AUTISM SPECTRUM DISORDER

2014 Edition

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Parents and patients with autism spectrum disorder demonstrating in Kiev, Ukraine, April 2012 ("Mother, I do not have schizophrenia, I have autism" reads the plackard). The demonstration was organized by the Child with a Future Foundation and supported by the Association of Psychiatrists of Ukraine. This resulted in a change in diagnostic practices. Until then, children with autism whose symptoms persisted after the age of 18 years were not diagnosed with autism but with mental retardation or schizophrenia (Photo D Martsenkovskyi).

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Autism spectrum disorder (ASD) refers to a neurodevelopmental condition defined by a number of behavioral features. According to DSM-5, the core clinical characteristics of ASD include impairments in two areas of functioning (social communication and social interaction), as well as restricted, repetitive patterns of behavior, interests or activities. These symptoms are present in the early developmental period, but may not be fully manifest until social demands exceed the child's limited capacities, or may be masked by learned strategies in later life. Despite its early unfolding, this condition is not diagnosed until a few years later. The increased identification of this disorder, its emotional impact on families and the challenging financial demands associated with its treatment and support currently make ASD an important illness at the scientific, clinic and public health levels. The treatments now available can achieve a far better quality of life for sufferers than was the case just a few years ago but it must be recognized that ASD cannot be cured yet and that most people with ASD, particularly in developing countries – with a few fortunate exceptions – are not receiving specialized treatment or any treatment at all.

This chapter summarizes the current knowledge of the classification, epidemiology, etiology, clinical picture, assessment, prognosis and treatment of ASD. Because many of the symptoms and behaviors mentioned are difficult to describe, hyperlinks are provided to view a variety of video clips illustrating these and other relevant issues. Readers are encouraged to access them. It is hoped this material will be useful for clinicians committed to changing global health practices involving these patients and their families.

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HISTORY

Eugen Bleuler (1857–1939) coined both the terms *schizophrenia* and *autism* in Switzerland. He derived the latter from the Greek word *autos* (meaning 'self') to describe the active withdrawal of patients with schizophrenia into their own fantasy life in an effort to cope with intolerable external perceptions or experiences (Kuhn, 2004). The use of the term 'autism' in its current sense started 30 years later when the Austrian pediatrician Hans Asperger adopted Bleuler's terminology of 'autistic psychopaths' in a lecture he delivered at the Vienna University Hospital (Asperger, 1938). Asperger subsequently published his second PhD thesis in 1944 (first transcribed in 1943) (Asperger, 1944) where he described a group of children and adolescents with deficits in communication and social skills and also with a restrictive, repetitive pattern of behaviors.

At the same time, in 1943 – separated by distance, the Second World War and apparently unaware of each other's work – Leo Kanner, at Johns Hopkins University Hospital in the US, described in his classical paper *Autistic disturbances of affective contact* (Kanner, 1943) 11 children with striking behavioral similarities to those depicted by Asperger. Most of the nuclear characteristics described by Kanner such as 'autistic aloofness' and 'insistence on sameness' are still part of the criteria to diagnose ASD in current classifications. Children described by Asperger differed from those of Kanner in that they had no significant delays in early cognitive or language development.

Asperger's paper, published in German, remained largely unknown until Uta Frith translated it into English (Asperger, 1944), making the findings widely

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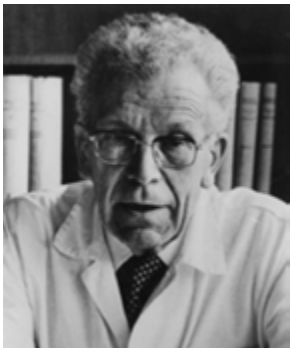


Hans Asperger (1906-1980), Austrian pediatrician, described the symptoms of autism in 1938.

available. These ideas were further disseminated by Lorna Wing (Wing, 1997) in the UK. Subsequently, there was a gradual acknowledgement that autism constitutes a spectrum, culminating in the adoption of this term in DSM-5. Thus, ASD, with its range of severity levels and support needs, includes what was labelled in previous classifications as autism *and* Asperger's disorder.

Leo Kanner (1894-1981), American psychiatrist, described autism in 1943.

It was a misfortune that the original meaning of Bleuler's term and its theoretical association with schizophrenia, combined with the psychoanalytic theories dominant in the mid twentieth century, amalgamated ASD with psychotic disorders under the rubric of 'childhood schizophrenia.' The apparent withdrawal observed in ASD patients was misinterpreted as being the same as that in schizophrenia – a defensive retreat from an intolerable external situation, the result of a pathogenic family (as it was then widely conceptualized). Unfortunately, some of these discredited ideas are still held by some. The relative importance of ASDs in relation to other health conditions continues to be underestimated by governments and international agencies (Lavelle et al, 2014). In Africa, for example, clinical work on ASDs did not start until three decades after Kanner and Asperger had published their work (Lotter, 1978; Bakare & Munir, 2011).

CLASSIFICATION

ICD-10 (World Health Organization, 1990) classifies autism under the *pervasive developmental disorders*, a group of conditions characterized by qualitative abnormalities in reciprocal social interaction, idiosyncratic patterns of communication and by a restricted, stereotyped, repetitive repertoire of interests and activities. These qualitative abnormalities are a feature of the sufferer's functioning in all situations. DSM-5 (American Psychiatric Association, 2013) has made significant changes to this in its latest edition. Both ICD-10 and DSM-5 utilize a list of behaviors, require that a number of criteria be met in order to warrant a diagnosis, and the two taxonomies are periodically reviewed to incorporate new research findings. DSM-5 was released in May 2013 and the revision of ICD-10 (ICD-11) is expected to be approved by the WHO in 2015. Current ICD-11 working drafts seem to incorporate similar modifications to those in DSM-5.

Lorna Wing is an English psychiatrist and physician who promoted the concept of an autism spectrum. She is one of the founders of the National Autistic Society in the UK

Some of the changes incorporated in DSM5 have been controversial in scientific and lay circles. Further research is required to assess the impact of these modifications on research, clinical practice and public health policy. DSM-5 has eliminated the distinction in DSM-IV between autism, Rett's disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified, creating a unique ASD category, characterized by:

- Persistent deficits in social communication and social interaction across multiple contexts
- Restricted, repetitive patterns of behavior, interests or activities either current or elicited through the clinical history
- Clinically significant impairment in social, occupational, or other important areas of functioning
- Presence from early childhood (although it may not become fully manifest until social demands exceed the child's limited capacities), and
- Not explained better by intellectual disability or global developmental delay.

