coinheritance of multiple weak alleles and environmental factors that influence epigenetic state as well as brain development and function. Despite this complexity, some mechanistic themes are beginning to emerge:

1. Defects in molecular pathways that link synaptic and nonsynaptic signals with changes in protein synthesis that can modulate neural response properties (FRMR1, MET, NGLN3/4, PTEN, SHANK3, and TSC1/2).
2. Defects in transcriptional regulation of neural genes (DLX2/5, EN2, and MeCP2).
3. Defects in neural excitatory state (CACNA1C, CACNA1H, SLC6A4, SCN1A, and SCN2A).
4. Defects in signals within specific neural circuits important for social behavior (AVPR1a; OXTR) (Rubenstein & Merzenich, 2003; Levitt et al., 2004; Hong et al., 2005; Belmonte & Bourgeron, 2006; Persico & Bourgeron, 2006).

In the end, we will need to understand how these molecular lesions disrupt neural systems that process cognition and social behaviors. For instance, mutations that alter the balance of excitatory and inhibitory synapses in key brain regions may impede the ability to detect salient sensory signals above ambient noise (Rubenstein & Merzenich, 2003; Levitt et al., 2004). Mutations in many of the genes described above cause epilepsy, which is a gross manifestation of dysregulated excitatory/inhibitory balance. One of the several questions raised by these genetic studies is whether certain brain regions or certain cell types are selectively affected in autism. To address this question, we turn next to an overview of the neuropathology of autism.

**Neuropathology**

**Structural Magnetic Resonance Imaging Studies**

While early computed axial tomography studies carried out on individuals with autism described abnormalities such as ventricular enlargement (Damasio et al., 1980), later studies determined that there were no consistent tomographic findings in children with classic autism (Prior et al., 1984). One of the most consistent findings from MRI studies (Piven et al., 1997; Sparks et al., 2002; Brambilla et al., 2003) is an increase in total cerebellar volume. 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. In a comprehensive review of the structural MRI studies through May 2003, Brambilla et al. (2003) concluded:

despite a growing number of quantitative MRI studies, few robust findings have been observed. Structural abnormalities involving total brain volume, the cerebellum and, recently, corpus callosum have been consistently replicated. … In order to overcome design limitations of the previous morphometric neuroimaging reports, future quantitative MRI studies should focus on identifying possible morphological brain markers including homogeneous groups of well characterized individuals with autism and healthy controls, matched for aged, gender, SES and IQ and should longitudinally investigating (sic) these groups (p. 567).

The notion that cortical development may be altered in autism arose initially from clinical observations indicating that the head circumference of children with autism is larger than general population controls. For example, Bailey et al. (1993) found that 37% of their subjects had a head circumference above the 97th percentile (macrocephalic), while Lainhart et al. (1997) found that 14% of autistic subjects had macrocephaly. Fombonne and colleagues (1999) conducted a meta-analysis of published literature and concluded that an average estimate of macrocephaly in autism was 20.6%. These data would suggest that large head and thus brain size might be a common, although by no means universal, feature of individuals with autism.

A number of studies have indicated that cortical development may be altered in autism. Piven et al. (1990) noted malformations of the cortex such as polymicrogyria, but these observations have not been replicated. Piven et al. (1995) were also the first to use a computer-aided assessment system to evaluate the cerebral cortex in adults with autism. They concluded that there were increases in the volumes of the temporal, parietal, and occipital lobes but not of the frontal lobes. Neither Aylward et al. (1999) nor Schumann et al. (2004) observed a difference in total brain volume.

Courchesne and colleagues have published a series of studies that demonstrate abnormal brain growth in autism (Courchesne et al., 2001, 2003; Carper & Courchesne, 2005; Redcay & Courchesne, 2005). They propose that the brains of children with autism are either of normal size or perhaps slightly smaller than typically developing children at birth. However, the cerebral cortex, and preferentially the frontal lobe, undergoes a rapid and precocious growth (relative to control children) during the first two years of life. Subsequently, brain growth plateaus and ultimately the volume of the brains of typically developing children catch up. Thus, in older children with autism, the brain is either the same size or even slightly smaller than typically developing subjects. Importantly, this finding has recently been replicated by the Piven laboratory (Hazlett et al., 2005). This study indicates that precocious brain growth may not begin until near the end of the first year of life and is clearly evident by the second year of life.

