INTRODUCTION

Leo Kanner first described autism in 1943 in his classic paper “Autistic disturbances of affective contact”. Kanner wrote that we must “assume these children have come into the world with the innate inability to form the usual, biologically provided contact with people, just as other children come into the world with innate physical or intellectual handicaps”. Lack of interest in social contact and other characteristics that came to define the syndrome, such as delayed and deviant language development, restricted interest in activities, and stereotypical and repetitive patterns of behavior, were described in the first case report. Thus, from its first description autism was proposed as a neurobiological disorder.
In the following year Kanner proposed the diagnostic
category “early infantile autism”, terminology that was
subsequently used in the third version of the Diagnostic
and Statistical Manual of Mental Disorders (DSM-III) in
1980. Kanner excluded cases with known brain dysfunc-
tion and/or severe intellectual disability in making this
diagnosis. Subsequently, the diagnosis was broadened to
include infants, children, and adults at all cognitive levels
as well as those with neurogenetic syndromes if they met
behavioral diagnostic criteria. Thus, the current diagno-
sis is a broadly heterogeneous grouping. It includes indi-
viduals ranging from a severely intellectually disabled
and non-verbal child with motor stereotypies and self-
injury to a computer engineer with high-functioning
autism and fluent language who is self-centered, has
difficulty in gauging others’ emotions, and exhibits ide-
tional perservation about his obscure interests.

The neurobiology of affective contact and stereotyped/
repetitive behavior in affected children remains a major
theme in autism research. Autism may provide cues to
better understanding how social cognition and affective
engagement emerge in development and the functioning
of social neuronal networks in the brain.

DSM-5, the current classification, introduces a new
term, autism spectrum disorder (ASD), which replaces
the earlier DSM diagnostic category of pervasive devel-
opmental disorders. Moreover, it collapses the subgroups
listed in DSM-IV (autistic disorder, Asperger disorder,
Rett disorder, childhood disintegrative disorder, and
pervasive developmental disorder not otherwise speci-
ied) into this one broad category. ASD is entirely defined
by behaviors in DSM-5. Moreover, DSM-5 collapses
the three core diagnostic domains in DSM-IV into two
domains. In DSM-5 these are (1) deficits in social com-
munication and social interaction, and (2) restricted and
repetitive patterns of behavior, interests, and activities.

Ultimately, the identification of biomarkers – genetic,
biochemical, physiological, or anatomical – that are spe-
cific to one or more of the features of ASD is expected to
resolve controversies about clinical classification. Studies
of identical twins make it clear that there is high heritabil-
ity for ASD. However, ASD is not inherited in a simple
Mendelian fashion. Many genes have been identified that
may contribute to risk. Current neurobiological research
focuses on social and affective neuroscience. Studies of
affective development, social cognition, interpersonal
reciprocity, and repetitive behaviors using neurobiologi-
cal measures are guiding themes in research.

This chapter reviews the history, clinical features, clas-
sification, epidemiology, course, differential diagno-
sis, assessment, diagnostic instruments, etiologies, mod-
els, developmental issues, neurobiology, and treatment
of ASD. Although most of the research summarized here
comes from studies of typical autism, consideration is
given to the full range of severity. The main emphasis is

on understanding ASD from a neurobiological perspec-
tive as a grouping of disorders of early brain develop-
ment that begin in utero but dynamically change over
time and continue throughout life.

**HISTORY**

The descriptive term “autism” was chosen by
Kanner to emphasize the sense of social aloneness appar-
ent to those who observed children with this condition.
“Autism” refers to paucity of social self-awareness in
relationship to others and in the use of the imagina-
tion. Kanner described case histories of 11 children, 2–8
years of age, who presented with previously unreported
behavior. He described them as socially remote, insis-
tent on maintaining sameness in their environment, and
with stereotypies and echolalia, the repeating of speech
sounds made by others. These children failed to initi-
ate socially meaningful anticipatory gestures. They did not
reach to be picked up, ignored animate people in the
environment, and appeared to be “in a world of their
own”. Kanner’s initial report documented similarities in
their behavior. His follow-up of these cases 28 years later
documented the differences among them.

Despite Kanner’s early description of its features,
autism was classified as a childhood form of schizophre-
nia in DSM-I. It was not until 1980 with the publication of
DSM-III that specific diagnostic criteria for autism were
introduced in a DSM. Before DSM-III, “childhood schizo-
phrenia” or “childhood psychosis” was broadly used to
diagnose children with severe psychiatric disturbances
beginning in early life. Research in the 1970s made clear
that autism was distinct from childhood schizophrenia
based on the age of onset, symptom presentation, and
clinical course. Thus, 37 years after the original descrip-
tion of infantile autism (with onset before age 30 months)
as a diagnostic category, it entered the official classifica-
tion system. In DSM-III the term pervasive developmental
disorder was introduced to describe deviant develop-
ment in multiple developmental lines involving social
skills, language, attention, and perception. The DSM-III
definition specified an age of onset before 30 months of
age, pervasive lack of responsiveness to others, deviant
language development, unusual responses to the envi-
rnoment, and the absence of hallucinations and delusions
as found in schizophrenia (see Chapter 39). Further revi-
sions were made in DSM-III-R in 1987 because the origi-
nal criteria applied best to younger and more severely
impaired individuals and were considered too restrictive.

The DSM-III-R recognized the importance of changes
in syndrome expression during development and included
more developmentally focused criteria, lead-
ing to a change in the name of the category from “infan-
tile autism” to “autistic disorder”. Furthermore, its

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differentiation from schizophrenia was further clarified so that an individual with an autistic disorder might have both diagnoses if the additional diagnostic criteria for schizophrenia, such as the presence of hallucinations and delusions, were met. The major change in DSM-III-R was the introduction of the developmentally focused criteria. Yet DSM-III-R broadened the concept of autistic disorder substantially so that more false-positive cases were reported. DSM-III-R identification of more atypical cases complicated its use for both clinical and research purposes, leading to additional modifications in DSM-IV.

The changes introduced in DSM-IV in 1994 were developed to provide greater simplicity in diagnosis while maintaining compatibility with the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) of the World Health Organization, but with greater emphasis on clinical judgment. Moreover, additional categories were added in DSM-IV under the “pervasive developmental disorder” terminology to include Rett disorder, childhood disintegrative disorder, and Asperger disorder.

“Asperger disorder” was introduced in DSM-IV based on renewed interest in people with high functioning autism. Hans Asperger, in 1944, described the clinical presentation of four children whose intelligence was in the normal range, with good grammar and vocabulary, but who were odd socially, and had poor non-verbal communication, limited interests, and poor social communication. Asperger’s paper (in German) drew little attention until 1981, when Lorna Wing brought it to general attention. In DSM-5 Asperger disorder was incorporated under the umbrella term ASD.

**CLINICAL FEATURES**

**Deficits in Social Communication and Interaction**

ASD is characterized by persistent impairment in reciprocal social interaction and communication. The severity and nature of the social deficit vary with the child’s age and developmental level but the deficit is present from very early childhood and impairs functioning at home, in school, and in the community. Because there is a range of presentations depending on developmental level, severity, and chronological age, the term “spectrum” is used. The impairment is sustained throughout the lifetime, however, compensation for some clinical features may occur across development thus the condition is dynamic, not static.

In infancy, children with ASD may resist cuddling and not mold to the parent when held. As toddlers and during their preschool years, they often ignore others, even bumping into them or walking over them as if they were unaware of their existence. They may not turn in recognition of being called by name or look at or towards someone seeking to engage them in conversation. Gaze avoidance may continue into school age and even into adulthood in a less striking form. Lower functioning individuals may be mute. Others who speak are one-sided in conversation and do not engage in reciprocal social exchange. Thus, they ignore the social conventions of taking turns in conversation and waiting for a reply before speaking again. As adults their deficits in social emotional reciprocity may be most apparent when having to respond to complex social cues, not knowing when to initiate a conversation or how to sustain one with others, and not appreciating what is socially intuitive in typical development.

Higher functioning children, adolescents, and adults may have learned many social skills but continue to have social deficits. These are recognized through socially intrusive behaviors, an inappropriate lack of awareness of others’ feelings, and general misunderstanding of the negative impact that their behavior can have on others. This may result from limited ability to interpret the tone of voice or facial expression of another person. These higher functioning individuals have difficulty making friends when they wish to do so and in engaging others in play. Those who seek friends may be ostracized for their social awkwardness when they attempt to socialize. Thus, people with an ASD are rigid and often stereotyped in their social responses and need to be taught simple social rules and patterns of proper interacting, such as greeting another person. The verbal individual with an ASD may learn social rules, often by rote, but not apply learned rules appropriately in a social context.

