Autism: Definition, Neurobiology, Screening, Diagnosis

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KEYWORDS

- Autism
- Genetics
- Epidemiology
- Synapse
- Connectivity
- Sensorimotor deficits
- Brain imaging
- Electrophysiology
- Immunology

DEFINITION

Articles from the medical and lay press about clinical aspects of autism bombard pediatricians virtually every day. Therefore, this review focuses on recent developments and some of the less well known aspects of this disorder. The authors emphasize up front that autism is not a "disease." Rather it is a symptom of atypical development of the immature brain. Its diagnosis is not biologic, and responsible diagnosable etiologies are numerous but infrequent. Autism is a behaviorally distinct syndrome with many known and unknown causes. It has a wide range of severity and is defined dimensionally, which means that it has fuzzy borders that overlap normality at one extreme and profound intellectual impairment with other evidence of severe brain malfunction at the other. Children who have autism are not "sick" or "fragile," nor are they "emotionally disturbed," despite the behavioral nature of many of their symptoms.

The defining symptoms of autism almost invariably become overt in toddlers and preschoolers. They tend to persist throughout life, although often in more muted form. As discussed later, symptoms may be noted from infancy or become evident after a period of normal or more normal development.\textsuperscript{1} There are three key manifestations of autism:

1. Impaired sociability, empathy, and ability to read other people’s moods and intentions, with resulting inadequate or inappropriate social interactions
2. Rigidity and perseverance, including both stereotypies (purposeless repetitive movements and activities), the need for sameness, and resistance to change
3. Impaired language, communication, and imaginative play

Speech is typically delayed or may regress. Comprehension is impaired, if not at the word level, then at the level of sentences. Nonverbal and verbal language are affected, and pretend play is delayed or absent. Some children are nonverbal or have sparse, impoverished, poorly articulated, and agrammatical speech. A mostly nonverbal child may utter a rare, well-articulated sentence. In other children who have or do not have delayed talking, speech is abundant and rich but with an atypical vocabulary and clearly abnormal features, notably echolalia, frequent verbatim use of scripts, and unusual prosody.

The severity of autism’s deficits is extremely variable. Therefore, the term autism spectrum disorders (ASDs), or the autisms, is appropriate because it denotes a bell-shaped curve of impairment. The Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision\(^2\) and the 10th Edition of the International Classification of Diseases of the World Health Organization\(^3\) refer to the autism spectrum as pervasive developmental disorders (PDD) and refer to autistic disorder (AD; widely shortened to autism in the literature) as the classic, more severe end of the distribution. This plethora of terms with somewhat different meanings is confusing. In this review, the authors use “autism” as short for ASD and PDD but not for AD, which is named specifically when referred to. Asperger’s syndrome refers to ASD children in whom speech was not delayed and whose IQ is at least 70. The acronym PDD-NOS (PDD not otherwise specified) applies to ASD children who do not fulfill criteria for Asperger’s syndrome or AD; these children form a heterogeneous group generally less severely affected than those who have AD.

In addition to autism’s impact on the three defining domains of behavior already mentioned (sociability, rigidity, communication), children—and adults—who have ASD are likely to have a variety of other symptoms, depending on what parts of the brain’s circuitry are affected. The most prevalent of these are listed in Table 1. The authors emphasize that no single sign, symptom, clinical feature, associated handicap, or diagnosis suffices for a diagnosis of autism or invalidates it, and that no individual presents all the impairments listed.

**NEUROBIOLOGY**

Parent-initiated advocacy groups, the largest of which in 2008 is Autism Speaks, which fused with Cure Autism Now and National Alliance for Autism Research, have not only raised money to support pilot research over the past 15 years or so but also publicized autism so effectively that it is now fully in the public eye. The result is an enormous increase in federal funding for research and state funding for specialized education services. Among the many areas of progress in unraveling the neurobiology of autism are genetics, immunology, imaging, and electrophysiology.

**Genetics**

Autism is highly heritable, yet most (perhaps 80%–90%) of affected individuals are the only affected members of their families, usually with no explanation for their condition (Table 2). Some of the remaining 10% to 20% have a plausible nongenetic cause such as intrauterine rubella\(^4\) or cytomegalovirus.\(^5\) A few have a chromosomal abnormality; for example, an alteration in chromosome number or a balanced or unbalanced duplication, deletion, or translocation microscopically visible on banded preparations.\(^6\) Such chromosome rearrangements may inactivate one or more genes and thus
provide information on the locus of a gene or genes potentially relevant to the etiology of a brain dysfunction responsible for the autism phenotype. Cytogenetic abnormalities are often, but not always, associated with major or minor anomalies on physical examination. In some families, autism is but one symptom of a defined mitochondrial or mendelian disorder expressed in the brain, such as fragile X syndrome or tuberous sclerosis. Thus, although a large variety of diagnosable disorders has been associated with autism (some in very few individuals or families), each disorder is rare, and by no means do all individuals who have that condition have autism.