Click on the image to hear Susan Swedo MD discuss briefly the changes to autism spectrum disorder in DSM-5 (2:28)

DSM-5 has thus eliminated the separate diagnosis of Asperger's disorder while formalizing the 'spectrum' concept espoused by Lorna Wing, who favored considering Asperger's disorder a sub-category of a unified ASD construct (Wing et al, 2011). Many people think that these demarcations, although officially may go away, are likely to continue to be used in clinical and lay settings. For a brief description of these changes follow the hyperlink in Susan Swedo's video clip on the previous page; for a more detailed description follow the hyperlink to Andrés Martin's presentation.

Click on the image to view a lecture by Andrés Martin (Yale University, US) about **the new definition of ASD in DSM-5** (available in English, Basque, Spanish, and French); from the International Society for Autism Research (INSAR) meeting at Donostia/San Sebastian (Spain) in 2013. (28:23)

Several welcome aspects have been incorporated in DSM-5, such as placing ASDs under the more appropriate heading of 'neurodevelopmental disorders' – instead of 'pervasive developmental disorders'— and the recommendation to consider 'specifiers' (descriptors), aimed at a more homogeneous subgrouping of individuals who share certain features (a known medical, genetic or environmental condition; intellectual and/or language impairment; another neurodevelopmental, mental or behavioral disorder, or catatonia). This improvement is accompanied by the recognition of some symptoms that, while often experienced by patients, were not considered in previous classifications: those related to hyper- or hypo-reactivity to sensory stimuli or unusual interest in sensory aspects of the environment, for example, apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement.

Specifiers

Specifiers are extensions to a diagnosis that further clarify the course, severity, or special features (descriptors). In the case of ASD, some of the specifiers are: current severity, with or without intellectual impairment, associated with a known medical or genetic condition etc.

Finally, in a salutary move towards clarifying the functional needs of the individual and the planning of support required, DSM-5 offers a table describing severity levels, which can be summarized as:

- ***Level 1****: Requiring support* (e.g., without supports in place, deficits in social communication cause noticeable impairments. Difficulty initiating social interactions, and atypical or unsuccessful responses to social overtures of others. Inflexibility causes significant interference with functioning in one or more contexts.)
- ***Level 2****: Requiring substantial support* (e.g., marked deficits in verbal and nonverbal social communication; social impairments apparent even with supports in place; limited initiation of social interactions. Inflexibility of behavior, difficulty coping with change or other restricted or repetitive behaviors appear frequently and interfere with functioning)
- ***Level 3****: Requiring very substantial support* (e.g., severe deficits in verbal and nonverbal social communication that cause severe impairments in functioning, very limited initiation of social interactions, and minimal response to social overtures from others. Inflexibility of behavior, extreme difficulty coping with changes, which markedly interfere with functioning)

Click on the image to listen to Dr Temple Grandin talk about hyper reactivity to sensory stimuli. She is a writer, biologist and educator who suffers from autism (0:47)

Perhaps the most controversial change in DSM-5 has been the creation of a new category – *social (pragmatic) communication disorder* – separate from ASD. According to many, social (pragmatic) communication disorder is identical to what in DSM-IV was described as pervasive developmental disorder not otherwise specified, a condition that constitutes in some specialist programs for ASD as many as 50% of their patients.

Initial research on the impact of DSM-5 criteria has produced conflicting results, some positive and some negative. It would appear that, at this point, the new criteria provide better specificity at the expense of reducing sensitivity, especially for older patients, those with comorbid intellectual disability, and those with Asperger's disorder and partial clinical pictures (Grzadzinski, 2013; Volkmar, 2013). Providing more specifiers has been remarked as a useful way to identify key aspects in these patients (Lai, 2013).

Finally, to further complicate classification issues, the influential US National Institute of Mental Health has launched for research purposes, the *research domain criteria* (RDoC), a new way of classifying psychopathology based on dimensions of observable behavior and neurobiological measures.

Click on the picture to access the CDC website about ASD with a lot of useful information.

EPIDEMIOLOGY

Autism was once considered a relatively rare condition. Recent epidemiological data have radically altered this perception. Based on large surveys in the US, the Centers for Disease Control and Prevention (CDC), estimates the prevalence of ASD as 1 in 68 children, occurring in all racial, ethnic and socioeconomic groups, although it is five times more common among boys (1 in 42) that girls (1 in 189). The CDC website also offers data from numerous studies in Asia, Europe and North America showing an average prevalence of ASD of about 1%. A recent survey in South Korea, which screened children in schools, reported a prevalence of 2.6% (3.7% among boys and 1.5% among girls) (Kim et al, 2011). Another study in England estimated the prevalence of ASD at almost 1% in adults (Brugha et al, 2011).

However, epidemiological studies are difficult to compare. They vary in the composition of the population surveyed, recruitment mechanisms, sample size,

Table C.2.1 Prevalence of autism spectrum disorders, Autism and Developmental Disabilities Monitoring (ADDM) Network 2000-2010 (combining data from all sites)

Survey year	Year of birth	Prevalence per 1,000 children (range)	Frequency
2000	1992	6.7 (4.5–9.9)	1/150
2002	1994	6.6 (3.3–10.6)	1/150
2004	1996	8.0 (4.6–9.8)	1/125
2006	1998	9.0 (4.2–12.1)	1/110
2008	2000	11.3 (4.8–21.2)	1/88
2010	2002	14.7 (14.2-15.1)	1/68

Source: CDC website

design, awareness, participation rates, diagnostic criteria, instruments used as well as whether impairment criteria are included (Fombonne, 2009). Nevertheless, using the same methodology over a period of ten years, the CDC's Autism and Developmental Disabilities Monitoring Network has found increasing rates of ASD in the US (Table C.2.1).

Although studies do not rule out temporal or external demographic factors (such as being born to older parents, survival of premature or high risk low birth weight babies, earlier diagnosis of young children with higher IQ who spontaneously make progress over time that would not have been diagnosed years ago, or only counting older children receiving special support), experts in the field explain this rising prevalence by increased awareness and improvement in the recognition and detection of the disorder. This may explain why the prevalence of ASD is reported to be lower in China (6.4 in 10,000) (Li et al, 2011). While there is much research on ASD in Europe and North America, there is not a single community based epidemiological study of ASD in sub Saharan Africa (Bakare & Munir, 2011). There are small studies examining the prevalence of ASD in children with intellectual disability in Northern and Sub-Saharan Africa but no studies of ASD in those without intellectual disability (Bello-Mojeed et al, 2013). However a significant increase of ASD among children of Ugandan mothers (Gillberg et al, 1995) and of Somali women living in Sweden (Barnevick-Olsson et al, 2008) has been reported.