The failure to acquire language at the chronologically expected age is the most frequent presenting concern by parents of preschool children with ASD. Early in life, children who are verbal may be echolalic, that is, they repeat a question back rather than responding to it (immediate echolalia). Such echolalia, a repetitive behavior, may be associated with a reversal of pronouns, that is, the child refers to himself as “you” or by name, rather than using the word “I” appropriately in conversation.

Most affected preschool children have some type of developmental language difficulty. These difficulties are not simply in language expression but often involve impaired comprehension and pragmatic use of language. Some may be mute, and others may have problems understanding conversation directed towards them. Others do develop language but speak unintelligibly or do not use appropriate sentence structure. Those who speak late may use jargon that does not have communicative intent. This includes phrases they have heard or memorized from cartoons or television commercials. Verbal children may speak in a monotone, too softly or loudly, or in a singsong manner. Typically, there is a deficit in the use of speech rhythm and intonation (prosody) and failure to question to clarify the meaning of another’s speech.
An abnormality in inner language development is also a characteristic feature and is most often demonstrated in observations of play routines that reveal the lack of flexibility in inner language use and imagination that is characteristic in ASD.

Acquired speech fluency can be misleading because many children with ASD lack comprehension of what is said to them. This is especially evident when questions are addressed to them about their personal life experiences. Others show relatively normal language development and speak more appropriately; however, they are often preoccupied with a narrow range of their own favorite topics. They pursue these topics in conversation, showing little regard for the interests or responses of the person with whom they are speaking. Moreover, they may perseverate by asking the same questions over and over again, even though they have already heard the answers. In some instances, they may repeat and recite phrases they have heard. In doing so they may exactly imitate the tone of voice and rhythm of the original speaker.

Deficits in pragmatic language use, a form of non-verbal communication, are most evident when the affected child does not use gestures in initiating social contact or conversation. Young children with ASD generally do not initiate anticipatory gestures, for example, to be picked up when approached or when they approach others. They demonstrate limited or no joint attention when engaged. This is shown through not using eye contact to engage another person when pointing to an object. They do not bring items to show to others and fail to follow the gaze of an adult looking towards an object.

Although children typically begin to point to things they like with one finger at about 9 or 10 months and begin shaking their head “no” by 1 year of age, affected children are limited in developing such non-verbal behaviors. Instead of pointing at a desired object, they may seek out objects for themselves or move the parent’s hand towards the preferred object. Lacking the use of gesture for their communicative intent, an affected child may become distressed and cry or have a tantrum until an adult has guessed, often by trial and error, what the child seeks or needs. They must be taught how to participate in a person-to-person conversation: to look at the conversational partner; to interpret tone of voice, facial expression, and body language; to maintain the topic in conversation; to take turns.\(^\text{10}\)

**Restricted, Repetitive Patterns of Behavior, Interests, or Activities**

Children with diagnoses of ASD routinely show restricted patterns of behaviors, interests (ideological perseveration), and activities. The presentation varies with age, cognitive ability, and the extent of environmental support. Behaviors may be simple repetitive patterns of movement (stereotypies and mannerisms) that include hand flapping (especially when excited), twirling, rocking, head banging, finger posturing, and sensory preoccupations. More complex behaviors can include repetitive use of objects (lining up toys), repetitive speech (echolalia, stereotyped use of phrases), and restricted interests (preoccupation with train schedules) and activities (insistence in following the same route when traveling).

Commonly, affected children may resist changes in routines in their everyday environment, preferring to maintain sameness. For example, they may be quite distressed when a familiar object is moved to a new location. Repetitive use of objects is common. This includes flicking a string, turning light switches on and off, repetitively tearing paper into shreds, or turning a toy car over and spinning the wheels rather than rolling it along. Some children may become preoccupied with objects, have odd food preferences, react negatively to changes in lighting, hold their hands over their ears to block out certain sounds (a vacuum cleaner, sirens), and show increased or decreased sensitivity to pain.

A lack of imagination in play is apparent in ASD from the preschool years. Play figures may be manipulated, used for self-stimulation, lined up, and used in repetitive ways rather than with imagination. Recognition that figurines, used in play, represent people is delayed. Higher functioning children can show forms of pretend play, such as feeding a stuffed animal or putting it to sleep. However, such pretend play tends to be repetitious and lacking in flexibility.

Verbal children, adolescents, and adults often become preoccupied with topics of interest and programming [those with higher intelligence quotient (IQ) and better language] learn to suppress their repetitive behaviors in public but pursue them in private. Such interests may continue to be a source of pleasure for them and may be used as motivators in behavioral treatment and education.\(^\text{10}\)
DEFINITION AND CLASSIFICATION

In DSM-5 clinical features of ASD are summarized as persistent deficits in social communication and social interaction across multiple settings – home, school, or community – and restricted, repetitive patterns of behavior, interests, or activities. These include deficits in social reciprocity, non-verbal communicative behaviors used for social interaction, and skills in developing, maintaining, and understanding relationships. Because behaviors change with development, diagnostic criteria may be met based on a history of having met the criteria in the past.

Specifiers and moderators replace DSM-IV subgroups. Thus, within the diagnosis of ASD individual clinical characteristics are recorded using specifiers that include (1) with or without accompanying intellectual impairment, (2) with or without accompanying structural language impairment, (3) associated with a known medical/genetic or environmental/acquired condition, and (4) associated with another neurodevelopmental, mental, or behavioral disorder. Other specifiers focus on the autistic symptoms themselves (age at first recognition; onset with or without loss of established skills) and severity. Severity is based on the level of support needed for each of the two domains, social communication impairments, and restrictive, repetitive patterns of behavior. Table 2 in the DSM-5 manual gives examples for three levels of support for each domain: level 1, requiring support; level 2, requiring substantial support; and level 3, requiring very substantial support. The severity of each of the domains is recorded separately.

Specifiers provide clinicians with an opportunity to individualize the diagnosis and communicate a more complete clinical description of an affected person to others. For example, many individuals previously diagnosed with Asperger disorder in DSM-5 would be diagnosed as ASD without language or intellectual impairment. Specifiers are needed for a full clinical characterization. Specifiers can also be used to facilitate identifying subgroups for research case identification. It is expected that new research studies will require additional specifiers when developing research protocols. Those wanting more detail about the diagnostic criteria for ASD should consult the DSM-5.

EPIDEMIOLOGY

The prevalence of individuals diagnosed with ASD has risen substantially since the 1980s. The rate for classic autism based on community samples in the 1960s was 2–4 per 10,000. Currently, the rate of the ASD (including classic autism) is 30–100 per 10,000. For classic autism it is 13–30 per 10,000. The major rise in prevalence is not fully accounted for by identifying ASD associated with severe intellectual disability. It is more likely that more individuals are being identified with non-verbal IQ in the normal range help to account for the difference.

This substantial increase in rates is documented in the USA, Japan, Scandinavia, and several other European countries. Because the increase is found in so many different countries it seems unlikely that the cause is environmental because an environmental factor would have to act simultaneously across diverse settings. The increase in rate started in the 1980s when the diagnostic term “pervasive developmental disorder” was introduced, broadening the diagnosis. With the change in definition, more high-functioning cases with better language skills and higher IQ were diagnosed. The focus in diagnosis shifted from a focus on a severe, highly deviant, discontinuous grouping to a continuum of deficits that were less severe. This new dimensional view reduces boundaries and makes differences from other developmental disorders and psychiatric syndromes more difficult to establish.

A substantial proportion of the increase is believed to be the result of changes in diagnostic practices. Because of changes in criteria over time, trend analyses of data sets or of national registries are not sufficient to determine differences. Exploration of environmental risk factors should be based on prospective cohort or population-based case-control studies. Thus, increased awareness of the diagnosis, inclusion of subthreshold cases, and changes in study methodology using systematic standardized instruments are important factors in understanding the increasing rates.

The claim that increased prevalence is linked to the measles–mumps–rubella (MMR) vaccine or the mercury-containing preservative thimerosal in the vaccines has no empirical support. The original 1988 paper making this claim was retracted by the journal The Lancet as scientifically flawed, and well-designed trials and meta-analyses have found no evidence of any association. In Japan, removal of MMR vaccine from use was not followed by any fall in the rate of autism, or even by a reduction in the rate of rise. Similarly, the discontinuation of use of the vaccine preservative thimerosal in Scandinavia was not followed by any change in the rising rate of autism. Although there may be a link to other prenatal or postnatal factors or other toxins, so far there has been no confirmation of the involvement of any environmental factor in the rising rates of ASD. One element that could contribute to a rise in rates, if one truly has occurred, may be the rising age of parenthood. There is evidence that increased parental age is associated with ASD; thus, older parenting may contribute to an increased rate of autism. Older parental age, particularly paternal age, is correlated with an increased risk of copy number variation (CNV) (submicroscopic chromosomal duplications or deletions) and of de novo single nucleotide variation.
(SNV) (or mutation). An increase in both CNV and deleterious de novo variants is reported in autism.