Whole-genome searches using newly developed comparative microarray techniques applied to large samples of rigorously diagnosed unaffected control subjects and probands in families that have several affected members (multiplex families), in families that have only one affected member, and in monozygotic and dizygotic twins have identified several recurrent single-stranded DNA microdeletions, microduplications, or other gene rearrangements. Very recently, deletions or duplications at 16p11.2 fragile site were found in approximately 1% of three different populations of individuals who have autism. These gene copy number variations (CNVs), which are dominantly heritable but most of which arise from new (de novo) mutations, are revolutionizing our views of the genetics of autism and have profound consequences for genetic counseling. They may be more numerous in autism than in the general population. A reliably replicated CNV, even if infrequent, points to a region of the genome where one or more still-to-be-identified causative or risk-conferring genes for autism reside. Most CNVs are found only de novo in the proband, not in the patient’s parents. Therefore, one is justified in assuming that the mutation occurred in the gonad of one or the other CNV-negative parent who passed it on to the affected offspring but who is at vanishingly low risk of having another affected child. Which parent is more likely to have undergone the mutation is disputed, some studies implicating older fathers on the basis of the life-long turnover of sperm. The situation is radically different for carrier offspring and for a carrier parent who is unaffected or only affected with a milder developmental disorder such as an attention-deficit disorder, a language or learning disability, bipolar disease, or difficult personality. For reasons yet to be determined, CNVs are transmitted to 50% of male offspring, as expected from a highly penetrant dominant mutation, but to only 20% to 30% of female offspring, which explains well-documented male-to-male transmission in some families. This sex-skewed transmission contributes to, but does not fully account for, the preponderance of male patients who have autism because up to now, replicated CNVs have been identified in so few individuals who have autism; it supports the contention that a number of genes, each contributing only slightly to the risk of autism, interact in its cause. The most likely explanation for the finding that CNV deletions and duplications can be associated with autism suggests that the breakage site inactivated one or more non-coding regulatory genes, resulting in the silencing of one or more other genes.

The observation that monozygotic twins are not 100% concordant for diagnosis—and especially not for severity, even when autism occurs in association with a known mendelian trait like tuberous sclerosis or Joubert’s syndrome—argues for potent posttranslational environmental or epigenetic editing of the genome. Genes that code for proteins account for only 2% of the human genome, some of which, like most of the second X in females, are permanently silenced by methylation, whereas others are turned on and off repeatedly depending on local need. The remaining 98% of the genome includes conserved regulatory genes for nontranscribing RNAs responsible for this posttranslational control of the genome. These nontranscribing RNAs repress permanently or alter reversibly the messenger RNAs of the protein
### Table 1
Clinical deficits characteristic of autism