EARLY DETECTION

It is acknowledged that early detection constitutes a major advance in that it enables prompt intervention that may improve prognosis in a significant proportion of children with ASD, but also because it clarifies the doubts and anguish of parents and allows adequate planning for future school placements and community support.

It has been known for some time that there is a higher incidence of ASD among siblings of already identified cases; this observation led to a more detailed examination of newborn siblings and follow up during their first years of life. Trying to identify early developmental signs that precede a diagnosis of ASD in siblings that eventually develop the disorder has been a fruitful area of investigation. This change, from a retrospective view of abnormal development to a prospective follow-up of children at risk, has led to remarkable advances. It has been shown in these high-risk infants that there is a lack of findings during the first six months in those who later develop ASD, except perhaps unspecific motor development delays.

To improve recognition of the early signs of ASD among professionals, parents, and early intervention providers, Dr Rebecca Landa of Kennedy Krieger Institute has developed a brief video tutorial on ASD behavioral signs in one-year-olds. The tutorial consists of six video clips comparing toddlers who show no signs of ASD to toddlers who show early signs of ASD. Click on the picture to view (9:02).

However, in the following six months, social interaction problems start to become apparent (Zwaigenbaum et al, 2005). By two years of age, toddlers in the spectrum show clear problems in social communication, play, language and cognition, as well as other sensory and motor difficulties (Zwaigenbaum et al, 2009). These findings confirm the notion that ASD can be identified earlier than usual in some cases and that for many children 24 months of age coincides with a peak in the onset of new symptoms that would facilitate recognition. Click here to access a one-hour webinar by Dr Zwaigenbaum discussing research on so-called 'baby siblings' of children with autism as well as the implications of recent advances

Figure C.2.1 Red flags to identify autism spectrum disorders and developmental delay

Source: First Words

in the early detection of the disorder.

Relevant information to guide clinicians comes from longitudinal research conducted by the First Words Project (Florida State University) that identified red flags for ASD, although they insist that there is no pathognomonic symptom that guarantees the presence of ASD. Not all children with ASD show all and every one of the symptoms all the time – this should prevent clinicians from saying "this child does not have autism, because I saw him looking at the eyes of others" or similar. The First Words Project came up with nine red flags that help to distinguish children with ASD from children with developmental disabilities and typically developing children, and four red flags that distinguish children with ASD and developmental disabilities from normally developing children (Wetherby et al, 2004).

Many questionnaires have been developed as potential screening tools for the developmental assessment of children as well as for ASD screening, too many to list here. Description of these developmental screening tools, whether there are translations in languages other than English, their sensitivity and specificity, and where they can be found are available in this American Academy of Pediatrics' table.

Common myths shared by many professionals and policy-makers about developmental screening are summarized in Table C.2.2. A variety of practice flowcharts are also available, largely produced by national societies, but the one produced by the American Academy of Pediatrics represents the current gold

Click on the image to view a lecture by Rebecca Landa (Kennedy Krieger Institute, Baltimore, US) about "**Early diagnosis and course in ASD**" (available in English, Basque, Spanish, and French); from the International Society for Autism Research (INSAR) meeting at Donostia/San Sebastian (Spain) in 2013. (34:32)

Table C.2.2 Myths about developmental screening

Myth # 1	*"There are no adequate screening tools for preschoolers"*
Fact	Although this may have been true decades ago, today sound screening measures exist. Many screening measures have sensitivities and specificities greater than 70%
Myth # 2	"*A great deal of training is needed to administer screening correctly"*
Fact	Training requirements are not extensive for most screening tools. Many can be administered by paraprofessionals
Myth # 3	*"Screening takes a lot of time"*
Fact	Many screening instruments take less than 15 minutes to administer, and some require only about 2 minutes of professional time
Myth # 4	*"Tools that incorporate information from the parents are not valid"*
Fact	Parents´ concerns are generally valid and are predictive of developmental delays. Research has shown that parental concerns detect 70% to 80% of children with disabilities

Source: CDC / Autism website

standard for screening ASD in developed countries (Johnson & Mayers, 2007).

Screening instruments for ASD

Among the many instruments available (click here for a list: Table 1 in the Practice Parameters of the AACAP), there are currently two that merit special mention since they are free to use, deal with different age groups (one younger children and the other older ones), have undergone cross-cultural adaptation and translation to many languages, and have been researched in various countries. These are the Modified Checklist for Autism in Toddlers (M-CHAT) (Robins et al, 2001) and the Childhood Autism Spectrum Disorders Test (CAST) (formerly known as Childhood Asperger Syndrome Test) (click here for an on-line version of the test)

The M-CHAT can be complemented with the M-CHAT Follow-Up Interview, also available at the M-CHAT website. It is recommended that M-CHAT users also incorporate the M-Chat Follow-up Interview into the screening given recent findings that use of the follow up interview greatly reduces false positive cases, avoiding unnecessary referrals. The CAST is also freely available for non-commercial purposes and in many languages at the website of the Autism Research Centre of the University of Cambridge.

Click on the picture below to access an instant-scoring, on-line, free, English version, with all the required materials and references

The American Academy of Pediatrics recommends screening for ASD all 18 and 24 month old children using a staged procedure (Johnson & Meyers, 2007). However, there are practical and ethical difficulties in doing so and it is questionable if screening should be routinely implemented worldwide. First, the psychometric properties of these instruments are far from perfect. Some, like M-CHAT, identify a proportion of cases that turn out not to have ASD (false positives), although health authorities may not consider this a problem since it detects children that

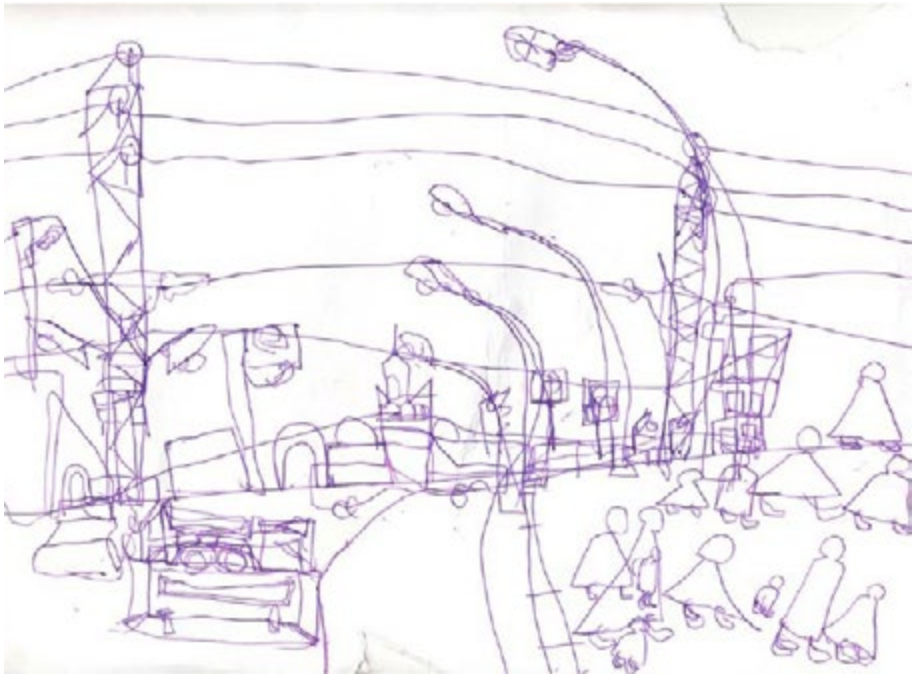
require support for other conditions anyway (e.g., developmental delays, speech problems). There are also false negatives: a proportion of children having the condition are not identified by the screening. A study that combined observation of the child's social interaction and parent reports, showed a significant increase in the sensitivity and specificity of screening. The Three Items Direct Observation Screen (TIDOS) (Oner et al, 2013) is such a screening device. It was developed in a middle income country but may be useful in low and middle income settings also.