ASD is diagnosed four times more often in males than in females. The reason for male vulnerability for ASD and other neurodevelopmental disorders is an area of ongoing interest. Females with an ASD diagnosis are more likely to have a co-occurring intellectual disability. Girls without intellectual impairments or language delays may go unrecognized, potentially because of subtler social or communication problems.

Intellectual deficits co-occurs in a substantial number of ASD cases. The prevalence of intellectual deficits in classic autism is approximately 60%, with rates of severe and profound ID deficits ranging from 8% to as high as 40%. This raises issues about when to diagnose and how to apply the criteria, because the social deficit may lack specificity in low-functioning children. In contrast, when the full autism spectrum is considered, the rate of intellectual deficits is approximately 30 to 40%.

Approximately 5–10% of ASD cases are associated with a variety of neurogenetic disorders. When large community samples of cases of ASD are surveyed, neurogenetic syndromes are rare. Certain syndromes such as tuberous sclerosis and fragile X syndrome (see Chapter 8) include significant numbers (30%) who meet ASD criteria.

Finally, epilepsy (see Chapter 17) is associated with autism, with estimates of the occurrence of seizure that vary from 5 to 44%. Onset of epilepsy follows a bimodal distribution, with some children presenting with epilepsy in the first few years of life, often preceding the diagnosis of autism, and more commonly, others developing epilepsy in the teenage years. Signs of epilepsy may be present on electroencephalograms in children with ASD who have no clinical evidence of seizures. It is unclear whether these children are at higher risk of developing epilepsy later in life.

**NATURAL HISTORY**

There is considerable heterogeneity in the age of recognition of an ASD. Most children with an ASD are recognized in the second year of life. However, parents may report non-specific problems earlier with feeding, settling, and sleep. There may be limited responsiveness to others, reduced anticipatory gestures, and excessive quietness during infancy, or, in contrast, excessive irritability and screaming. If there is another child in the family with an ASD diagnosis, parents may be more sensitive in recognizing social deficits. Home videos from 12–18 months or earlier in life may document subtle abnormalities of development.

In most children with ASD, early language development is deviant, with difficulties in both the comprehension of speech and the expression of ideas. Although markedly impaired in verbal and non-vocal symbolic processes, affected children may be good at non-symbolic matching and assembly tasks.

Approximately one-quarter to one-third of all children with ASD in studies carried out in the USA, the UK, and Japan lose previously acquired language skills, most often between 18 and 24 months. Attention deficits and new stereotypical movements sometimes accompany loss of language use. These children may initially show near-normal development until as late as 18–24 months of age, when they regress. However, their clinical picture is generally indistinguishable from those with early onset.

Academic achievement and social adaptability may improve with special education. Verbal skills are the best predictor of social adaptive functioning. Academic achievement is related to intellectual functioning, and early non-verbal IQ shows a positive relationship to outcome. However, academic achievement declines when task demands for abstract reasoning exceed rote memory skills. Academically high-functioning children may be returned to special education classes because of deficits in interpersonal skills. For example, high-functioning affected children who have been mainstreamed in grade school sometimes return to special education during the high-school years.

Approximately 15–20% of children who show some autistic behavior in their early years gradually emerge from autistic social withdrawal. Some make a relatively good social adjustment although they may continue to have unusual and eccentric behaviors as adults. Adult adjustment is judged based on the capability for independent living and employability. Moderately impaired individuals may work successfully in areas where their careful attention to detail and preoccupations can be channeled into jobs requiring completion of repetitive tasks. They may be most successful in job settings that require the least interaction with others. Other employees who are aware of an obvious disability may help and support them. Achievement by the group who are most successful academically may be limited by their social deficits, particularly by difficulty in language comprehension and poor judgment in social situations. Employers may not appreciate the extent of their limitations in social problem solving and social adjustment. Successful social adjustment requires self-awareness of difference from others on the part of the person with ASD as well as special education programs specifically focused on his or her social, language, and cognitive impairment.

In one study, the outcome of a supported employment program over a period of 6 years was examined for adults with autism or Asperger syndrome (with an IQ of 60 or above). Approximately two-thirds found employment. Of the 192 jobs obtained, most were permanent contracts and involved administrative, technical, or computing work. IQ, language skills, and educational attainments predicted success. Supportive employment is also
beneficial for those with lower abilities. Job coaches are used to provide support for them at the job site.

Affective Development

Kanner’s initial report focused on deficits in affective contact with others. Learning to recognize and respond to another’s emotional state is a developmental milestone. When affective development is monitored in children with ASD, aggression towards others, sadness when frustrated, and apparent joy when pursuing interests are reported. Although fears, for example of animals, may be expressed, general awareness of risk and danger and an understanding of dangerous situations are lacking. The transition from lack of social awareness to social engagement and perplexity about social situations may be heralded by exaggerated emotions and behavioral difficulties, including intrusive behavior.

Studies of affective development address the ability to comprehend affect in social relationships. Overall, people with an ASD do not attend to faces or use information from faces, as do typically developing children. In the preschool years (ages 2–4), children with ASD show fewer observed intervals of affective response, positive or negative, when interacting with familiar adults than age-matched controls. They may perform better than matched control subjects in recognizing faces that are shown to them upside down, suggesting that the lower portion of the face, rather than the upper portion, is used in facial recognition of another person. Thus, they may focus more on the mouth than on the eyes to identify facial expressions in others. They have more difficulty in matching videotaped segments or pictures of gestures or vocalizations, and more trouble understanding the situational context of photographed or drawn pictures of facial expressions. If given a choice on which cue to use to identify others, affected children may use items of dress, such as hats, rather than facial expression to identify. They are less able to imitate an emotion when asked to do so, or to imitate an affect demonstrated by another person. Affective responses are generally reported to be flat and not contingent on the particular situation observed. Familiar teachers and caretakers suggest that children with ASD show all facial expressions except for surprise. When they look at themselves in the mirror, children with ASD show less positive affect and less self-consciousness than control children.

Psychiatric Disorders and Forensic Issues

As children with ASD reach adulthood, they often develop co-occurring psychiatric disorders. Depression and anxiety (discussed in Chapters 43 and 37, respectively) are particularly common. Depressive symptoms lead to poorer global functioning. In one follow-up study of 135 children to age 21 years, 16% developed a definite new psychiatric disorder. Five were diagnosed with an obsessive–compulsive disorder and/or catatonia. Eight were diagnosed with an affective disorder with marked obsessional features and three with complex affective disorder. One was diagnosed with bipolar disorder (discussed in Chapter 40) and one an acute anxiety state complicated by alcohol excess. There were no cases of schizophrenia, consistent with earlier studies that these are distinct conditions. However, there are reports of psychotic symptoms with hallucinations and delusions that tend to be diagnosed as brief reactive psychosis.

Because of their inappropriate social behavior, people with ASD may have legal problems. These range from misunderstandings caused by socially inappropriate behavior with strangers to apparent criminal activity linked to their obsessional interests and perseverations (see Chapter 38), and violent outbursts. Their deficits are important in forensic evaluations of culpability and determination of ASD as a mitigating factor when determining criminal responsibility. This is particularly important when considering whether incidents of criminal or violent behavior are intended or unintended. Three characteristic deficits that are pertinent in forensic settings are theory of mind (understanding another person’s perspective), regulation of emotions, and moral reasoning (understanding the consequences of one’s actions). Published studies suggest rates of about 2% in a special hospital for criminal offenders for high-functioning ASD, although in one study violent behavior was rare.

Predictors of Outcome

In children with an ASD, language skills are the best predictors of social outcome. Because of the frequent wide discrepancy in verbal and non-verbal IQ, non-verbal IQ is frequently used in determining outcome. Those with non-verbal IQ in the normal range have the best outcomes. Those with non-verbal IQ less than 50 in the preschool years are far less likely to acquire useful spoken language and have an increased risk of poor social functioning during adolescence and adulthood.