<table>
<thead>
<tr>
<th>Symptom Category</th>
<th>Subtypes of Deficits</th>
<th>Characteristics, Examples, Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive symptoms</strong></td>
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<tr>
<td>Cognition</td>
<td>Extremely variable, not a defining feature</td>
<td>Ranges from severe impairment (low-functioning autism) to average or even superior (high-functioning autism) Uneven profile of abilities Most often nonverbal skills are greater than verbal skills; the opposite profile can occur, notably in Asperger’s syndrome Often and at all intelligence levels enhanced memory for details</td>
</tr>
<tr>
<td>Executive functions</td>
<td>Impaired</td>
<td>Impaired planning, prioritizing, organization, decision making</td>
</tr>
<tr>
<td>Attention</td>
<td>Overfocus</td>
<td>Very long for some self-generated activities; unusual tolerance for monotony Inattentiveness Disorganization; short attention, especially to activities introduced by someone else</td>
</tr>
<tr>
<td>Mood/affect</td>
<td>Lability</td>
<td>Unpredictable fluctuations Decreased Flat affect, depression, catatonia Increased Irritability, tantrums, aggression, mania</td>
</tr>
<tr>
<td>Responsiveness</td>
<td>Decreased</td>
<td>Lack of response, passivity Increased Aggressiveness, destructiveness</td>
</tr>
<tr>
<td>Memory</td>
<td>Decreased</td>
<td>Impaired procedural or episodic learning Increased Music, letters, numbers, speech and vocabulary, maps, itineraries, drawings, unusual items or details, and so forth</td>
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<th>Symptom Category</th>
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</thead>
<tbody>
<tr>
<td><strong>Expressive language</strong></td>
<td>Defining characteristic</td>
<td>Impaired pragmatics (ie, the drive to communicate verbally or nonverbally)</td>
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<tr>
<td></td>
<td></td>
<td>Talk to talk, severely impaired conversational use of language</td>
</tr>
<tr>
<td></td>
<td>Decreased</td>
<td>Late to develop or absent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May be minimally and unexpectedly verbal; if verbal, often impoverished language with impaired articulation and grammar</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May have difficulty with word retrieval</td>
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<tr>
<td></td>
<td>Increased</td>
<td>Chatter in gibberish or in full well-formed, often-perseverative sentences (semantic–pragmatic language deficit syndrome); perseverative questioning</td>
</tr>
<tr>
<td><strong>Pathologic features</strong></td>
<td></td>
<td>Echolalia, pronominal reversal, use of scripts, perseverative questioning</td>
</tr>
<tr>
<td><strong>Language comprehension</strong></td>
<td>Impaired</td>
<td>Always impaired in young children, even in the face of adequate expression</td>
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<tr>
<td></td>
<td></td>
<td>Particular difficulty with open-ended questions</td>
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<td></td>
<td></td>
<td>Variable in older children, but often remains impaired for complex language, irony, implicit meaning, and so forth</td>
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<tr>
<td><strong>Play</strong></td>
<td>Impoverished</td>
<td>Little interest in toys, games; absent or impoverished and repetitive pretend play</td>
</tr>
<tr>
<td><strong>Sensorimotor symptoms/signs, epilepsy</strong></td>
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<tr>
<td><strong>Somatosensory</strong></td>
<td>Decreased responsiveness</td>
<td>Insensitivity to pain, self-injury; craving for deep pressure</td>
</tr>
<tr>
<td></td>
<td>Increased responsiveness</td>
<td>Intolerance for some textures, including foods</td>
</tr>
<tr>
<td><strong>Vision</strong></td>
<td>Decreased responsiveness</td>
<td>Unawareness of obstacles, impaired facial recognition, gaze aversion</td>
</tr>
<tr>
<td></td>
<td>Increased responsiveness</td>
<td>Enhanced perception of details</td>
</tr>
<tr>
<td><strong>Audition</strong></td>
<td>Decreased responsiveness</td>
<td>Failure to respond; blunted awareness of tone of voice/prosody</td>
</tr>
<tr>
<td></td>
<td>Increased responsiveness</td>
<td>Intolerance to loudness and certain frequencies; Absolute pitch relatively frequent</td>
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<tr>
<td><strong>Vestibular function</strong></td>
<td>Decreased responsiveness</td>
<td>Tolerance for upside-down posture, spinning</td>
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<tr>
<td></td>
<td>Increased responsiveness</td>
<td>Motion sickness</td>
</tr>
<tr>
<td><strong>Taste/olfaction</strong></td>
<td>Decreased responsiveness</td>
<td>Smelling or licking of people or objects; pica</td>
</tr>
<tr>
<td></td>
<td>Increased responsiveness</td>
<td>Extreme selectivity of acceptable foods; gagging to smells and tastes</td>
</tr>
</tbody>
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coding genes by editing their base sequences. Epigenetics refers to stable heritable or potentially heritable postmitotic alterations in gene expression that do not entail a change in nucleotide sequences. Among noncoding RNAs, microRNAs (miRNAs), only approximately 22 nucleotides long, make a major contribution to RNA editing in postmitotic neurons. miRNAs thus modulate brain development, function, maintenance, and repair by orchestrating the timing of protein synthesis, metabolism, and destruction. The very numerous miRNAs differ widely among cells and brain regions. They play crucial roles in cognition and learning because their exquisite sensitivity to environmental stimuli regulates neural transmission. Therefore, they not only alter individual genetically determined risk factors for diseases but also alter the expression of talents like language, music, or sports that require variably intensive environmental stimulation for their instantiation.

In summary, genetics plays an important etiologic role in autism, but in an extraordinarily complex fashion because of the crucial role of multiple gene interactions and environmental epigenetic influences on the expression of each individual’s genome. Consequently, unless a known gene defect with a defined inheritance pattern and predictable phenotype is detected, only general risk factors can be provided to families and, even then, prediction of the severity of the expected phenotype is often uncertain.