Al-Qabandi et al (2011) challenge the belief that screening should be done because there is an effective treatment (e.g., early behavioral intervention). Although promising, treatments are not equally effective in all children with ASD and we are just beginning to understand who will be best served with what treatment, but many questions remain and there is no *cure* yet. It is widely recognized that screening for a condition without having the resources or effective treatment (as it happens for ASD in most regions of the world) may be unethical. In the same line, it is not clear whether young children with ASD are more easily recognized using universal screening instruments administered by professionals than, for example, through a culturally sensitive, community campaign. Despite all these controversies it is accepted that increasing information, educating families, teachers and medical staff to recognize ASD is a step forward.

Bernard Rimland, PhD (1928-2006), American psychologist, was the founder and director of the Autism Research Institute and founder of the Autism Society of America. He opened the way for the current understanding of autism by introducing the notion that it was a disorder of brain development.

The mechanisms used to detect ASD are likely to be different for each country and region, depending on culture and child rearing practices, but will mainly depend on the availability of developmental surveillance (not isolated checking for a specific condition). Most children in the world do not have access to 'well-baby programs' and to developmental surveillance. Access to health should include empowering communities and health systems to identify the most prevalent disabilities in a given community. In developed countries these include intellectual disability, cerebral palsy, deafness, blindness, and ASD. In other parts of the planet, the priorities for surveillance might be very different. In summary, we propose that context-friendly developmental surveillance should be conducted

There are practical and ethical difficulties in screening for ASDs and it is questionable whether screening should be routinely implemented worldwide



Drawing by Khalil, an 11 year old child with ASD

for all children with administration of screening instruments to those suspected of having ASD.

Click on the image to view a lecture by Thomas Bourgeron (Pasteur Institute, Paris, France) about "**Explaining ASD: genetic aspects**" (available in English, Basque, Spanish, and French); from the International Society for Autism Research (INSAR) meeting at Donostia/San Sebastian (Spain) in 2013 (26:42)

ETIOLOGY AND RISK FACTORS

In the US, in the 1950s and early 1960s, autism was thought to be due to the defective upbringing of children by cold and rejecting parents, thereby leaving the child with no alternative but to seek comfort in solitude, as once claimed by Bruno Bettelheim. In his book "The Empty Fortress: Infantile Autism and the Birth of the Self", Bettelheim compared autism to being a prisoner in a concentration camp (something he had experienced himself in Germany during WWII) (Finn, 1997). In 1964, Bernard Rimland opened the way for the current understanding of autism by introducing the notion that it was a disorder of brain development with his seminal book "Infantile Autism: The Syndrome and its Implications for a Neural Theory of Behavior" (Rimland, 1964)

Genetic factors

Evidence for the importance of genetic factors in the etiology of autism comes from many sources, including twin and family studies (Muhle et al, 2004). Autism is, for example, 50 to 200 times more prevalent in siblings of autistic probands than in the general population. Among probands' relatives who do not have autism, there is also an increased prevalence of milder forms of developmental difficulties related to communication and social skills (broad phenotype). Concordance rates for autism range from 36% to 96% in monozygotic twins but only 0% to 27% in dizygotic twins (Shadock & Shadock, 2008).

Although the heritability of autism has been estimated to be as high as 90% (Freitag, 2007), genetic factors are heterogeneous, complex and for the most part poorly understood. The precise mechanisms are being explored through whole-genome screening, cytogenetics, and evaluation of candidate genes (Muhle et al, 2004). In studies of candidate genes, there are replicated findings of increased risk for autism associated with variants in single genes on chromosomes 2, 3, 4, 6, 7, 10, 15, 17 and 22 (Freitag et al, 2010). Cytogenetic studies have implicated abnormalities at the 15q11-q13 locus in individuals with autism (Muhle et al, 2004; Smalley, 1991). Genome-wide association studies have found slight effects on autism risk with genetic variants at the 5p14.1 and 5p15 loci (Ma et al, 2009; Weiss et al, 2009). Also, replicated copy number variations, found in genome-wide association studies to be more common in individuals with autism than in controls, are located on chromosome regions 1q21, 2p16.3, 3p25-26, 7q36.2, 15q11-13, 16p11.2 and 22q11.2 (Freitag at al, 2010). Future directions for genetic research in autism lie in identifying specific gene-environment interactions. Click here to access a detailed recent review of genetics in ASD and guidelines for genetic studies from the American College of Genetics and Genomics (Schaefer & Medelsohn, 2013).

Neuroanatomic and neuroimaging findings

Neuroanatomic and neuroimaging findings, though not diagnostic, have consistently revealed increased cerebral volume that affects both grey and white matter, as well as enlarged ventricles. Neuroimaging findings also include

Etiology

Interested readers can learn about ongoing studies on the etiology of ASDs by checking the following websites:

- Childhood Autism Risks from Genetics and the Environment (CHARGE)
- Norwegian Autism Birth Cohort Study (ABC)
- Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE)

abnormalities in brain chemistry, serotonin synthesis, and brain electrophysiology (Courchesne et al, 2004; Hazlett et al, 2005; Lainhart, 2006).

