Introduction
Leopold Kanner, an Austrian born American psychiatrist first described autism in 1943. His observations of a small group of children with behavioral symptoms of social withdrawal, impaired language/communication and obsession with sameness led to recognition of autism as a specific pervasive developmental disorder. At about the same time Austrian psychiatrist Hans Asperger independently described similar symptoms in a small group of children except that the “Asperger” children were high functioning with better language and cognitive skills than those described by Kanner. Both Kanner and Asperger used the word autistic to describe the pathology in the children they observed—a term rooted in the Greek “autos” (self) and coined by Swiss psychiatrist Eugen Bleuler to describe symptoms in his schizophrenic patients. Before Kanner and Asperger defined autism as a specific disorder, children with autistic symptoms were most likely classed and treated as mentally retarded or, if they were high functioning, perhaps as schizophrenic.

The symptoms described by Kanner and Asperger remain the core diagnostic symptoms for autism and associated disorders. Autism Spectrum Disorders (ASD) as specified in the DSM-IV TR (a text revision of the DSM-IV) include autistic disorder (classic autism), Asperger’s disorder, pervasive developmental disorder not otherwise specified, Rett’s disorder, and childhood disintegrative disorder. This chapter will be limited to discussion of autistic disorder and Asperger’s disorder.
Increased Prevalence of Autism: It’s not the vaccine

Is the prevalence of autism increasing? Considerable media attention has been devoted to a potential increase in the prevalence of autism and autism spectrum disorders over the past couple of decades. Speculation about reasons for such an increase in the rate of autism has included most prominently a concern over the role of environmental factors, particularly childhood vaccination. A comprehensive review by Canadian psychiatrist and epidemiologist Eric Fombonne compiled survey data from 14 different countries over the last several decades to track changing rates of autism. Fombonne reported that early surveys using Kanner’s strict diagnostic criteria estimated rates of autism at 3.8 per 10,000 while later surveys using DSM-IV and ICD-10 diagnostic criteria estimated autism rates at 20 per 10,000. A Finnish study reviewed by Fombonne illustrates the result of using less strict diagnostic criteria. Using Kanner’s criteria, this survey estimated autism prevalence at 2.3 per 10,000 while the prevalence in the exact same large sample using DSM-IV and ICD-10 criteria was estimated to be nearly 3 times larger—7.6 per 10,000.

In spite of growing evidence that increased rates of autism most likely reflect changes in diagnostic criteria and an increased awareness of the symptoms of pervasive developmental disorders and not an epidemic rise in autism, concerns have persisted that environmental factors are responsible for the purported rate increase. The major focus of these hypotheses have been the measles-mumps-rubella (MMR) vaccine and a mercury-based preservative (thimerosal) used in many other childhood vaccines. Numerous studies have found no evidence for the association of these vaccines and the increased rate of autism in this country or worldwide (review: ). Some of the strongest evidence that there is no such association comes from large ecological studies showing the rise in incidence of autism has occurred in countries where the vaccines in question were not used, or that there is no difference in the incidence of autism in vaccinated and unvaccinated children, or that the rate has continued to increase after discontinuation of the vaccine (e.g., ). There is also no biological evidence to support these allegations (for reviews see: ). An unfortunate result of these unsupported speculations can be seen in recent outbreaks of measles in unvaccinated children in Europe, Japan and the US.

Is there a true increase in the prevalence of autism? Probably not. The diagnosis has become increasingly inclusive, and the signs and symptoms are more commonly recognized by parents and physicians. Do autism and related autism spectrum disorders pose an important public health problem? Absolutely. As many as 1 in 150 children have some form of pervasive developmental disorder that affects their ability to learn and to function in a social environment. Early diagnosis and treatment is crucial.

Diagnosis

Increased awareness of autism in the general public has resulted in increased recognition of symptoms in infants and toddlers. The majority of parents (80%) of children with ASD recognize symptoms in the first two years of life and approximately 30% recognize symptoms before their child is 12 months old. Concerns most commonly reported by parents are speech and language delays, abnormal social behavior, problems with attention and disruption of sleep and eating. In 25-30% of children, ASD manifests as a regression of communication and social skills after 15-24 months of apparently normal development. There is reasonable evidence that ASD can be reliably diagnosed in the second year of life and some possibility that there are much earlier behavioral markers associated with ASD. A large prospective study of
high-risk infants with ASD siblings found reliable markers in infants less than 12 months who were later diagnosed with ASD. These behaviors included abnormalities in eye contact, visual attention, imitation, social smiling, orienting to name, temperament and unusual sensory behaviors.