**Immunology**

A third of parents, if asked, report the occurrence of language regression or a developmental plateau associated with loss of sociability in their child between approximately 12 to 30 months of age, usually with no known trigger. Although this may suggest a potential environmentally based deleterious influence in genetically susceptible children,

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<tbody>
<tr>
<td>Motor</td>
<td>Gait</td>
<td>Toe walking</td>
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<tr>
<td></td>
<td>Muscle tone/joint laxity</td>
<td>Decreased (hypotonia); increased joint mobility</td>
</tr>
<tr>
<td>Stereotypes</td>
<td></td>
<td>Purposeless repetitive rhythmic movements, gestures, or gaits, or humming of sounds. Are generally multiple, involve various body parts, are often precipitated by anxiety, boredom, or excitement, and are temporarily suppressible. Frequent ones are flapping, pacing, and object manipulation. Rarer but strongly suggestive are staring “out of the corner of the eyes.”</td>
</tr>
<tr>
<td>Clumsiness, apraxia</td>
<td></td>
<td>Delays and difficulties in learning to dress, tie, use eating utensils, ride a bike, and so forth. Large, sloppy, slow handwriting; denote impaired procedural learning?</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Increase</td>
<td>In one fourth to one third of cases; related to low-functioning autism and other signs of brain dysfunction</td>
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</tbody>
</table>
none has been found to date. Research studies provide no support for a causal relationship between the measles-mumps-rubella vaccine or thimerosal and autism.24,25

The retrospective finding of elevated levels of certain cytokines in the cord bloods of infants who were later diagnosed as autistic with or without cognitive impairment or as mentally retarded without autism (but not in the bloods of normal children or of those who have cerebral palsy) supported covert intrauterine inflammation as a potential causative factor.26 The widespread activation of microglia and astrocytes (part of the innate immune system) found in 11 brains of individuals aged 4 to 44 years who had autism (but not found in control subjects) gave a boost to inflammation as a contributory factor.27 There was no evidence of T- or B-lymphocytic infiltration to suggest activation of the adaptive immune system in these brains.

The potential role in autism of genetic risk factors for covert infection or autoimmune inflammatory factors has been investigated for over a decade. There are reports of linkage of autism to several classes of HLA genes.28–30 A survey in the families of affected children indicated a higher prevalence of autoimmune disorders like rheumatoid arthritis, lupus, and thyroiditis compared with control families,31 a finding not corroborated in another study.32 Raised levels of brain-specific autoantibodies were reported in the sera of children who had autism.33,34 The contribution of elevated cytokines, antigens, antibodies, and other evidence for dysregulation of the immune system in particular subtypes of autism are subjects of active investigation in humans and animal models;35 however, coherent evidence has yet to emerge.

**Brain Imaging**

An early focus of imaging studies in autism was determining whether there were anatomic differences in areas of the brain in which the limited number of pathologic studies had shown abnormalities. Areas of pathology included the limbic system, cerebellum, and related inferior olive.36 In the 1980s and early 1990s, the cerebellum, notably abnormalities in vermal lobules VI and VII, was an area of intense interest in the imaging of children who had autism.37 The pathology and the imaging of autism over the years have implicated numerous brain structures, including the frontal lobes, amygdala, and cerebellum, cortical white matter,39 and a tendency toward unusually large brains in young autistic children, with later growth deceleration.40

An area of interest in imaging is mapping regions of the brain relevant to social competence. Theory of mind, or metacognition, refers to an individual’s ability to understand that others possess covert mental intentions. Understanding another person’s inner state requires the ability to interpret emotional expressions and behaviors. Difficulty understanding that others have beliefs, intentions, and desires is a crucial skill that, when deficient, leads to impairment in reciprocal social interaction.41 Functional MRI (fMRI) studies done with paradigms to investigate the “social brain” suggest the involvement of networks that include, in particular, the orbitofrontal cortex, superior temporal gyrus, and amygdala. fMRI studies suggest that individuals who have autism activate frontotemporal regions, but not the amygdala, when making mentalistic inferences from the eyes, as opposed to typical individuals who activate the superior temporal gyrus, amygdala, and parts of the prefrontal cortex.42 Presented with stimuli of varying fearfulness, typical individuals activate the left and right amygdala differentially, but those who have high-functioning autism or Asperger’s syndrome do not.43 Perception of facial expression and facial recognition is linked to the fusiform area of the ventral temporal lobe.44 This linkage and that of the amygdala in emotional processing suggest that deficits in the amygdala–fusiform network may underlie the social cognitive impairments characteristic of individuals who have ASDs.45
Table 2  
Types of genetic approaches applied in autism studies