The autism *spectrum* is now understood to be neurodevelopmental, meaning that there are differences in the pattern of brain development. For example, early brain overgrowth has been documented in the first two years of life (Courchesne et al, 2001) and, in later development, there are clear differences in the function and structure of the 'empathy circuit' of the brain (amygdala, ventromedial prefrontal cortex, temporo-parietal junction, orbitofrontal cortex, anterior cingulate, and other related brain regions) (Lombardo et al, 2011). There are also differences in connectivity between frontal and parietal lobe functions that are thought to relate to cognitive style, in particular an over-reliance on processing details and a relative under-reliance on processing gist or holistic information (Belmonte et al, 2004). Diffusion tensor imaging studies have suggested aberrations in white matter tract development (Wolf et al, 2012). Recent studies (Stoner et al, 2014) have identified discrete patches of disorganized cortex in the majority of post-mortem samples obtained from young autistic children. These patches occurred in regions mediating the functions that are disturbed in autism: social, emotional, communication, and language. Such abnormalities may represent a common set of developmental neuropathological features that underline autism and probably result from dysregulation of layer formation and layer-specific neuronal differentiation at prenatal developmental stages.

Click on the image to view a lecture by Joe Piven (Carolina Institute for Developmental Disabilities, US) about "**Explaining ASD: neurobiological aspects**" (available in English, Basque, Spanish, and French); from the International Society for Autism Resarch (INSAR) meeting at Donostia/San Sebastian (Spain) in 2013. (30:00)

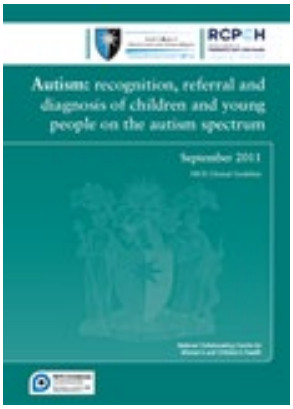
Environmental factors

A number of environmental factors have been claimed, particularly in the

Clay art by Santiago, an 11 year old with autism spectrum disorder. Photo: Lynn Albrink

Internet, as playing a role in the etiology of ASDs, including mercury, cadmium, nickel, trichloroethylene, and vinyl chloride (Kinney et al, 2010). It is important to note that the previously suggested link between MMR vaccines and autism spectrum disorders (Wakefield et al, 1998) has been debunked by international agencies that include Centers for Disease Control and Prevention, Institute of Medicine of the US National Academy of Sciences, the UK National Health Service and the Cochrane Library. The Wakefield et al (1988) article published in Lancet that suggested the association between the MMR vaccine and autism has since been declared fraudulent and officially withdrawn (Goodlee et al, 2011).

Associations between different environmental factors contributing to vitamin D deficiency and increased risk of autism have also been proposed (Grant & Soles, 2009). Population based studies in Scandinavia found that the use of prenatal folic acid supplements around the time of conception was associated with a lower risk of autistic disorder (Surén et al, 2013), while maternal use of valproate during pregnancy was associated with a significantly increased risk of ASD and childhood autism in the offspring, even after adjusting for maternal epilepsy (Christensen et al, 2013).



Click on the picture to access the NICE guideline: "Autism: Recognition, Referral and Diagnosis of Children and Young People on the Autism Spectrum"

Epigenetic factors

There are indications that, in addition to genetic and environmental factors, epigenetic factors also play some role through the fact that several genetic syndromes that are comorbid with ASD show dysregulation of epigenetic marks that help regulate gene expression (Grafodatskaya et al, 2010). The epigenetic line of research also holds promise in offering an explanatory model to understand the putative increased incidence of autism suggested by epidemiological findings.

Risk factors

The NICE (2011) guideline *Autism: Recognition, Referral and Diagnosis of Children and Young People on the Autism Spectrum*, while stressing the low quality of evidence found, lists the risk factors for ASDs that are clinically and statistically important as:

- A sibling with autism
- A sibling with another ASD
- Parental history of schizophrenia-like psychosis
- Parental history of affective disorder
- Parental history of another mental or behavioral disorder
- Maternal age older than 40 years
- Paternal age between 40 and 49 (ASD)
- Paternal age older than 40 years (autism)
- Birth weight less than 2500 g
- Prematurity (under 35 weeks)
- Admission to a neonatal intensive care unit
- Presence of birth defects
- Male gender
- Threatened abortion at less than 20 weeks

- Residing in a capital city
- Residing in suburb of a capital city.

In relation to medical conditions associated with ASD, with the same proviso of low quality of the evidence, the NICE guideline lists the prevalence of ASDs in several medical conditions (prevalence of ASDs between parentheses):

- Intellectual disability (8%-27.9%)
- Fragile X syndrome (24%-60%)
- Tuberous sclerosis (36%-79%)
- Neonatal encephalopathy/epileptic encephalopathy/infantile spasms (4%-14%)
- Cerebral palsy (15%)
- Down syndrome (6%-15%)
- Muscular dystrophy (3%-37%)
- Neurofibromatosis (4%-8%).

Neonatal physical illnesses such as post-encephalitic infections and sepsis had been documented to precede the onset of symptoms of ASDs, especially in Sub-Saharan Africa. Autoimmune factors have also been claimed as a possible etiological factor in ASDs. This would result, if finally demonstrated, from reactions between maternal antibodies and the fetus (Bakare & Munir, 2011).

In summary, although heritability of autism has been estimated as extremely high, the challenges faced in understanding the etiology of autism lie in the observation that genetic factors are heterogeneous, complex, and the interaction between genes and environment are poorly understood. There are on-going and ambitious individual and familial longitudinal studies that promise to give us useful data in this regard.

Future directions for genetic research in autism lie in identifying specific gene-environment interactions. Research must overcome the challenges of elucidating the roles of genetic heterogeneity, epigenetic mechanisms and environmental modifiers. It is hoped that technological advances, combined with longitudinal projects, will help us understand in the near future the etiological complexities of these disorders and will advance specific ways to treat and to prevent them.

CLINICAL ASPECTS

Qualitative impairments in social interaction and social communication

Of the core symptom domains that define autistic disorder, impairment in social interaction and communication is central. This includes impairment in non-verbal behaviors used to regulate social interactions, failure to develop peer relationships appropriate to the child's developmental level, and lack of spontaneous seeking to share enjoyment, interests or achievements with others (e.g., by a lack of showing, bringing or pointing objects of interest to the attention of others). Children with impairments in these areas lack social or emotional reciprocity.