A family physician or pediatrician is frequently the first to be consulted when parents are concerned about symptoms of autism. If neurological signs, such as seizures, are among the symptoms of concern, the child may be referred to a pediatric neurologist. The American Academy of Pediatrics has provided guidelines for the diagnosis and ongoing care management for children with Autism Spectrum Disorders. The Council on Children with Disabilities has provided a screening tool for identification of children at risk for ASD. The screening tool and updated recommendations are available on-line from the American Academy of Pediatrics (http://www.pediatrics.org/cgi/content/full/118/1/405). Routine screenings to identify at risk children are recommended at 9-, 18-, 24- and 30-month visits.

Clinical criteria for the diagnosis of autism are based on the DSM-IV TR and ICD10 specifications. The three diagnostic domains in which symptoms are evaluated are social relationships, language and symbolic capacity, and repetitive behaviors. Criteria for a diagnosis of autism require impaired behavior in each of these domains. While the clinical diagnosis is most commonly based on the DSM criteria and expert judgment, there are a number of assessment instruments used to enhance the specification of clinical features in research and treatment settings. The current gold standard for diagnostic instruments are the Autism Diagnostic Interview, Revised, (ADI-R), and the Autism Diagnostic Observation Schedule, (ADOS). These instruments score impairment in a number of domains and have excellent reliability and validity. Both instruments are, however, relatively expensive, require extensive training for the test administrator and a lengthy administration time. A number of additional assessments are commonly used to evaluate clinical features of autism. For example, the Scales of Independent Behavior-Revised (SIB-R) assess adaptive functioning. The Social Responsiveness Scales (SRS) provide measures of social function and social communication including social awareness, social information processing, capacity for reciprocal social communication, social anxiety/avoidance, and autistic preoccupation/traits. The Childhood Autism Rating Scale (CARS) is broadly used as a measure of symptom severity. For a brief review of additional assessment and screening instruments, see.

EEG Abnormalities and Seizures

Autism is associated with other psychiatric and medical conditions including in a small percentage, Fragile X (1%) and tuberous sclerosis (0.4-2.8%). The diagnosis of other psychiatric conditions in ASD is controversial, but there seems to be an elevated rate of depression and anxiety disorders in Asperger patients while the there is no elevation in the rate of schizophrenia (for a review see Volkmar et al.).

The most common medical condition associated with autism is epilepsy, and even in the absence of epilepsy there may be an elevated incidence of epileptiform abnormalities in the EEG. Epileptiform abnormalities in individuals with ASD are most often multifocal, and there is considerable disagreement in the literature over the distribution of these abnormalities. Recent studies with large sample sizes (more than 100 subjects)
result in reduced long-range connectivity\cite{132-134}. Lewis and Elman used neural network modeling to examine this hypothesis, and demonstrated that increased conduction delays presumably associated with early brain overgrowth lead to reduced long-range structural and functional connectivity, and also poorer performance\cite{134}. Their results provide theoretical support for a tie between the early brain overgrowth and reduced connectivity in autism. Using diffusion tensor imaging (DTI) with tractography, Lewis demonstrated that in healthy young adults, a larger brain is associated with reduced long-range connectivity\cite{135}. New studies by Lewis and colleagues have subsequently provided the first direct evidence of structural reduction in long-range connectivity in adults with autism. These studies used DTI with tractography in adults with autism to demonstrate reduced long-range frontal lobe interhemispheric connections via the anterior corpus callosum\cite{136,137}. The anterior of the callosum is a particular focus of development during the period of maximal brain overgrowth in autism, and so this finding is consistent with the hypothesized impact of the early brain overgrowth on connectivity.

In summary, developmental growth patterns reported from imaging\cite{84,114} and postmortem studies\cite{71} are consistent with an on-going pathologic process\cite{57} that involves early overgrowth followed by slowed growth during maturation. These abnormal developmental patterns may result in abnormal white matter connectivity\cite{124-126} and an accelerated loss of brain tissue with aging\cite{57}.

### Cognitive Models

Several major current models attempt to explain neuropsychological function in autism (for reviews see: Baron-Cohen et al.\cite{138-140}; Russell\cite{141}; Hill and Frith\cite{142}; Levy\cite{143}). The Theory of Mind (TOM) deficits model, proposes that the origin of social communication in autism is an impaired ability to attribute feelings and thoughts to others—in essence to understand one’s own or another’s state of mind. This model was first tested by Baron-Cohen\cite{144} and has subsequently been tested many times. The results are robust and many (though not all) children with autism consistently show TOM deficits. These deficits are not necessarily specific to autism and are found in other disorders as well\cite{145}.

Executive Function deficits\cite{146,147} are impairments typically associated with frontal lobe function including planning, set shifting, perseveration, working memory and control of action and inhibition. Children and adults with autism have been shown to be impaired on a variety of executive function tasks\cite{142}. The Weak Central Coherence model is based on the bias in autism to process details that results in enhancement of segments of information at the expense of context (reviewed in the sensory/perception section below). This model suggests a weakened ability to integrate or bind details into a coherent whole that affects many domains of behavior in autism\cite{148-150}.