Higher IQ and language skills alone are not sufficient to ensure good social outcomes. Targeted psychoeducational experiences beginning early in life are needed, and care must be directed towards ensuring appropriate transitions from primary to secondary school and into adult life. Even higher functioning people with ASD may find gaining employment and living independently challenging, and the support of the family and social agencies may be needed to maintain life in the community.

Key to good outcomes is appropriate early intervention. This entails understanding the autistic nervous system. Early interventions target social engagement. In early life, focused interventions may begin with
facilitating joint attention, verbal imitation, and social communicative aspects of adaptive skills.

**DIFFERENTIAL DIAGNOSIS**

**Selective Mutism**

In selective mutism, children speak normally in the home environment but do not speak in one or more other settings. In these children, early development is normal and includes appropriate social engagement and communication skills. Even when mute, the child demonstrates social reciprocity and does not show restricted or repetitive patterns of behavior and stereotypies.

**Language Disorders**

With language disorders, difficulty in communication may be associated with secondary social problems. However, specific language disorders (receptive and expressive) ordinarily are not associated with deficits in non-verbal communication, nor are they associated with restricted, repetitive patterns of behavior, interests, or activities.

**Social (Pragmatic) Communication Disorder**

Social (pragmatic) communication disorder is a new diagnosis in DSM-5. As a disorder of pragmatic language it involves persistent deficits in social use of language and communication (e.g. greeting others, sharing information socially), impaired flexibly in changing context to meet the needs of the listener in a conversation, and impaired ability to follow the rules of social reciprocity in conversation (taking turns in speaking and listening, using verbal and non-verbal signals to regulate social conversation, making inferences, and understanding metaphor and humor in social exchange). An individual with a diagnosis of social communication disorder differs from a person with an ASD because he or she does not show restricted and repetitive behavior or interests. An ASD diagnosis supersedes that of social communication disorder if the criteria for ASD are met. When there are deficits in social communication it is essential to ask about past or current restricted or repetitive behavior to rule out ASD.

**Intellectual Disability (Intellectual Developmental Disorder)**

Behavior in individuals with intellectual disabilities may be difficult to differentiate from ASD in very young children and those with severe and/or profound levels of intellectual disability because of a failure to have developed language or symbolic skills and because simple repetitive behavior can occur in cases of intellectual disability. The diagnosis may be made when social communication and interaction are significantly impaired relative to the developmental level of the individual’s non-verbal skills (e.g. fine motor skills, non-verbal problem solving). Conversely, intellectual disability is the appropriate diagnosis if there is no apparent discrepancy between the level of social communicative skills and other cognitive and intellectual skills.

**Stereotypic Movement Disorder**

Because motor stereotypies are diagnostic features of ASD, the diagnosis of stereotypic movement disorder is not made when repetitive behaviors are better explained by ASD. Moreover, certain repetitive behavior such as lining up objects and patterns of hand flapping are more consistently found in ASD. However, when stereotypies causing self-injury are a focus of treatment, both diagnoses may be given.

**Attention Deficit/Hyperactivity Disorder**

Deficits in executive functioning, sustained attention, overly focused attention, easy distractibility, and hyperactivity are common in individuals with an ASD [see Chapter 4 for a presentation of attention deficit/hyperactivity disorder (ADHD)]. When criteria are met in DSM-5, both diagnoses may be given when attention dysregulation, impulsiveness, or hyperactivity exceeds that typical for children of comparable mental age.

**Schizophrenia**

In early-onset child schizophrenia (see Chapter 39), a prodromal state with social impairment and atypical interests and beliefs may occur, which may be confused with the social deficits identified in ASD. However, hallucinations and delusions, which are defining features of schizophrenia, are not characteristic of an ASD. In differential diagnosis clinicians must recognize that thinking in individuals with an ASD is generally concrete and associational. For example, when responding to questions such as “Do you hear voices when no one is there?” a person may respond concretely (e.g. “Yes [on the radio]”), or when asked what you do when you cut your finger may make an associational response, “San Diego Clippers” and proceed to list statistics for each team member. Such responses are the result of a language disorder in ASD and do not indicate schizophrenia.

**Rett Syndrome**

Rett syndrome is a rare genetic disorder of known etiology (disruption of the X-linked gene MECP2, a
translational repressor) that was categorized in DSM-IV as a pervasive developmental disorder (see Chapter 7). Unlike ASD, it occurs almost entirely in girls (rather than boys) and is phenotypically distinct from ASD. Moreover, unlike in ASD, where there may be a period of accelerated brain growth and macrocephaly, in Rett syndrome there is microcephaly and slowing of brain growth. In Rett syndrome, hand stereotypes are simple midline hand clasping (with loss of pincer grasp), whereas in ASD hand stereotypes are peripheral and complex, often hand flapping. Those with Rett syndrome test in the severe/profound range of intellectual disability, have seizure onset in early childhood, and show a distinct difference in postmortem neuropathology. In Rett syndrome there may be an encephalopathic regressive phase of social withdrawal (typically between 1 and 4 years of age) that differs from characteristic social deficits in ASD. After this period, a substantial proportion of affected young girls improve in their social relatedness. Because of these differences Rett syndrome is no longer classified as an ASD.

Severe Environmental Deprivation

When institutionalized children are both psychosocially deprived of interpersonal care and environmentally deprived of sensory stimulation from the beginning of life beyond 6 months of age, the term quasi-autism has been used. About one in six Romanian orphans who experienced this degree of severe deprivation have ongoing social deficits. Such deficits result from failure of environmental provision and lead to disturbed attachment behavior. However, these environmentally deprived children do not show the typical features of ASD.

ASSESSMENT

Confirmation of the diagnosis of ASD is based on the clinical history, neuropsychiatric interview, and observational assessment. An interdisciplinary team of professionals who meet after the assessment period to develop a comprehensive treatment plan conducts the assessment. This interdisciplinary assessment includes a standardized intelligence test and other psychological tests, speech and language testing, and assessment by occupational and physical therapists and social workers as appropriate. Hearing testing may be indicated. When the child cannot cooperate in standard behavioral audiometry, brainstem auditory evoked response measures may be carried out.

Several psychometric assessment instruments are available for the assessment of ASD symptoms and behaviors. Structured instruments and rating scales are used in conjunction with diagnostic information drawn from the child’s developmental history and reports from informants about behavior at home, in school, and in the community. The most comprehensive interview and observation scales are the Autism Diagnostic Interview™, Revised (ADI-R) and the Autism Diagnostic Observation Schedule™ (ADOS). These instruments were designed to evaluate children with a diagnosis of idiopathic autism. The validity of the ADI-R and ADOS in evaluating children with intellectual disability has poor to moderate agreement between the ADI-R and clinical judgment. The sensitivity and specificity of both the ADI-R and the ADOS are diminished in very young children and individuals with lower developmental ages.

Although family members may inquire about blood and urine tests, genetic assessment, electrophysiological studies, and neuroimaging to confirm a diagnosis of an ASD, there are no specific biomarkers. However, testing is carried out to assure that the condition is not progressive and to rule out known metabolic disorders, neurological conditions, or neurogenetic syndromes that may be associated with the diagnosis.

The clinical history emphasizes the development of sociability, language development, imaginative play, the presence of stereotypes, and abnormal responses to sensory stimuli. Although autistic symptoms ordinarily are not related to birth events, birth history and history of intrauterine infections and postnatal infections and accidents that may involve the brain are included in the assessment history. Because of potential heritability, a family history of autism and/or other developmental disorders, specific psychiatric disorders, such as mood disorders, and conditions involving the brain are assessed.

The physical examination evaluates for signs of specific disorders that have been associated with autistic-like behavior, such as tuberous sclerosis, congenital rubella, and fragile X syndrome. The mental status examination is primarily observational for younger children. It includes efforts to engage the child in meaningful social interactions and, for verbal children, in conversation. Imaginative play is assessed using toys in younger children. For those with less severe involvement, subtle difficulties in the child’s relatedness and imaginative play must be assessed. Observations are carried out to evaluate gaze avoidance, difficulties in initiating social communication, and problems with joint attention, stereotypes, and repetitive behaviors and interests.

NEUROPSYCHOLOGICAL PROFILE/COGNITIVE FUNCTIONING

Cognitive impairment is a result of the neurodevelopmental disorder. The neuropsychological phenotype includes attention/arousal, long-term episodic memory, executive function, and social cognitive deficits. People with ASD generally have uneven profiles on subtests of versions of the Wechsler Adult Intelligence Scale (WAIS) and the Wechsler Intelligence Scale for
Children (WISC), in contrast to IQ-matched controls. The major differences are on subtests dealing with verbal abstraction, sequencing, visuospatial skills, and rote memory. These deficits are thought to impair normal language acquisition and social functioning.