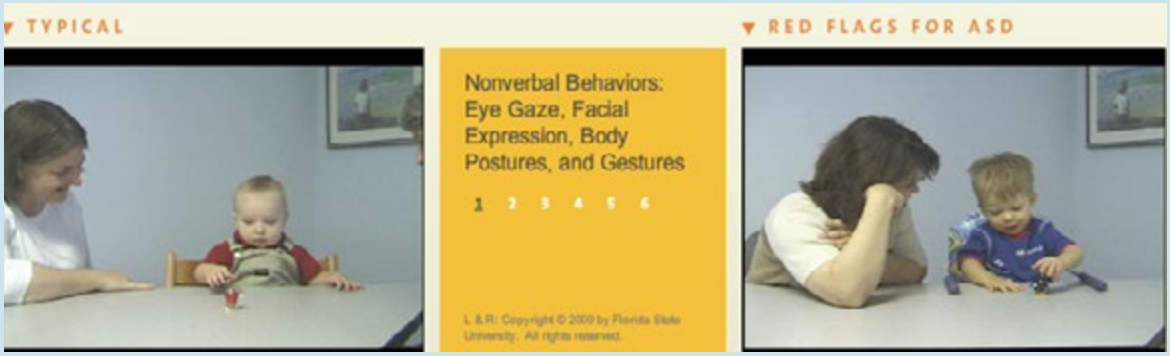
Responding to joint attention and initiating joint attention is very important in social learning and is associated with language and cognitive development.

Impairment in joint attention is a very important early symptom that can be seen even in very young children with autism.

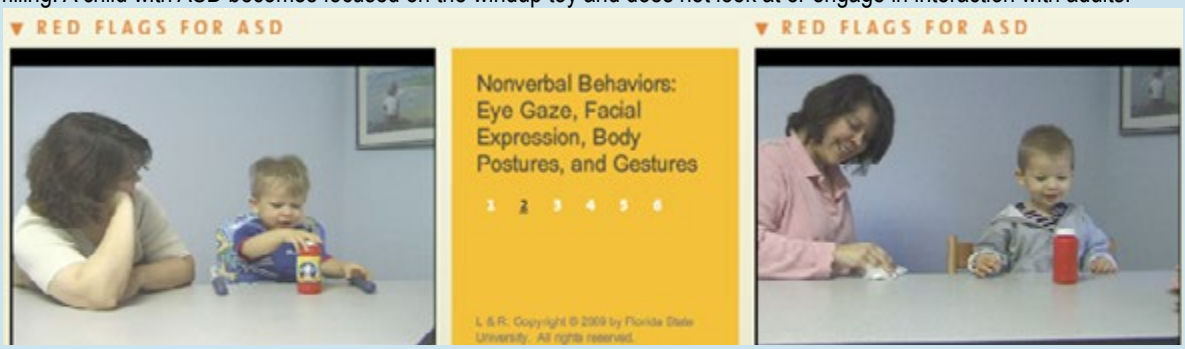
Research on the *theory of mind* has shown that children's ability to imitate others lies at the origin of understanding the perspective of others. Theory of mind enables one to have an idea of the mental state of others and, to some extent, predict their actions.

Theory of mind is also related to the ability to understand deception and other people's emotions (empathy). Theory of mind impairments negatively affect pretend play, empathy, sharing, social and emotional reciprocity and peer

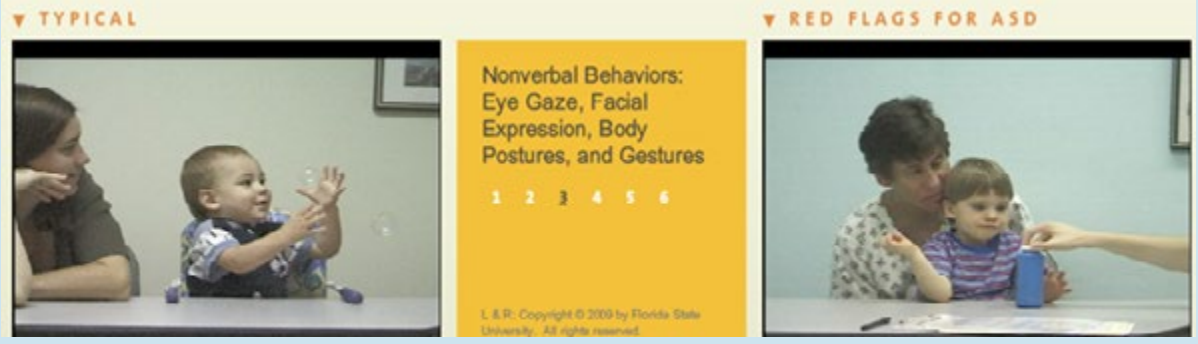
Figure C.2.2 Photographs illustrating "red flags"; video clips available at the Autism Speaks video glossary



A typical child at 12 months shifts his eye gaze from the windup toy to the clinician and then coordinates his eye gaze with smiling. A child with ASD becomes focused on the windup toy and does not look at or engage in interaction with adults.



A child with ASD at 18 months looks at the bubble jar and his mother's hands but does not shift his eye gaze from the jar to his mother's face to convey what he wants. The same child at 27 months has been in an early intervention program and, although he still has significant language challenges, he is now able to look at his mother's face in coordination with a sign or gesture and word.



A typical child at 15 months demonstrates facial expression; the movements of the face are used to express his emotions and to communicate with others nonverbally. A child with ASD at 20 months has a marked impairment in the use of facial expressions and other nonverbal behaviors.

relationships. Theory of mind impairments can be seen in all individuals with ASD regardless of age and intelligence when mental age-appropriate tests are used (Baron-Cohen, 2009). However, theory of mind deficits are not exclusive to ASD and can be seen in schizophrenia and in some personality disorders.

Another important concept is *stimulus overselectivity*: children with ASD exhibit overly selective attention to some particular stimuli, not to the *gestalt* of what is being seen or heard (like making a puzzle not using the image to be built but paying attention only to the shape of the pieces). This is also not unique to ASD and can be seen in children with intellectual disabilities.

Stimulus overselectivity can be due to restricted attention or bias towards non global, local information. The latter has been described as the *weak central coherence theory* (Happe & Frith, 2006). The bias explanation allows individuals with ASD to have superior local information processing ability. *Enhanced perceptual functioning theory* (Mottron et al, 2006) posits that individuals with ASD have biased perception, which is more locally oriented; detail perception is enhanced and movement perception is reduced. Baron-Cohen and associates (2009) argue that sensory hypersensitivity leads to excellent attention to details and *hyper-systemizing* leads to law-based pattern recognition, which can produce talent.

Children with ASD use nonverbal behaviors such as eye contact, gestures, body postures and facial expressions less often than typically developing children. One of the most important findings in recent years has been the observation that two-year-olds with autism fail to orient towards biological motion – human bodies in motion (Klin et al, 2009) – and they do not preferentially look to the eyes of approaching adults (Jones et al, 2008).

Even high-functioning individuals with ASD have problems in peer relations. Some persons with ASD do not have any interest at all in relating to peers while others may not be able to play in different sides of a game (e.g., seeking and hiding). Some may want to relate to peers but have problems in interpreting other's actions and responding accordingly. Many subjects with ASD do not comprehend the nature of social relations, that is, the intuitive or deductive hidden norms or meanings that govern our relationships and may fail to develop adequate empathy. All of these difficulties lead to impairments in social relations.