Although all of the major cognitive models of autism have been associated with underlying neural systems, they are largely descriptive and none explains all of the clinical symptoms. All are important, however, as frameworks within which to advance research and develop treatment interventions.

Some newer explanatory models incorporate development and underlying neural mechanisms. Brock has proposed a temporal binding deficit which postulates that many features of autism, such as superiority in processing of detail (local processing) and
disadvantage in global processing necessitating integration of information either over space (visuo-spatial perception) or context (integration of words into meaningful sentences), can be explained by a failure of temporal integration, or binding, between cortical areas \(^{151}\). A related and promising model of abnormal functional connectivity based on developmental neuroanatomic findings is considered by some to be a logical extension of the “weak central coherence” model \(^{125, 140, 152}\) and may provide an explanatory base for many of the neuropsychological and social deficits in autism.

Abnormal brain overgrowth in early development (discussed in the previous section) may result in abnormal white matter under- and over-connectivity \(^{124-126, 134}\). Excessive short-distance and reduced long-distance pathways that would result in a failure to integrate processing across brain systems could predict many of the neuropsychological processing abnormalities to be discussed below. There is growing evidence in support of such abnormal functional connectivity in autism. The first of these studies was conducted by Horwitz and colleagues more than two decades ago \(^{153}\). This early positron emission tomography (PET) study demonstrated that in subjects with autism there was reduced correlation in resting cerebral metabolism in brain regions that serve directed attention including frontal and parietal cortex and the thalamus. These authors were the first to suggest the failure of integrated long-distance communication in the autistic brain.

Modern FMRI studies have also begun to provide evidence for reduced long-distance connectivity. Just and colleagues found decreased functional connectivity during a language task among brain region pairs including mid-range (occipito-temporal, occipito-parietal) and long-distance (e.g., occipito-frontal) connections \(^{154}\). FMRI studies of working memory, spatial attention and selective attention suggest dependence upon short-distance local connections (e.g., processing of visual features) rather than integration of attention and verbal networks during these tasks \(^{155-158}\). A study that combined structural and functional measures demonstrated reduced functional connectivity during an executive function task, and associated reduced size of regions of the corpus callosum through which the identified networks communicate \(^{159}\). The authors concluded that their results supported a model of cortical underconnectivity in autism, which proposes deficits in neural and cognitive integration.

A recent study of resting state EEG in autism also demonstrated patterns that suggest increased short-range and reduced long-range functional connectivity \(^{160}\). See Figure 1. This study, the first to use reference independent dense array EEG coherence to examine functional connectivity in autism, is of particular importance as EEG coherence directly reflects synchrony in oscillations of cortical neural cell assemblies (i.e., a direct functional connection in real time).
**Summary and Conclusion**

Sixty-five years after Kanner's initial description of autism, we have failed to find biological markers and so the diagnosis of autism remains behavioral and must rely on subjective observations. The cause of autism remains unknown. There is limited consensus about neuroanatomic abnormality, and limited agreement about specific cognitive impairment and effective treatments.

While we may not yet understand the underlying mechanisms in autism, the underlying cause for inconsistent findings in autism research is quite clear. Given a subjective behavioral diagnosis and particularly the recent broader diagnostic criteria, the samples drawn for study are extremely heterogeneous. There is as yet no reliable method for creating sub-groups. Of the studies considered here (and many many more that we were unable to include) few have sample sizes larger than 15-20 and sample sizes of fewer than ten are not uncommon. With small heterogeneous samples and widely different methods and tasks, it is no surprise that findings are inconsistent. In spite of this, important patterns have begun to emerge.

A few findings have been replicated often enough to be considered robust. Among those are neuroanatomic abnormalities in the cerebellum and brainstem and overall enlargement of the brain in young children. Evidence for a bias toward local (detailed) processing, particularly in the visual modality appears to be robust, and this processing bias has been noted in many domains including face processing and language. While the exact nature and underlying neural basis for attentional problems remains somewhat controversial, the finding of difficulty in disengagement of visual attention (“sticky” attention) has been replicated in a number of different ways by several independent groups and has reasonable consensus as well. A number of newer studies reviewed above have demonstrated that sometimes simple directions that alter attentional bias can normalize both behavior and the underlying neural response.

A promising model that has the potential to explain a profile that includes both strengths and weaknesses in cognition and behavior is based on work identifying unique patterns of brain development in autism. Abnormal early brain overgrowth may result in reduced long-distance (and perhaps excessive short-distance) white matter connectivity that disrupts integrated processing across brain systems. Such under- and over-connectivity could predict many of the neuropsychological and behavioral abnormalities discussed above and explain neural underpinnings of dysfunction in attentional, language and social brain networks. This model can provide a framework for studies with translational implications to guide development of specifically targeted interventions. One of the major advances in autism research and treatment is that diagnosis can now be made in children as young as two years of age and so treatment intervention can begin very early when it has the potential to provide maximal amelioration of clinical symptoms.