The “theory of mind” paradigm may be assessed. Theory of mind refers to the ability of normal children to attribute mental states, that is, beliefs, desires, and intentions, to themselves and to other people as a way of predicting and making sense of the mental states of others. Metarepresentational deficits are thought to impair an autistic person’s comprehension of the mental states of others’ behavior. Individuals with an ASD may show significantly poorer performance on tests of their understanding of others’ beliefs and knowledge. However, an autistic person’s social problems are not fully accounted for by conceptual impairment in interpersonal understanding, although this may be an essential feature. As Kanner proposed, children with ASD lack a capacity to form affective contact with others and to develop intimate friendships as they grow older, despite their wish to do so. Their lack of understanding of others’ beliefs and desires may not be an adequate explanation for the quality of their non-verbal communication disorder and relationship difficulties. Although executive dysfunction may be present, it is not a core neuropsychological deficit in ASD.

**NEUROBIOLOGY**

Although autism was first described in 1943, the first studies of possible neurobiological bases for ASD did not begin to appear until the late 1980s, almost half a century later. Many of these are neuroimaging studies of the brains of people with ASD diagnoses that seek to correlate the behavioral features and core impairments with differences in brain anatomy. Figure 6.1 shows brain regions that are proposed to be linked to social and communicative impairments and repetitive behaviors.

The sections that follow review other neurobiological findings.

**Trajectory of Brain Growth**

ASD is a heterogeneous disorder with multiple behavioral and biological phenotypes. Accelerated brain growth during early childhood is a well-established biological feature of autism. Macrocephaly occurs in approximately 20% of affected individuals and was recognized in Kanner’s original publication. It is usually due to megalencephaly (abnormal enlargement of the brain). At birth, head circumference is essentially in the typical range. Overgrowth is recognized during the first 18 months of life, when head growth typically accelerates. By 3–4 years of age there is an average increase in brain size by about 10% in those affected. Accelerated brain growth begins before most clinical features. Brain changes have been demonstrated using magnetic resonance imaging (MRI) and other imaging methods. These studies document the overall mean volume of the brain. Increased white matter and gray matter lead to increased volume of the cerebral cortex. These findings are not accounted for by the intellectual disability quotient, psychotropic medication use, or comorbid psychopathology.

Cortical thickness, like brain volumes, may follow a period of early overgrowth followed by early arrested growth. One study evaluated 330 head circumference measures collected longitudinally between birth and 18 months of age from 35 male children with autism and a comparison group of 22 typically developing control subjects. Analyses revealed significantly thinner cortex in the ASD group with findings located predominantly in the left temporal and parietal lobes. Participants with ASD in another study had thinner cortex in the left fusiform/inferior temporal cortex compared with typically developing individuals. Thus, there may be a second period of abnormal cortical growth when greater thinning may be involved.

Various mechanisms have been proposed with regard to whether the changes reflect an excess of neurons and/or reduced synaptic pruning during development. Neurogenesis is complete during uterine development in the prefrontal cortex and throughout the entire cerebral cortex. Developmental programmed cell death (apoptosis) occurs before and soon after birth. Such processes affect the net number of neurons in childhood. Thus, an increase in neurons would be consistent with prenatal origin. Postmortem cortical gray matter in the prefrontal cortex was examined in an autopsy study. The investigators found 79% more neurons in the dorsolateral prefrontal cortex and 29% more in the mesial prefrontal cortex when seven brains of boys with autism were compared with matched controls. These authors proposed that increased neuron number in the prefrontal cortex is correlated with accelerated postnatal brain growth and macrocephaly in early childhood. However, because the relationship is complex, research on neuron numbers in the prefrontal cortex is needed in both children and adolescents. Studies are required for those who do not have brain overgrowth as well as for non-autistic children with benign megalencephaly to clarify whether increased prefrontal neuron count in autism is associated only with autism. Cortical neurons are generated in prenatal life; therefore, a pathological overabundance of neurons indicates early developmental disturbances in critical brain regions.

The pattern of symptom onset has been closely studied in ASD but little is known about how it may be related to brain growth. Failure of developmental progression with loss of acquired skills is documented in
25–35% of affected children in epidemiological studies. Typically, in the second year of life in affected children attention become diffuse, acquired word use is lost, and motor stereotypes become apparent. The relationship between total brain volume and onset of ASD symptoms was examined in affected 2–4-year-old boys and girls and comparisons were made between 53 cases with no regression and 61 who regressed, along with a comparison group.\textsuperscript{31} When head circumference measurements from birth to 18 months of age were examined, abnormal brain enlargement was found most often in boys with behavioral regression. Evidence was found that brain enlargement is associated with ASD in preschool-age boys but not girls. In boys without regression the brain did not differ from controls. Thus, rapid head growth may be a risk factor in boys with onset of regression in the second year of life.

ASD is typically diagnosed by around 18 months of age. Little information is available on brain development at 6 and 12 months of age. A prospective infant sibling study...

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Social impairment & Communication deficits & Repetitive behaviors \\
\hline
OFC – Orbitofrontal cortex & IFG – Inferior frontal gyrus & OFC – Orbitofrontal cortex \\
ACC – Anterior cingulate cortex & (Broca’s area) & ACC – Anterior cingulate cortex \\
FG – Fusiform gyrus & STS – Superior temporal sulcus & BG – Basal ganglia \\
STS – Superior temporal sulcus & SMA – Supplementary motor area & Th – Thalamus \\
A – Amygdala mirror neuron regions & BG – Basal ganglia & SN – Substantia nigra \\
IFG – Inferior frontal gyrus & SN – Substantia nigra & Th – Thalamus \\
PPC – Posterior parietal cortex & PN – Pontine nuclei cerebellum & PN – Pontine nuclei cerebellum \\
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\end{tabular}
\caption{Major brain regions that may be relevant to the core features of autism spectrum disorder.} \end{table}
completed longitudinal MRI scans at three time-points along with behavioral assessments. Fifty-five infants were examined: 33 “high-risk” (with an affected sibling) and 22 “low-risk” infants were imaged at 6–9 months; 43 of these (27 high-risk and 16 low-risk) were imaged at three time-points (6–9, 12–15, and 18–24 months of age). The 10 infants who developed ASD had significantly greater extra-axial fluid at 6–9 months, which persisted and remained elevated at 12–15 and 18–24 months, characterized by excessive cerebrospinal fluid in the subarachnoid space, particularly over the frontal lobes. The amount of extra-axial fluid detected as early as 6 months was predictive of more severe ASD symptoms at the time of outcome. Infants who developed ASD also had significantly larger total cerebral volumes at both 12–15 and 18–24 months of age. This is the first MRI evidence of brain enlargement in autism before 2 years of age. Studies are needed in children with ASD who do not have brain overgrowth, and other regions of interest such as the temporal lobe and amygdala should be examined. Early amygdala enlargement is reported in ASD on neuroimaging studies. The age at which abnormal amygdala enlargement begins was studied in 45 boys with ASD and 25 typical controls, and growth trajectories of the amygdala were examined longitudinally 1 year later. The amygdala was larger in children with ASD at baseline and 1 year later. Amygdala enlargement was present by 37 months of age in ASD, although substantial heterogeneity exists in amygdala and total cortical growth patterns. Clinical characterization of different amygdala growth patterns may have implications for treatment.

NEUROIMAGING

Structural and functional MRI has been used extensively to examine the neuroanatomy of the brain in people with ASD. Current studies benefit from careful identification of cases using ADI-R research criteria for childhood autism. These studies have been carried out longitudinally and cross-sectionally as described above, in both children and adults. Adult studies allow the examination of regional brain changes that persist into adult life. However, our understanding of the relationship between ASD and the anatomy of specific brain regions is complicated by the non-replication of findings and small sample sizes. To clarify these relationships a large-scale multicenter MRI study was conducted in the UK. Comparisons were made between 89 men with ASD and 89 age-matched male controls. Subjects were high functioning, with full-scale IQs of 110 in those with ASD and 113 in controls. Although the men with ASD were not significantly different from those in the control group on global volume measures they had regionally specific differences in gray and white matter volume. Increased gray matter was found in the anterior temporal and dorsolateral prefrontal regions, but decreased gray matter in the occipital and medial parietal regions in the ASD subjects. When gray matter brain systems were examined, adults with ASD showed changes in the cingulate gyrus, supplementary motor area, basal ganglia, amygdala, inferior parietal lobule, and cerebellum. Additional regional differences were found in the dorsolateral prefrontal, lateral orbitofrontal, and dorsal and ventral medial prefrontal cortices. These were accompanied by spatially distributed reductions in regional white matter volume.