Beyond the cerebral cortex, other brain regions have also been found to have an abnormal brain 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. Interestingly, the amygdala undergoes a very protracted development in boys (Giedd et al., 1996). It increases in size by nearly 40% between the ages of 8 and 18 years (Schumann et al., 2004). This is striking since the rest of the brain actually decreases in size during this same time period by about 10%. For boys who have been diagnosed with autism, the amygdala demonstrates precocious growth and has reached adult size by 8 years of age.

Many studies have gone beyond simply evaluating the volume of brain regions and have analytically broken the tissue down into compartments representing gray and white matter. There have been some indications that alterations in white matter volumes may actually be a more sensitive indicator of pathology in autism than gray matter differences (Courchesne et al., 2001, 2003; Carper & Courchesne, 2005; Herbert et al., 2004; Herbert, 2005). In fact, some have proposed that the enlarged brain volume that has been reported can be accounted for, in large part, by disproportionate increases in the volume of white matter. There are reports of greater white matter volumes in boys with autism aged 2–3 years, when compared to controls. Interestingly, this pattern was not found in adolescence, further supporting an abnormal early development. Other analyses of white matter have suggested that those compartments of white matter that develop latest (i.e., the radiate regions that mature late in the first year and into the second postnatal year and beyond) are of greater volume than the earlier maturing sagittal and bridging fibers (Herbert et al., 2003). Recent studies using diffusion tensor-weighted imaging of white matter indicate that in autism regionally specific disruptions of white matter integrity may persist into adulthood (Keller et al., 2007).

To summarize, despite the heterogeneity of findings, a few clear directions are emerging:

1. Autism is clearly not a disorder that affects a single brain region.
2. The kind of brain pathology in a particular individual may depend on the phenotypic characteristics of autism (e.g., presence versus lack of developmental delays) as well as comorbid features of the disorder (e.g., seizures versus no seizures).
3. 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 the connections of the brain.

**Microscopic Neuropathology**

There is no obvious lesion in the brains of individuals with autism. In fact, at first blush the brain looks remarkably normal. One consistent finding in autism has been the lower number of Purkinje cells in the cerebellum (Ritvo & Garber, 1988). When using neural stains that mark cell bodies, there are noticeable gaps in the orderly arrays of Purkinje cells. Whether Purkinje cell loss is due to autism, epilepsy, or the co-occurrence of both disorders is not
currently clear. It is also not clear whether loss of Purkinje cells is characteristic of autism or a more general finding in many neurodevelopmental disorders. Thus, cerebellar alterations have been reported in idiopathic intellectual disability, Williams syndrome, and many other childhood disorders. There have also been a few reports of alterations of brainstem nuclei, such as the olivary complex, that is connected to the cerebellum (Bailey et al., 1998). These findings might inform the time frame of neural insults responsible for autism, but they are currently based on too few observations to be considered typical of autism.

The cerebral cortex has also been reported to be abnormal at a microscopic level in autism. There have been some published examples of migration defects such as heterotopias and increased number of cells within both layer I and the subplate region (Bailey et al., 1998; Avino & Hutslers, 2010; Wegiel et al., 2010). Neuropathological changes of a dysplastic nature have been described in the cerebral cortex of autistic individuals. These changes include an effacement of the normal lamination pattern, minicolumnar abnormalities, and variations in neuronal density (Casanova et al., 2002, 2006; Courchesne et al., 2011). These provocative findings are awaiting confirmation in larger studies using sophisticated quantitative strategies. Finally, the amygdala has been found to have fewer neurons in the mature brain (Schumann & Amaral, 2006). Since this study was carried out with cases that did not have comorbid epilepsy, this could be a real component of autistic neuropathology.