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<tr>
<th>Genetic Approach</th>
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<tbody>
<tr>
<td>Twin and family studies</td>
<td>Provide information about the heritability of the disorder even when there is no information about its specific cause (eg, &quot;idiopathic&quot; autism)</td>
</tr>
<tr>
<td>Association studies</td>
<td>Study the association of autism or particular symptoms (endophenotypes) with known genetic or nongenetic causes of autism (eg, tuberous sclerosis, congenital rubella)</td>
</tr>
<tr>
<td>Cytogenetic studies</td>
<td>Study (1) missing or duplicated chromosomes (aneuploidies; eg, monosomy, trisomy, or other aberrant chromosome numbers) and (2) deletions, duplications, inversions, or translocations of chromosomal fragments detectable by microscopic analysis of high-resolution banded preparations. These changes are not random but occur at fragile sites on particular chromosomes and are often associated with recognizable syndromes (eg, Williams syndrome); their consequences are variable depending on how many genes are affected</td>
</tr>
<tr>
<td>Linkage studies</td>
<td>Link autism (or an autism symptom, or endophenotype) to markers on particular chromosomes</td>
</tr>
<tr>
<td></td>
<td>Extensively used in families with multiply affected individuals to provide the likely pattern inheritance and a putative locus for a causative mutated gene; the many mutations with neutral phenotypic effects are considered polymorphisms (genetic variants)</td>
</tr>
<tr>
<td>Candidate gene studies</td>
<td>Search within families with one of more affected individuals for linkage with mutated genes that are candidates because (1) they were associated with autism in case reports (eg, the genes responsible for tuberous sclerosis or fragile X); (2) the protein the candidate gene codes for is part of a pathway known or suspected to be relevant to autism (eg, neurotransmitters and their receptors, ion channels, transporters, proteins controlling dendritic growth, and so forth); or (3) the detectable candidate gene dosage effect (amount of protein produced) in animal or tissue culture models produces effects relevant to the autism phenotype</td>
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Currently, there is no clinical indication for brain imaging to diagnose or subtype children who have autism. Multiple-subject research studies were required to bring out subtle differences from control subjects, which points to dysfunction in multiple networks as a basis for autism's social cognitive impairments. Four lines of evidence

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<thead>
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<tbody>
<tr>
<td>Full-genome screens for mutations (microarrays and other methodologies)</td>
<td>Search the human genome for molecular abnormalities such as single nucleotide polymorphisms (SNPs): substitutions, insertions, deletions, trinucleotide repeats, and other DNA rearrangements resulting in amino acid substitutions, protein truncation, inactivation, and other changes. Interpretation of these alterations in the genome and their relevance to the condition of interest requires statistical analysis of the strength of the linkage in the population of interest versus control subjects. Genome-wide risk-association studies may examine large numbers (hundreds or thousands) of SNPs but require large populations.</td>
</tr>
<tr>
<td>Copy number variations</td>
<td>Copy number variations are generally de novo (i.e., not found in parents of probands) single-stranded DNA microdeletions, duplications, translocations, and other mutations involving one to several hundred or more nucleotides, identified by high-resolution microarray genomic analysis. They are transmitted as dominant traits to subsequent generations, and their phenotypic consequences are highly variable depending on where they are located in genes or in untranslated sequences.</td>
</tr>
<tr>
<td>Epigenetic effects</td>
<td>Epigenetic effects are the phenotypic effects that arise from microRNAs, which are noncoding RNAs that regulate messenger RNA translation, turning protein production on and off repeatedly in specific cell populations depending on need. MicroRNAs have profound effects on brain development and on moment-to-moment function of vast neuronal networks; because epigenetic effects are highly sensitive to environmental influences, they affect brain development and function as a function of experience.</td>
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strongly support this view: alterations in neocortical minicolumns in the frontal and temporal lobes, abnormal trajectory of head growth, atypical fMRI activation, and diffusion tensor imaging of white matter tracts during early development. The current working model, supported by imaging studies, is brain underconnectivity. This model has shifted conceptual thinking about autism from a focus on fixed anatomy to function within a developmental framework.