In terms of qualitative impairment in communication, symptoms may include:

- Delay in, or a total lack of development of spoken language, which is not accompanied by compensatory attempts
- Marked impairment in the ability to initiate or sustain conversations
- Stereotyped, repetitive or idiosyncratic language; and
- Lack of varied, spontaneous imitative or make-believe play.

Language delay, lack of language, and peculiarities in spoken language are common in ASDs and they are often the parents' initial concern. The important distinction lies in the compensatory attempts; children with other developmental and sensory disabilities usually try to compensate by using non-verbal means – such as gestures – for communication. In children with speech, functionality and social directedness of the speech is very important, often lacking in those with ASD. Repetition of another person's words, echolalia, is frequent in ASD. The

Click on the image to view a lecture by Francesca Happé (King's College London, UK) about "**Understanding the person with ASD**" (available in English, Basque, Spanish, and French); from the International Society for Autism Research (INSAR) meeting at Donostia/San Sebastian (Spain) in 2013. (41:45)

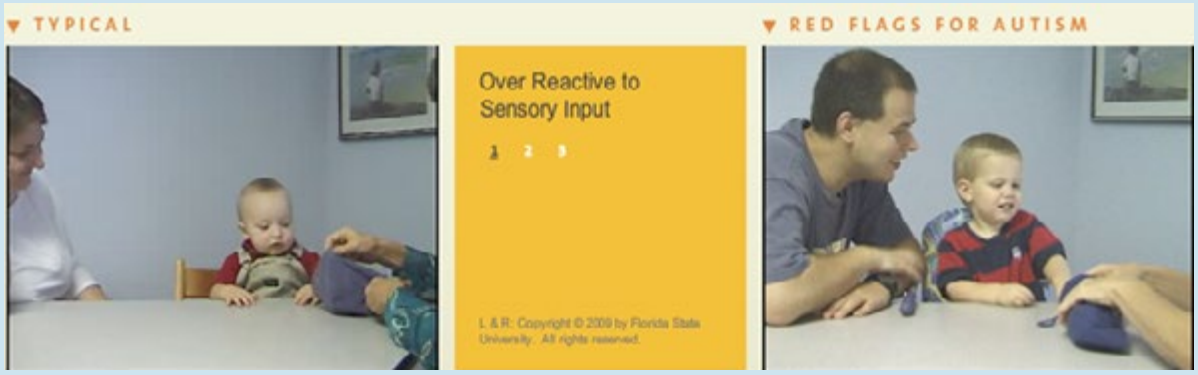
Joint attention

This term describes children's capacity of being able to look at another person's eyes and face in order to get information such as how that person feels, what that person is looking at, or what that person is trying to do. It is also being able to follow another person's eye-gaze to then look at the same thing and being able to sustain joint attention, which is harder in an activity where you cannot predict what the other person will be doing, feeling or planning. Certain social situations require shifting attention frequently to monitor the other person.

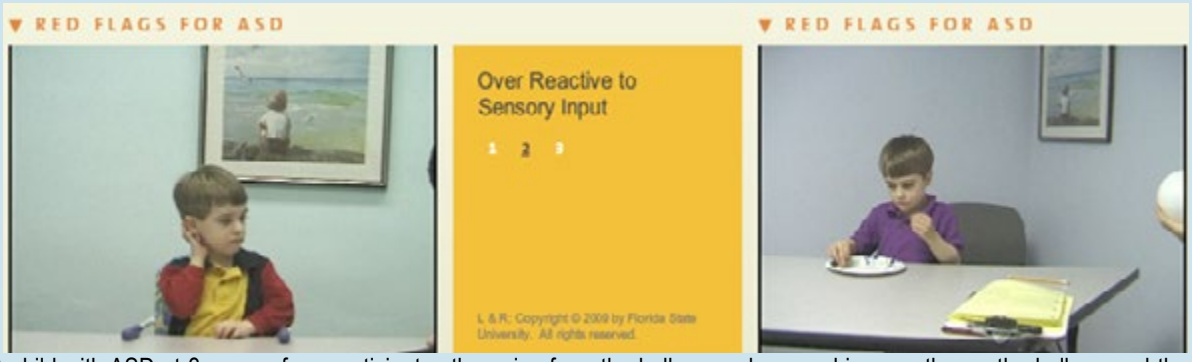
Click on the picture to hear Uta Frith (University College London, UK) describe weak central coherence and its role in ASD (4:00)

rate, volume and intonation of speech can be abnormally high, low, fast, slow, jerky, monotonous, etc. Individuals with ASD may invent their own words or phrases and language can be repetitive, may repeat the same phrases even when they are inappropriate to the context. Even high-functioning individuals with ASD can have problems initiating and sustaining a conversation. This includes lack of small-talk, not providing enough information, not asking for information and not building on other people's comments. When combined with restricted interests, conversation with persons with ASD can be very difficult to sustain.

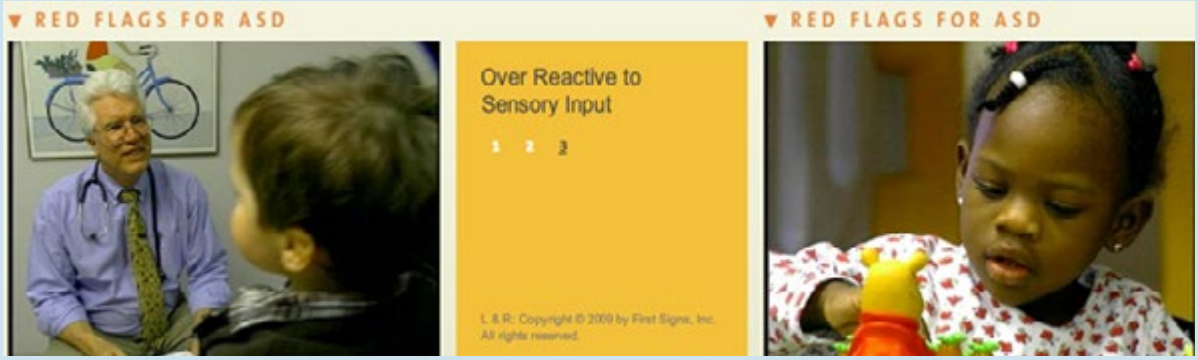
Figure C.2.3 Photographs illustrating "red flags"; video clips available at the Autism Speaks video glossary



A typical child at 12 months reaches cautiously into the bag, looks at the clinician for reassurance and actively explores the Koosh "cat" ball by touching and mouthing it, and shows it to his mother. A child with ASD at 20 months has good eye gaze, however he is very reluctant to touch the Koosh "cat" ball. His strong negative reaction is known as "sensory defensiveness".