**Functional Neuroimaging**

Another approach to establishing which brain regions are most impacted by autism is the use of functional imaging. While this literature is growing rapidly and has provided important insights into the neural impairments of autism, it also applies only to the high-functioning segment of the population who can be compliant with the demands of the behavioral and imaging conditions. Many of the functional imaging studies have focused on brain regions thought to be involved in social function, such as the frontal lobe and amygdala, and on behaviors thought to be selectively impaired in autism, such as perception of social stimuli and theory of mind. Given that more than 400 papers have appeared in recent years dealing with functional imaging of individuals with autism, we only briefly highlight some findings related to the amygdala that, as described earlier, has shown evidence of neuropathology in autism. For recent, more extensive reviews of fMRI in autism see Philip et al. (2012).

The amygdala has been the focus of a large number of functional imaging studies in autism prompted, in part, by the “amygdala theory of autism” proposed by Baron-Cohen and colleagues (2000). Functional neuroimaging studies have indicated that individuals with an autism spectrum disorder show abnormal patterns of amygdala activation in response to social stimuli. High-functioning adults with autism or Asperger syndrome demonstrate deficits in the ability to infer the mental state of another person from viewing images of their eyes (Baron-Cohen et al., 1997). This task activates the amygdala and superior temporal gyrus in control subjects. In contrast, individuals with autism or Asperger syndrome activate the frontotemporal regions but not the amygdala when performing this task (Baron-Cohen et al., 1999). Pierce et al. (2001) found that the amygdala was activated when typically developing individuals viewed unfamiliar faces, but the amygdala was not activated in individuals with autism during this task (Figure 23–2). Children and adolescents with autism spectrum disorders show abnormal amygdala activation while matching faces by emotion and assigning a label to facial expressions (Wang et al., 2004). While children in the control group showed more amygdala activation when matching faces by emotion than assigning a verbal label, the
children with autism spectrum disorders did not demonstrate this pattern of task-dependent amygdala modulation.

One caveat to interpreting findings from face processing studies is that subjects with autism are reluctant to make eye contact, and there is some controversy as to whether they are actually examining the face in a similar manner as controls (Davidson & Slagter, 2000). In fact, when viewing faces, patients with autism show abnormal visual scan paths during eye-tracking studies, typically spending little time on the eyes (Pelphrey et al., 2002; Klin et al., 2003) (Figure 23–3). Whether these findings represent active avoidance of the eye region, potentially involving the amygdala, or a more global lack of social interest or motivation is unclear. An emerging hypothesis is that the amygdala may play a role in mediating or directing visual attention to the eyes (Adolphs et al., 2005; Grelotti et al., 2005; Schultz, 2005).

Research from typically developing children indicates that children who are physiologically aroused by a distressing film were more likely to avert their gaze from the stimulus. It is plausible that children with autism utilize a similar strategy of gaze aversion in response to arousing social stimuli. Given the amygdala’s role in fear and anxiety, one would predict heightened amygdala activation during eye contact in persons with autism if they found the eye contact aversive. Dalton and colleagues (2005) found that the amount of time persons with autism spent looking at the eye region of the face was strongly positively correlated with amygdala activation, but this was not the case in control subjects. The autism subjects also showed greater left amygdala activation relative to controls in response to unfamiliar faces and greater right amygdala activation in response to both familiar and unfamiliar faces. This suggests a heightened emotional, or even fearful, response when autistic individuals look at another person’s eyes, regardless of whether they are familiar or a stranger. Nacewicz et al. (2006) recently found that individuals with autism (8–25 years of age) who had a smaller amygdala were also slower to distinguish emotional from neutral expressions and showed least fixation on the eye regions of the face. These same individuals were also the most socially impaired in early childhood.

Recently, Ashwin et al. (2007) found that during the perception of fearful faces, Asperger syndrome patients showed less activation in the left amygdala relative to controls. However, these results may again be due to the abnormal way in which individuals with autism view faces. Spezio et al. (2007a,b) confirmed that participants with autism show less fixation on the eyes and mouth, but also a greater tendency to saccade away from the eyes when information was present in those regions. This study provides insight into the aberrant manner in which people with autism view faces, which likely influences face processing and subsequent functional imaging study results. Additional studies would benefit from measuring the physiological responses associated with arousal and anxiety (i.e., increased heart rate, skin response, etc.) during face processing in individuals with autism.