**Electrophysiology**

Starting in the 1970s, electrophysiology has been a powerful tool for investigating children who have autism. Electroencephalograms (EEGs) can be used as a clinical tool and a research tool. The utility of the EEG in children who have and do not have autism/language regression and the role of epilepsy and its relationship to autism have been reviewed extensively. Epilepsy does not cause autism. Despite higher rates of epileptiform activity in children who have autism (with and without regression) compared with typical control subjects, the role (if any) of epileptiform electrical discharges in the development of autism and their impact on behavior have not been established. Children who have isolated language regression are more likely to have epileptiform activity on their EEGs than children who undergo language regression within the context of a broader autistic regression. The current clinical recommendation is to obtain an EEG in children who have epilepsy or when epilepsy is suspected clinically but not in every child who has autism with or without language regression.

Electrophysiology as a research tool has the unique strength of providing evidence down to the millisecond range, as opposed to fMRI, which images activity in the minute domain. Electrophysiology enables dissection of sensory-perceptual-memory-readiness correlates of brain processing following trains of stimuli or preceding motor responses and thus has a unique place in research on autism. These properties have been used to demonstrate that in children who have autism, automatic discrimination of infrequent changes in tonal stimuli matures later than in control subjects; detection required active attention until age 9 years compared with its automaticity from age 4 years in control subjects. Such low-level auditory processing deficits have a likely impact in the development of language skills.

A new area of interest in autism research is the role of “mirror neurons” in the sensorimotor cortex, which are activated during the performance of motor acts and while watching others perform them. Discovered in primates, mirror neurons play a critical role in learning by imitation and in understanding similarities between oneself and others, and thus participating in the development of social cognition. There is preliminary electrophysiologic data linking the EEG—specifically, mu frequency (8–13 Hz) wave suppression—to specific imitation skills in children who have autism. The role of mirror neurons in imitation skills and empathy has led to the suggestion that dysfunction of the mirror neuron system may play a significant role in the development of autism, but more research data to support this hypothesis are needed.

Another electrophysiologic technique with significant promise in autism research is magnetoencephalography (MEG), because of its fine resolution in time and space. It has shown itself to be an extremely sensitive tool for detecting auditory processing deficits in children who have autism and deficient language. High-frequency EEG rhythms in the gamma range (30–100 Hz) are thought to be of importance in perceptual and cognitive processes and in intersensory synchronization and binding. Using MEG and a steady-state auditory stimulus, investigators assessed the integrity of local circuits in the auditory cortex of children and adolescents who have autism and found that the production or maintenance of left-hemispheric gamma oscillations was abnormal. It has been hypothesized that the high-frequency EEG rhythms found in
some children who have autism may reflect an imbalance in the excitation-inhibition homeostasis of their brains.62 The developmental dysfunction of γ-aminobutyric acid-transmitting interneurons, minicolumn abnormalities mentioned earlier, and gamma rhythm abnormalities suggest that the sociocognitive deficits found in ASDs may be reflections of abnormal development of neuronal network connectivity.63 Investigators using quantitative EEG in children who have ASDs demonstrated impaired integration of frontal and posterior brain regions suggestive of a pattern of neural underconnectivity.64 Electrophysiologic and imaging technologies are defining the neural networks and interconnectivities that underlie the complex deficits that characterize autism.

**Summary**

The authors have reviewed what they consider to be highlights of promising recent biologic research on autism but stress two caveats. The first is that they consider none of the reviewed advanced technologies applicable to the individual child in the clinic unless they specifically said otherwise. The second is that much of the evidence for relevance to autism that these technologies provide rests on studies of small samples (often no more than a dozen or fewer subjects). Evidence is far from ready for prime time, despite the fanfare with which it is often announced in the press or on the Internet. Yet pediatricians need to be at least as well informed as the parents of the children they care for, which is why this new information is included in this review.

**SCREENING**

The definition of autism as a spectrum disorder, the limitations of our present understanding of the neurobiology of autism, and the heterogeneity at a clinical and biologic level of children who have autism challenge our ability to screen for autism. Nevertheless, recognition of the early signs of autism has progressed significantly. Screening instruments like the Modified Checklist for Autism in Toddlers65 use social behaviors to identify toddlers at risk for autism and distinguish autism from other developmental disorders. More recent understanding of the dimensional nature of social deficits has led to the development of the Quantitative Checklist for Autism in Toddlers.66 The identification and evaluation of children who have ASDs has recently been reviewed comprehensively.67 This report from the American Academy of Pediatrics has excellent tables and algorithms for the different levels of assessment; consequently, the authors do not focus on the screening instruments themselves but instead highlight what they consider to be some of the more salient points at a clinical and research level.