These findings are consistent with regional neuroanatomical abnormalities in ASD persisting into adulthood. Moreover, regional differences in neuroanatomy in this study were correlated with the severity of specific autistic symptoms based on the ADI-R. Adult males with an ASD diagnosis have differences in brain anatomy and connectivity associated with specific autistic features and traits consistent with ASD, a syndrome involving atypical neural connectivity. Thus, structural brain mapping may be used to study morphological connectivity in ASD. Differences between genders must be considered as one source of heterogeneity, as studies suggest that ASD manifests differently in males and females. Males with autism have been disproportionately represented in research.

Neuroanatomical differences are reported between high-functioning males and females with ASD whose intelligence is in the average to above average range. Lai and colleagues used neuroimaging to study the brains of 30 right-handed males and 30 right-handed females and matched controls. They found differences in males and females in gray matter and white matter regions of interest. In the females there was overlapping with brain structures that showed evidence of sexual dimorphism in matched controls. These findings suggest gender-dependent neuroanatomy in ASD require replication but indicate the importance of stratifying by biological sex in neuroimaging studies. Future studies are needed to clarify whether these differences between males and females are linked to cognition and generalize to males and females whose intelligence is in the mild to severe range of intellectual disability (intellectual developmental disorder).

Understanding brain connectivity is important because structures are tightly coupled in development; they grow at the same time to establish networks. Correlations between frontal lobe gray matter volume and temporal lobe, parietal lobe, and subcortical gray matter are disrupted in ASD. Despite agreement that ASD is associated with altered brain connectivity, the nature of the deficit is poorly understood. There is evidence to suggest a complex functional phenotype characterized by both hypoconnectivity and hyperconnectivity.
involving large-scale brain systems. Studies involve task-based functional connectivity (synchronization of activation of a brain region to a cognitive challenge task) and resting-state functional connectivity in the absence of a task. Discrepant findings may be reconciled using a developmental perspective. A review of functional MRI studies of functional connectivity in children, adolescents, and adults suggests dynamic changes with aging. While in adolescents and adults with autism connectivity seems reduced compared with age-matched controls, in younger children functional connectivity seems to be increased. Thus, a developmental framework that considers prepubertal, adolescent, and adult subjects may resolve the conflicting results on hypoconnectivity and hyperconnectivity, and lead to a better understanding of the neurobiology of ASD. As shown in the resting state, functional connectivity MRI studies are consistent with widespread hyperconnectivity in children, in contrast to hypoconnectivity in adolescents and adults (Fig. 6.2).

**NEUROPHYSIOLOGY**

Cognitive deficits in ASD result in strategies that excessively engage sensory systems, to the detriment of the more integrative processing needed for a person to be aware of contextual subtleties required for prediction. Thus, people with ASD manifest unusual processing when faced with unpredictable events. They show deficits in orienting to changing, novel sensory stimuli. Studies of event-related potentials illustrate the psychophysiological mechanisms and neural bases underlying these deficits in ASD. Such dysfunction in building flexible prediction in ASD may result from impaired top-down control over several sensory and higher level information processing systems, consistent with underconnectivity.

Other neurophysiological studies found changes with power spectrum analyses in the analysis of brain regions. Studies using event-related potentials and magnetoencephalography to document face processing found decreased sensitivity to whether a face is upright or inverted, reduced responsiveness to repeated face presentation, abnormal eye-to-eye gaze, and abnormal hemispheric lateralization of processing in the cortex. Auditory processing and involuntary orienting to sound, in a wide network that involves the auditory cortex and multimodal sensory areas in the parietal lobe and dorsolateral prefrontal cortex, have been studied using these methods.

**NEUROPATHOLOGY**

Autism is a disorder of neural development. The typical brain develops in several stages. These involve neuronal proliferation and migration, the establishment of dendritic arbors and synaptic connections, and later dendritic pruning and programmed cell death. Disruption in one or more of these stages could result in detrimental downstream effects. MRI studies of people with autism demonstrate aberrant brain development during early childhood involving the whole brain and more specifically in some regions such as the amygdala. However, given the limited resolution in MRI studies, postmortem human brain research is required to determine the neurobiological basis of MRI results. Studies of postmortem tissue may use MRI findings to target specific brain regions for study. Both of these approaches facilitate our understanding of the neuropathology of ASD.
Neuroanatomical studies have demonstrated abnormalities in the emotional or limbic brain and cerebellum. Approximately 60 brains have been studied. In nine of 14 brains examined postmortem, increased cell packing density and smaller neuronal size were found. Twenty-one of 29 brains studied showed a decreased number of Purkinje cells in the cerebellum; in five cases changes were found in cerebellar nuclei and the inferior olive. More than half of the brains studied showed features of cortical dysgenesis in the cerebral cortex.

Unfortunately, most of the cases evaluated in earlier postmortem studies involved brains from individuals with a diagnosis of severe intellectual disability or who had comorbid seizure disorders. Epilepsy is associated with pathology of the cerebral cortex, amygdala, cerebellum, and hippocampal formation, regions implicated in autism. Therefore, comorbid disorders associated with ASD are of concern in interpreting the neuroanatomy of ASD. More neuropathological studies are needed, using new technologies with larger samples; it is essential to include and younger subjects free of comorbidities such as severe intellectual disability and epilepsy.

Most postmortem studies have not targeted regions of interest potentially linked to clinical features of ASD (Fig. 6.1). Abnormalities in face perception, a core feature of social disability in ASD, have been studied using functional MRI. The fusiform gyrus and other cortical regions supporting face processing in controls are hypoactive in patients with autism. One study, on seven postmortem brains of ASD subjects and 10 controls, examined this brain region for alterations in neuron density, total neuron number, and mean perikaryal volume with high-precision design-based stereology. Separate analysis of layers II, III, IV, V, and VI of the fusiform gyrus in patients with ASD showed significant reductions in neuron densities in layer III, total neuron numbers in layers III, V, and VI, and mean perikaryal volumes of neurons in layers V and VI, providing important insights into the cellular basis of abnormalities in face perception in autism. This hypothesis-based approach to neuropathology is to be encouraged.

### NEUROCHEMISTRY

Neurochemical investigations in ASD have focused on measuring neurotransmitter levels in blood and urine, dietary depletion of tryptophan [the dietary precursor of serotonin (5-hydroxytryptamine, 5-HT)], functional positron emission tomography (PET) and single-photon emission computed tomography (SPECT), and measurement of brain metabolites, especially N-acetyl aspartate (NAA), using proton spectroscopy. The most consistent finding is that of hyperserotoninemia in blood platelets in 30–50% of autistic people. Whole blood 5-HT levels are in the upper 5% of the normal range. Increases have also been noted in the broader ASD phenotype. More important is 5-HT function in the brain rather than the periphery because, in addition to being a neurotransmitter, 5-HT serves as a growth factor and regulator of early neuronal development in the developing brain. Studies involving dietary tryptophan depletion and PET studies support central 5-HT deficits. Acute depletion of dietary tryptophan reduces 5-HT in the brain, and a worsening of symptoms has been reported with such tryptophan depletion. PET studies using a serotonin precursor showed reduced synthesis. These findings are consistent with developmental dysregulation of 5-HT synthesis. There is evidence of significant reductions in 5-HT$_{1A}$ receptor binding density in superficial and deep layers of the posterior cingulate cortex and fusiform gyrus, and in the density of 5-HT$_{2A}$ receptors in superficial layers of the posterior cingulate cortex and fusiform gyrus.

In contrast to serotonin, evidence for dopamine and norepinephrine is less compelling. Levels of homovanillic acid, the primary dopamine metabolite, in blood, urine, and cerebrospinal fluid, were not significantly different between people with ASD and controls. However, a PET study suggested low medial prefrontal dopamine activity. There are no consistent findings of deficits in the norepinephrine system.

Proton MRI is a non-invasive way to study brain neurochemistry and perform in vivo quantification of biochemical and metabolite concentrations. Both glutamate and γ-aminobutyric acid (GABA) have been studied. Glutamate is the primary excitatory neurotransmitter in the brain and is important in neuronal plasticity and higher cortical functioning. GABA is the primary inhibitory neurotransmitter in the brain. Peripheral measurements of these two neurotransmitters in the blood have shown conflicting findings. Postmortem studies have shown changes in the receptors for both glutamate and GABA in the hippocampus.