**Behavioral Treatment**

Early on in autism treatment two main treatment approaches dominated the literature: treatment based on a psychodynamic conceptualization of autism (e.g., Bettelheim, 1967) and treatment based on the application of Skinnerian models of learning. The first empirically supported paper came from the latter tradition. In 1964, Wolf and colleagues published the first single-subject design of the application of behavioral principles to the symptoms of a young child with autism. The treatment was carried out virtually all day, every day, for several years in an institutional setting. The child eventually returned to his home, with greatly improved behavior, language, adaptive, and cognitive abilities. The teaching procedures involve massed
trial teaching, and many of the core approaches to teaching are still in use today (Lovaas, 1981; Leaf & McEachin 2001).

The view that autism was a neurobiological disorder, championed by Bernard Rimland (1964), had fundamental effects on treatments. Gradually, autism became viewed as a developmental disorder, like intellectual disability, for which rehabilitation (or, more exactly, habilitation) was the appropriate approach. Then, the passage of public law 94-142 in 1975 mandated appropriate free public education for all children with disabilities and cast tremendous responsibility on school districts for appropriate education and habilitative services.

Main Intervention Approaches

Three main philosophies guided the development of interventions. One strategy involved the continued application of learning theory to reduce behavioral deficits and to decrease behavioral excesses (Wolf et al., 1964). These strategies, under the umbrella of applied behavior analysis, were applied in two basic forms. The first involved massed trials with high levels of adult control and direction of the teaching (Lovaas, 1987; McEachin et al., 1993). A more naturalistic application of learning principles capitalized on children's own interests, preferences, and initiatives to assure high levels of motivation for learning. These approaches are best described in two well-known models: incidental teaching, first applied to autism by McGee et al. (1983, 1991), and pivotal response training, as developed by Schreibman and Koegel (Williams et al., 1981; Koegel et al., 1988; Schreibman & Pierce, 1993).

A second main approach was the TEACCH model of intervention (Schopler et al., 1984, 1995). This capitalized on teaching by directing tasks to children's visual-spatial skills, focused on developing skills for independent work and independent functioning, minimized the need for ongoing social instruction and verbal instruction, used visual communication systems to supplement verbal instruction, built a great deal of repetition and routine into the organization of the teaching, and reduced the sensory complexity of the environment to maximize attention. This approach also focused on parents as primary deliverers of child interventions.

The third main approach focuses on autism as a developmental deficit. This approach takes as a premise that early compromises in social-communicative development have increasingly large downstream effects that impair the development of triadic relations (Rogers & Pennington, 1991; Sigman & Capps, 1997; Meyer & Hobson, 2004). The developmental approaches have flourished and some of the better-known current models include Greenspan and Widers' floortime approach (Greenspan et al., 1997), Gutstein’s relationship development intervention (Gutstein, 2005), the Denver model (Rogers & Lewis, 1989), and the SCERTS model (Prizant et al., 2006). These approaches strongly emphasize the quality of the relationship between child and teacher and child and parent, use a child-centered approach based on following children’s interests and initiatives, and strongly emphasize progress in social communication skills.

A fourth treatment orientation focuses on the sensory and motor differences characteristic of autism. Some practitioners think that the sensory differences in autism are the primary impairments, with the social, communicative, and behavioral abnormalities resulting from the intense distress or confusion that the sensory impairments cause (reviewed in Baranek, 2002). Occupational therapists have led the way in evolving treatments targeted at sensory deficits in autism.

Treatment Delivery

Behavioral treatments may be delivered to change very targeted symptoms. Virtually all the main symptoms of autism have been demonstrated to be modifiable with targeted treatments (Schreibman, 2005). Two very important attributes of this literature deserve mentioning. First, positive treatment outcomes for targeted skills have been documented across the entire age range and functioning range for persons with autism spectrum disorders. The second important point is that the techniques used have changed considerably over the years. The use of aversive consequences has largely disappeared, as the field has become more sophisticated in the application of reinforcement strategies (Howlin, 1998; Lalli et al., 1995; Carr et al., 2002; Horner et al., 2002). It is now clear that autism is treatable.

The current science of early behavioral intervention in autism is targeting several main research questions: (1) Is “recovery” possible for more than an occasional child? (2) Are some treatments more effective than others? (3) What are the “active ingredients” of effective comprehensive treatments? (4) What child, family, programmatic, and environmental variables mediate and moderate early intervention outcomes? (5) Can we identify an aptitude by treatment interaction in autism that will allow us to know which subgroups of children with autism will respond best to which treatment approach or treatment elements?