The major lesson to be taken from the development and implementation of screening instruments for autism is that impairments of reciprocal social interaction are the hallmark of ASDs.68 In addition, social interaction is under strong genetic influence, with a continuous distribution of strengths and weaknesses in social interaction in the general population.69 This continuity suggests that the focus for early detection of autism must be to identify the early signs or the building blocks of social skills and that this should be done, when possible, in a quantitative fashion.

One powerful means for identifying the earliest signs of autism is to study the younger siblings of autism probands whose genetics puts them at heightened risk for autism. A number of investigators at multiple institutions in the United States and Canada are using this approach in a collaborative project, known as the “baby sibs project” and are following, prospectively from infancy, the siblings of children who have autism.70 Using the “baby sibs” model, variations in the development of children who have ASDs can be detected as early as age 24 months using a measure of general
development. Studies comparing the early social and communicative development of those younger siblings of children who have autism, aged 12 to 23 months and who turned out to be affected, identified differences in nonverbal problem solving, directing attention, understanding words, understanding phrases, gesture use, and communicative interactions with parents relative to unaffected control siblings. 

Joint attention refers to the capacity of individuals to coordinate attention with a social partner in relation to some object or event. It is one of the earliest and most critical foundations for the establishment of social communication and social cognition in children. One type of joint attention involves an infant’s ability to follow the direction of gaze, head turn, or pointing gesture of another person. This skill is referred to as responding to joint attention (RJA). Another type of skill involves the infant’s spontaneous use of eye contact or gestures (eg, pointing or showing) to initiate coordinated attention with a social partner. The latter type of protodeclarative act is referred to as initiating joint attention (IJA) skill. These early behaviors serve social functions that are impaired in children who have autism, with IJA particularly likely to persist. Studies of siblings show that RJA predicts the development of an ASD as early as 14 months of age. Screening to identify the early signs of autism has improved the ability to intervene early, when the brain is most plastic. The hope is that increasing social responsiveness at an early stage of development will ameliorate downstream sociability. Consequently, identification of specific early indices of social function, such as joint attention, has become a target of educational interventions.

There are no reliable biologic markers to identify and screen children who have autism, although the hope is that genetic or other biologic markers will be forthcoming. Pharmacologic treatment plays a secondary role compared with educational and behavioral interventions. The place of medication is to treat symptoms that interfere with integrating the child into the home and school environment when behavioral techniques have failed. Of note to the medical community: the recent approval of risperidone for the treatment of irritability in children and adolescents 5 to 16 years of age who have autism does not mean that it is “the autism medication.” The lack of outcome measures and data on long-term use of risperidone and other medications highlights severe limitations in the medical treatment of autism. The recent article from the American Academy of Pediatrics on the management of children who have ASDs considers issues in the use of medications and reviews the behavioral and educational interventions for the child who has autism.

**DIAGNOSIS**

The rigorous phenotyping of autism or phenotyping subgroups of children who have autism is essential. At a clinical level, there are many signs and symptoms of autism that also occur in other developmental disorders. Table 3 outlines some of the most salient diagnostic features that differentiate the diagnosis of ASDs from other developmental disorders. The authors emphasize that the one feature that differentiates autism from other developmental disorders is the social deficit. Although autism remains a clinical diagnosis, studies that use standardized criteria can home in on the neurobiology with much greater precision. In addition, outcome can be more clearly studied and interventions compared.

The diagnosis of autism has major implications for society, in that the lay press suggests that autism has become epidemic because its prevalence was previously quoted as 2 to 4 in 10,000 and is currently quoted as approximately 1 in 150. A major contributory factor is that parents and educators have become aware that appropriate, intensive early intervention is effective in many children. Such awareness has
helped to remove the stigma of an ASD diagnosis as a hopeless, untreatable condition (allowing autism to “come out of the closet”) but has also increased the economic burden of autism on our society.\textsuperscript{80}

In addition to increased visibility and awareness of autism, sound epidemiology indicates that changes in diagnostic criteria are a main contributor to the “epidemic.”\textsuperscript{81} In the past, autism was simply not identified in mildly affected individuals who were ignored or given some other label such as communication disorder, attention-deficit disorder with or without hyperactivity, or excessive shyness. Autism was not recognized in severely affected individuals who had profound mental retardation. Autism associated with a defined disease like tuberous sclerosis or fragile X or with a history of very premature birth was not counted because such children already had a diagnosis and there was lack of appreciation that autism was but one of the many symptoms caused by the underlying brain dysfunction. Another factor contributing to increases