ASD is associated with widespread reductions in NAA, creatine and phosphocreatine, choline-containing compounds, myo-inositol, glutamate, glutamine, and GABA. These reductions suggest impaired neuronal function and/or metabolism. However, findings vary depending on the study and region of interest. Studies should control for variability in subjects’ age and level of functioning to address neurodevelopmental levels and processes associated with ASD. A meta-analysis identified 22 articles satisfying the criteria with measures of NAA, creatine, choline-containing compounds, myo-inositol, glutamate, glutamine, and GABA. These reductions suggest impaired neuronal function and/or metabolism. However, findings vary depending on the study and region of interest. Studies should control for variability in subjects’ age and level of functioning to address neurodevelopmental levels and processes associated with ASD.
in NAA levels, especially in the frontal lobes, in ASD. These findings suggest that early transient brain expansion in ASD may be caused by an increase in non-neuronal tissues, such as glial cell proliferation.

Other investigators have correlated proton spectroscopy changes with social and cognitive functioning. In one study involving 77 3–6-year-old children with an ASD diagnosis (23 boys and eight girls), concentrations of NAA in the left amygdala and the bilateral orbitofrontal cortex were determined. Reductions in NAA were found in the left amygdala and in the orbitofrontal cortex bilaterally compared with those in a control group. NAA levels were correlated with ratings of the social quotient in the children with ASD, suggesting neuronal dysfunction in these brain regions.

Oxytocin

ASD is proposed to result from many rare genetic variants. These involve common neurotransmitter or neurodevelopmental pathways. Moreover, for ASD multiple common polymorphisms confer risks for the disorder. Genetic associations with ASDs and oxytocin, vasopressin, and related proteins pertinent to both social or repetitive behavior disorders. Oxytocin is integral to social sensitivity throughout the life cycle. It is involved in social cognition, interpersonal bonding, trust, and stress management. Its release is highly sensitive to emotional and social context and it plays an important role in emotional regulation through parent–child attachment. Polymorphisms of the oxytocin receptor have been implicated in sensitivity to social cues. Knowledge of polymorphisms in the oxytocin genetic pathways will become important as more is learned about the epigenetic effects of social interactions. Moreover, oxytocin is being considered as an adjunctive treatment to facilitate social cognition and emotion regulation in ASD. Oxytocin modulates emotions and social judgments in part through actions on the brainstem and autonomic nervous system. It may alter perceptions of the social environment as safe or threatening. An essential issue is to determine whether oxytocin administration could be a drug treatment for an identified disorder or disorders such as ASD or might better be used as an adjunctive treatment, taking into account the context dependence of its effects.

Any theory regarding the risk for development of ASDs must consider the significant male bias in risk for developing this constellation of symptoms. An awareness of gender differences in the central regulation and expression of oxytocin and vasopressin may help in understanding aspects of ASDs. Oxytocin is estrogen dependent, and in some cases levels of the peptide and its receptor are higher in females. Possibly relevant to ASDs is that levels of vasopressin in the extended amygdala–lateral septal axis of the nervous system are sexually dimorphic and higher in males. Moreover, males seem to be more sensitive than females to the actions of vasopressin, especially during development. Insensitivity to vasopressin or a lack of dependence on this peptide could be protective against ASDs in females. Oxytocin also could protect females, either directly or indirectly. A reduction in fear and an increased sense of safety or trust are expected to be protective in disorders such as ASDs that are associated with high levels of anxiety. Differences in coping mechanisms between males and females, especially to downregulate anxiety in social interactions, could be pertinent to ASDs. Disruptions in systems that rely on vasopressin may also increase the vulnerability to ASDs.

**GENETIC AND ENVIRONMENTAL RISK FACTORS**

Genetic research in ASD has accelerated in the past 10 years, led by advances in two areas. First, the development of standardized autism diagnostic tools such as the ADI-R and ADOS allowed international and cross-institutional collaboration and the collection of large datasets in the late 1990s and early 2000s. Second, genetic technology has advanced rapidly, as summarized by Geschwind (Fig. 6.3).

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**FIGURE 6.3** Methodological changes that have accelerated progress in autism spectrum disorder (ASD) genetics. Cytogenetic studies in the 1980s were followed by whole genome linkage studies, whole genome association studies [single-nucleotide polymorphism (SNP) and copy number variation (CNV)] and resequencing studies. ADOS: Autism Diagnostic Observation Schedule; ADI-R: Autism Diagnostic Interview, Revised.
Cytogenetic studies of macroscopic chromosomal anomalies were described in the 1980s and into the 1990s. Candidate gene association studies began in the mid-1990s. The first large-scale genome linkage studies were published in the early 2000s. Chromosomal microarray identification of CNVs followed in the mid-2000s, with genome-wide association studies (GWAS) soon afterwards. The current wave of next generation sequencing technology allows characterization of all variation in the exome or even the full genome.

With each advance in genetic methodology, new risk variants have been identified in ASD. In almost all cases, however, studies have identified uncommon genetic variants that individually lead to a substantial increase in ASD risk. No single one of these uncommon risk variants is present in more than about 2% of children with ASD. Other than syndromal disorders (discussed below), the most common contributors to substantial ASD risk have been CNVs, such as chromosome 16p deletion or duplication, maternal chromosome 15q11 duplication, or 7q11 duplication, each present in 0.5–2% of children with ASD. Collectively, CNVs that are likely to contribute to ASD risk are present in about 9–10% of children with ASD. Sequencing has identified more uncommon variants that, when added to CNVs and syndromal cases, may yield a substantial genetic risk variant in up to 20% of children with ASD. These variants disrupt a large number of brain-expressed genes, including synaptic cell adhesion molecules such as neurexin, neuroligin, and Shank family members. Advances in next generation sequencing have enabled the discovery of a vast number of de novo mutations that confer a risk for ASD that include a number of chromatin remodeling genes. Both de novo CNVs and de novo SNVs are more likely with advancing paternal age, which has been shown to be a robust risk factor for ASD.

Unlike most other behaviorally defined disorders, genetic testing is recommended in ASD. The American College of Medical Genetics recommends that every person with ASD should receive a chromosomal microarray (CMA) as the first line test to identify CNVs. However, whereas identified CNVs may indicate substantial risk, most are not specific for ASD itself. Many, such as chromosome 16p11 deletion, are also associated with intellectual disability and could potentially confer risk of ASD as a result of a more general cognitive “hit” that coincides with other ASD risk factors. Others, such as chromosome 16p11 duplication, appear to lead to risk that extends beyond ASD to ADHD and schizophrenia, but may also be observed in the absence of a neuropsychiatric phenotype. The clinical impact associated with most CNVs (and probably SNVs) is therefore likely to be probabilistic and not deterministic. Few can be understood as “causes” of ASD, even when the associated risk is substantial. Even when inherited within a family, the same CNV or SNV may be associated with multiple different neuropsychiatric phenotypes.

The other recommended genetic test for children with ASD is for fragile X syndrome (see Chapter 8), the most commonly observed genetic syndrome in ASD. A number of other syndromes, including tuberous sclerosis, also confer increased risk of ASD. The pattern of behavioral symptoms within these syndromes can be quite variable, with none leading to ASD in every case, and often in the minority of individuals. In contrast, most genetic syndromes associated with ASD risk confer intellectual disability in most or all cases. Even when ADI-R and ADOS results are consistent with ASD, the clinical presentation of individuals with these syndromes may differ from the overall group of people with ASD. For example, individuals with fragile X syndrome often show a characteristic pattern of aversion to eye contact and sensory sensitivity, yet may be quite socially engaged and motivated. These syndromes offer an opportunity to understand co-occurring risk factors that may result in a more autism-like picture in a subset of individuals. They may also offer a window into understanding the underlying neurobiology conferring risk of neurodevelopmental disorders in general. For example, mouse models of fragile X syndrome demonstrate increased signaling downstream of the glutamate mGlu5 receptor. Drugs that decrease mGlu5 receptor signaling can rescue many brain and behavioral phenotypes in the mouse and are now in clinical trials in fragile X syndrome. Although it must not be assumed that these drugs would benefit the broader group of individuals with ASD, an understanding of this specific syndromal disorder may yield new ideas about the neurobiology of neurodevelopmental disorders in general.