We still have no randomized controlled trials that compare the best-known comprehensive approaches. The few randomized controlled trials that exist have consistently demonstrated that well-planned and carefully delivered treatments, both developmental and behavioral, improve children's functioning, particularly IQ and language abilities, compared to no treatment, both over the shorter term and over the longer term (Jocelyn et al., 1998; Smith et al., 2000). The fact that IQ and language are so responsive to high-quality treatment delivered in the preschool period is quite promising, since these are the best predictors of outcomes over time in autism (Howlin, 2005). Given the findings from other models thus far, it is likely that a carefully planned intensive and comprehensive intervention with expert delivery will result in positive gains for children compared to a no-treatment condition.

Comprehensive intervention for older children occurs every day in classrooms across America, but these have not received the scrutiny of early intervention approaches. While some classrooms for older children also follow a very specific educational model, it is probably more often the case that public schools use a variety of teaching methods to teach the individual educational objectives that guide each child’s special education in the public schools. Two areas of research in this group involve the development of social skills, especially for children with milder symptoms (Wooten & Mesibov, 1986; Ozonoff & Miller, 1995; Simpson et al., 1997), and the questions about inclusive education (Simpson & Smith Myles, 1993; Kellegrew, 1995; Janney & Snell, 1997).
systems. The most common biological finding is precocious life skills. Autism affects the development of several brain and bolstering language, social interaction, and pragmatic literature are valuable for eliminating unwanted behaviors. Risperidone was the first approved drug for treatment of autism. Previously risperidone was studied as off-label medication to treat autism because of its increased safety and efficacy over conventional neuroleptics. Risperidone can be used as a potentially safe and effective treatment for disruptive behavioral symptoms in children with autism (West & Waldrop, 2006). The long-term use of these drugs in conjunction with the plethora of other alternative medications that are being used requires additional analysis pertaining to safety (McCracken, 2005).

Complementary Alternative Medicine Treatments
It would be fair to say that in no area of developmental pediatrict practice is there more controversy than in the selection of treatments for children with ASDs. An increasing number of complementary and alternative medical therapies are often tried because they are perceived as treating the cause of the children’s symptoms (Levy & Hyman, 2005). Current treatments range from various forms of restricted diet (Millward et al., 2004) to hyperbaric oxygen treatment (Rossignol, 2007) to a variety of vitamin and mineral supplemetations (Hanson et al., 2007). Secretin provides a good example of how an incidental perception of behavioral improvement following treatment leads to widespread clinical use despite little or no scientific rationale for the therapy. Even despite nearly unanimous negative results in placebo-controlled clinical trials (Esch & Carr, 2004), there still remains substantial parental interest in attempts at using secretin as one potential therapy. In many respects, this speaks to the desperate need of parents and practitioners alike to obtain more scientifically based approaches to the therapy of both the core and the comorbid symptoms of autism.

Conclusions
Autism is a spectrum disorder that is defined behaviorally as consisting of social/communication impairments and the presence of stereotyped behaviors and/or circumscribed interests. There is a general consensus that autism has a variety of etiologies that consist of different proportions of genetic and environmental contributions. While some 10% of autism cases are associated with a defined medical condition such as fragile X syndrome, the cause(s) of the remainder of idiopathic autism are currently unknown. Various behavioral therapies based on the operant conditioning literature are valuable for eliminating unwanted behaviors and bolstering language, social interaction, and pragmatic life skills. Autism affects the development of several brain systems. The most common biological finding is precocious brain development of the cerebral cortex and amygdala. However, the neuropathology of autism is still at a very early stage of understanding and both additional structural MRI and postmortem studies are needed to better define the neural systems involved. Beyond the nervous system, there appears to be a variety of dysregulated functions in the immune system of some individuals with autism and some mothers of individuals with autism. Whether the immune dysregulation is a cause or effect of autism remains to be determined. Finally, autism is generally agreed to be a polygenic disorder, with multiple genes showing weak association. This may be a reflection of the fact that better phenotyping of autism subtypes is essential before fruitful genotyping can be accomplished.

References