<table>
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<tr>
<td><strong>Useful differential diagnostic features with other developmental disorders</strong></td>
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<tr>
<td><strong>Autism Spectrum Disorder</strong></td>
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<tr>
<td><strong>Language impairments</strong></td>
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<tr>
<td>Pragmatics (language use, conversational skill) and prosody universally impaired</td>
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<tr>
<td>Semantics (word choices) often unusual</td>
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<tr>
<td>Grammar and speech articulation impaired in a minority of children; others may speak fluently and grammatically but with abnormal features</td>
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<tr>
<td>Abnormal features salient (eg, echolalia, scripts, perseveration, incessant questioning, answering besides the point frequent)</td>
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<tr>
<td>Comprehension may be worse than expression; often specific difficulty answering questions to which they know the answer</td>
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<tr>
<td><strong>Attention and sleep</strong></td>
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<tr>
<td>Most troublesome is impaired joint attention</td>
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<tr>
<td>Attention may be long for self-selected activities</td>
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<tr>
<td>Impulsivity reflects poor judgment</td>
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<tr>
<td>Multiple sleep awakenings, poor consolidation of circadian sleep cycle</td>
</tr>
<tr>
<td><strong>Sensorimotor issues</strong></td>
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<tr>
<td>Stereotyped or repeated purposeless rhythmic movements frequent, especially in low-functioning children</td>
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<tr>
<td>Decrease in number and amplitude with age in high-, not low-functioning children</td>
</tr>
<tr>
<td>Increased and decreased responses to sensory stimuli in any or all modalities</td>
</tr>
<tr>
<td>Self-injury frequent, especially in low-functioning children</td>
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Abbreviations: ADD, attention-deficit disorder; ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive-compulsive disorder.
in diagnosis is the increased availability and use of standardized screening instruments and measures in handicapped individuals who had or did not have a medical diagnosis, which revealed that many of these patients fulfilled criteria for an ASD. Statistics indicate that as the diagnosis of ASD is made in ever more children, other diagnoses such as intellectual deficiency have decreased, at least somewhat.82

As pointed out earlier, most cases of autism are sporadic, without apparent cause or overt genetic linkage. It is understandable that parents of such children actively search for an explanation for their child’s problem, especially when the toddler’s language and sociability regress and physicians can offer no explanation or specific treatment options. Despite the lack of convincing evidence, many parents bought into the thus-far-unsupported putative evidence for toxic effects on brain development such as thimerosal (ethyl mercury) additives to vaccines or toxic effects of the live measles vaccine. Recent evidence83 and a number of older research studies84 soundly refute these effects, yet parents are difficult to dissuade when no other convincing evidence is available. As more services became available, parents meet other parents, leading many of them to buy into the reality of an epidemic of autism.

When it became clear that very early intensive intervention results in significant improvement in some preschoolers, parents changed from shunning the ASD diagnosis to demanding it. In the United States under federally mandated early intervention, a diagnosis of AD between birth and 3 years brings with it more state-delivered habilitation services than other less specific labels (eg, language or developmental delay). Starting at age 3 years, most state departments of education provide specialized preschool education that ranges from all-day, 11-months-per-year schooling to several hours per week of speech/language/communication training, often physical and occupational therapy, and a variety of other interventions including training in social skills, reciprocal play, and joint attention. At present, the reality of an increase in diagnoses of autism is undisputed, but the reality of a biologically grounded increase remains to be documented. Autism has become part of our culture, and our increased understanding of autism continues to provide us a unique window into the sociocognitive development of all children. Pediatricians are in a unique position to identify children at risk for ASDs and to have a positive impact on their lives and that of their families.

REFERENCES

73. Bruinsma Y, Koegel RL, Koegel LK. Joint attention and children with autism: a re-
74. Alessandri M, Mundy P, Tuchman RF. [The social deficit in autism: focus on joint
76. Whalen C, Schreibman L, Ingersoll B. The collateral effects of joint attention train-
ing on social initiations, positive affect, imitation, and spontaneous speech for
77. Scott LJ, Dhillon S. Spotlight on risperidone in irritability associated with autistic
80. Ganz ML. The lifetime distribution of the incremental societal costs of autism.
81. Fombonne E. Epidemiological surveys of autism and other pervasive develop-
82. Croen LA, Grether JK, Hoogstrate J, et al. The changing prevalence of autism in
83. Schechter R, Grether JK. Continuing increases in autism reported to California’s
developmental services system: mercury in retrograde. Arch Gen Psychiatry
1477–82.