Heritability estimates and resulting models of ASD risk predict that common variants would also be identified that would have a smaller individual effect on risk but in a much broader portion of the ASD population. Unfortunately, however, GWAS have not identified replicable common gene variants in ASD, perhaps because of insufficient power. Encouraging GWAS results in schizophrenia have suggested that a larger sample size may yield these common variants in ASD as well. The heterogeneity that is characteristic in autism could potentially make finding common risk genes more challenging than in other neuropsychiatric disorders. Gene–gene and gene–environment interactions may also complicate the identification of risk factors. ASD could potentially involve epigenetic risk factors, or inherited or acquired changes in gene expression that do not result from change in the primary DNA sequence. Although there is limited evidence that epigenetic mechanisms are involved in ASD, one study reported a difference in epigenetic markers at the oxytocin receptor gene in ASD.55

I. DEVELOPMENTAL DISORDERS
With the exponential rise of genetic technology, risk genes appear to be much easier to detect than environmental susceptibility factors. Ongoing work suggests, however, that environmental risk factors, particularly prenatal and perinatal factors, play an important role. Emerging data suggest that extremely low birth weight is a robust risk factor for ASD, which is more common in survivors of the neonatal intensive care unit. Other risk factors, such as short interpregnancy interval and infection during pregnancy, have been reported in more than one study. Advanced parental age, particularly paternal age, also appears to be a robust risk factor and is increasing over time, particularly with the advent of reproductive technology. In the environmental arena, rare risk factors may also be easier to identify and study, such as fetal exposure to valproate, which has been identified as an environmental risk factor.

**TREATMENT**

Treatment programs for children with ASD are developmentally based, affectively oriented, and tailored to specific known deficits in an individual child. Early childhood behavioral interventions have been shown to be the most likely to be successful. Treatment programs must be sensitive to the needs and perceptions of the autistic child and provide guidance to parents. Even though our understanding of the neurobiological basis of ASD is growing and anatomical features are apparent, intervention can still be effective in helping children to compensate for their developmental deficits. Four general aims in the treatment of the autistic person are (1) to promote cognitive development, (2) to promote language development, (3) to promote social development, and (4) to promote overall learning. Besides these, behavior reduction and behavior enhancement strategies are needed, as is appropriate use of medications to treat for co-occurring conditions. The role of the parent is crucial for intervention in a child with ASD. The parent functions as cotherapist and plays an integral role in treatment. Parental counseling begins with clarification of the diagnosis and an explanation of the characteristics of an ASD.

Planned periods of interaction must be scheduled to promote social development. How intense they need to be is an area of ongoing study. Cognitive development strategies focus on facilitation of active, meaningful experiences with planned periods of interaction. Because there is reduced cognitive capacity, direct teaching at the appropriate developmental level is required. Language development is facilitated by planned social interactions and interpersonal conversational exchanges to deal with social isolation and the lack of social reciprocity. Social reciprocity problems result from deficits in joint attention that require structured reciprocal language between the person with an ASD and the therapist.

Direct instruction is necessary to teach the social use of language. It is carried out with differential reinforcement of language use rather than focusing only on speech. Since language development is limited, direct teaching must be targeted at the child’s level of language comprehension. Alternative means, such as the use of signing, are needed for non-verbal children. The promotion of social development involves positive personal interaction that is pleasurable to the child. The lack of social approach and lack of social reciprocity in social interaction require structured settings. The lack of social awareness characteristic of ASD is addressed through direct teaching of skills that lead to social competence as well as early interpersonal programs.

The basic principles of behavior modification are used in treatment based on a clear understanding of the deficits and types of abnormal behavior associated with ASD. The nature of the autistic deficit makes adaptability and generalization of targeted behaviors across settings difficult. A stable environmental context is necessary for treatment, and once this environment is established it should not be changed without careful consideration. Behavior management strategies are used to eliminate non-specific maladaptive behaviors. The behavioral approach is based on a functional analysis of behavior and application of learning theory. When using a behavioral technique, it is essential to determine which environmental features influence a behavior, not in children in general but in this particular child.

The types of behavior most commonly targeted in behavior management programs are aggression and self-injurious behavior. For these and other disruptive behaviors, avoidance of precipitants, help to establish coping skills, and differential reinforcement may be used as interventions. There is good evidence from randomized controlled trials that non-intensive interventions, especially those focused on communication and joint social interaction, may have a significant and positive impact on functioning in children with ASD. Future challenges include assessing which treatments work for which children and identifying the individual characteristics that predict responsiveness to specific programs and approaches.

**FUTURE DIRECTIONS**

ASD is a highly heterogeneous and complex disorder. Refinements are needed in classification with continued efforts at subtyping. Longitudinal follow-up studies will improve our knowledge of developmental trajectories to validate subgroups and allow examination of their neurobiology. The following recommendations build on current developments in neurobiology.
• **Complex genetics:** Although ASD is highly genetic, its genetics are complex. Rare variants of substantial effect have been identified in ASD, but more common risk variants have been elusive. Parallel work in schizophrenia suggests that detection of common risk variants will be possible in larger sample sizes in GWAS. Next generation sequencing technology that allows every exon of every gene (the whole exome) to be examined simultaneously may now be used to identify risk variants underlying linkage peaks that were identified in families with multiple affected individuals. Subgrouping by biomarkers or a well-defined clinical profile may be necessary to deal with heterogeneity.

• **Refinements in case identification:** ASD is a multifactorial disorder. For research purposes, separating the genetics of social deficits from those of repetitive behaviors and investigating the genetics of specific behaviors such as joint referencing deficits and dysregulated sensory modulation may be beneficial. The use of DSM-5 specifiers is one approach to assist in subtyping.

• **Longitudinal studies with large cohorts:** Developmentally focused, prospective, longitudinal MRI studies, both morphological and functional, are needed. A few such prospective studies have been conducted, but over only a short time-frame. Cross-sectional findings, such as enlarged amygdala size in young children and smaller amygdala size in adolescents and adults, will require longitudinal studies to evaluate whether the amygdala is truly shrinking within some individuals with ASD. Neuroimaging studies can be linked with longitudinal studies of ASD symptoms to better understand the relationship between brain connectivity and circuits and the resulting pattern of behavior and development. Results from MRI studies should guide the choice of regions of interest for postmortem studies.

• **Proton spectroscopy:** The continued use of *in vivo* proton spectroscopy may be able to identify abnormalities in brain metabolites or neurotransmitters that could subgroup individuals within the spectrum. Correlation of proton spectroscopy findings with brain regions of interest for brain connectivity and clinical findings may clarify the systems and circuitry critical for social function and repetitive behavior.

• **Age of onset:** From a developmental perspective, age of onset or recognition is an important element. Progress is being made in refining brain changes in children with the regressive type of ASD who show rapid deterioration between 18 and 24 months of age. Studies in high-risk populations, such as younger siblings of affected children or survivors of extreme premature birth with low birth weight, already point to early markers of risk, but more work is needed for earlier identification.

• **Neuropathological studies:** Neuropathological studies have been confounded by the co-occurrence of seizure disorder, severe intellectual disability, comorbid diagnoses, and broad age groups studied. The Autism Brain Bank can be used to expand the database. Neuroimaging studies can be used to identify regions of interest and test hypotheses linked to brain and behavior. There is a need to focus on developmental cohorts and compare subjects who did and did not show accelerated early brain growth.

• **Animal studies:** Since we lack an understanding of common risk factors for ASD, animal models best target rare genetic or environmental risk factors that contribute a substantial degree of risk. Models of environmental risk are more challenging, since drugs such as valproate increase autism risk within an ambiguous time-window that may be difficult to model in an animal. Rather than focusing on developing animal models of ASD, these models can be used to understand how ASD risk factors affect the brain, potentially yielding an understanding of pathophysiology.

• **Neuroimaging studies:** With the possible exception of findings in the amygdala and the striatum, neuroimaging studies suggest that ASD is a distributed disorder. Functional connectivity and structural connectivity studies implicate aberrant long-distance communication within the brain in ASD, although it remains difficult to assess whether this is causal or a result of abnormal neuronal function. Ongoing work should focus on functional imaging and evoked electrocortical response techniques to examine functional coherence in brain circuits in relation to specific symptom patterns and behavior.

• **Treatment interventions:** The dramatic heterogeneity in ASD calls for individualized treatment with a developmental focus. Early, intensive behavioral intervention clearly helps some children, but treatment studies have largely clustered all children with ASD together, rather than clarifying which ones benefit. Randomized and large-scale studies are needed to understand the required intensity of treatment for different children, as well as which specific symptom domains can be expected to improve. Studies in targeted subpopulations will be especially important when genetic findings or biomarkers can be connected to potential avenues for treatment. In addition to core ASD symptoms, careful management of
co-occurring symptoms is essential, especially because some “recovered” children were initially characterized as having significant co-occurring disorders such as ADHD or anxiety symptoms. Parental and professional advocacy for multifaceted, individual treatment plans will continue to be important as more evidence-based treatments emerge.

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