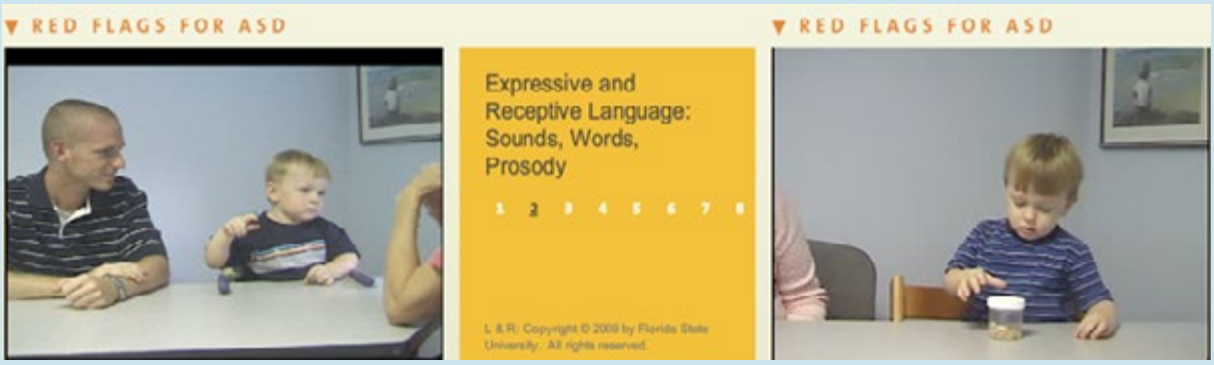
A child with ASD at 3 years of age anticipates the noise from the balloon and covers his ears, throws the balloon and then gives it to his mother to protest. The same child at 5 years again covers his ears in anticipation of the balloon being shot into the air. Although over-reactive to sensory input, he is now able to tell the clinician that he does not want her to let the air out.



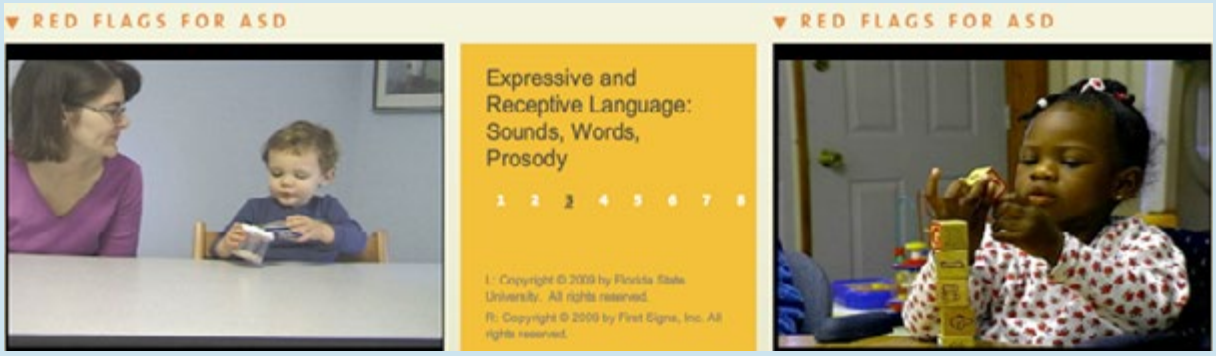
A child with ASD at 2 years is very over-reactive to light and starts engaging in self-stimulating behavior to soothe or comfort himself. A child with ASD at 3 years is very reactive to loud noises, like hand clapping. This child puts her hands over her eyes and reaches to her mother for comfort.

Figure C.2.4 Photographs illustrating "red flags"; video clips available at the Autism Speaks video glossary

A typical child of 15 months uses speech-like sounds or babbling in a meaningful, interactive way. The same typical child at 22 months uses clear words to name animals while pointing to pictures in the book.



A child with ASD at 22 months has desire and shows effort to communicate with a lot of gestures and minimal vocalization, but he does not have words yet. The same child at 28 months is trying to imitate the words "more" and "open" verbally.



A child with ASD at 28 months produces unusual sounds for language. A child with ASD at 36 months has unusual sounds for language. It seems more like self-talk since she never looks at others.

Click on the picture to access the Autism Speaks website. This is an excellent resource documenting all the symptoms and signs. The facility is free; information cannot be downloaded but can be used online by professionals who want to show these symptoms (video clips) to families or in training sessions. The video clips contrast the behavior seen in children with ASDs with that of typically developing children. The Video Glossary was created by Amy M. Wetherby, PhD, director of the Florida State University Autism Institute and Nancy D. Wiseman, founder and president of First Signs®.

I don't have any friends. The bullying started in kindergarten when I got my glasses. The teacher made a popular boy wear fake glasses so I'd have someone to connect with, but as it turned out, he didn't really want to talk about whether archaeopteryx should be categorized as a prehistoric bird or dinosaur. Needless to say, that friendship lasted less than a day. By now I have gotten used to kids telling me to leave, to sit somewhere else. I never get called on the weekends. I just don't get the social hints that other people do. So if I'm talking to someone in class and he says, "Man, is it one o'clock already?" I look at the clock and tell him that yes, it is one o'clock already, when in reality he is trying to find a polite way to get away from me. I don't understand why people never say what they mean... For me being in social situations—whether that's school, or Thanksgiving dinner, or the line at the movies—is like moving to Lithuania when you haven't studied Lithuanian.

Judi Picoult (2010). ***House Rules***. New York: Atria Books

Play can be functional or imaginative. Functional play is when toys are used as intended, for example using a toy fork as a fork or pressing the buttons of a cause-and-effect toy. Problems in make-believe and imitative play are apparent in many children with ASD. Typically developing children play with several materials in a flexible and creative way. For example, in typical make-believe play children can use a puppet as a general and a wooden block as the car of the enemy soldier (imaginative play). Everything can be used in an imaginative way.

Repetitive, restricted, stereotyped patterns of behavior, activities and interests

According to DSM-5, this core symptom domain includes preoccupation with stereotyped and restricted patterns, inflexible adherence to routines, stereotyped and repetitive motor mannerisms, and persistent preoccupation with parts of objects. It has been suggested that this domain is very broad and contains at least two subtypes of behaviors: (a) repetitive sensory motor behaviors (lower-order) and (b) insistence on sameness – and possibly circumscribed interests – (higher-order). Repetitive sensory motor behaviors are more frequently seen in young children and are associated with lower non-verbal intelligence.

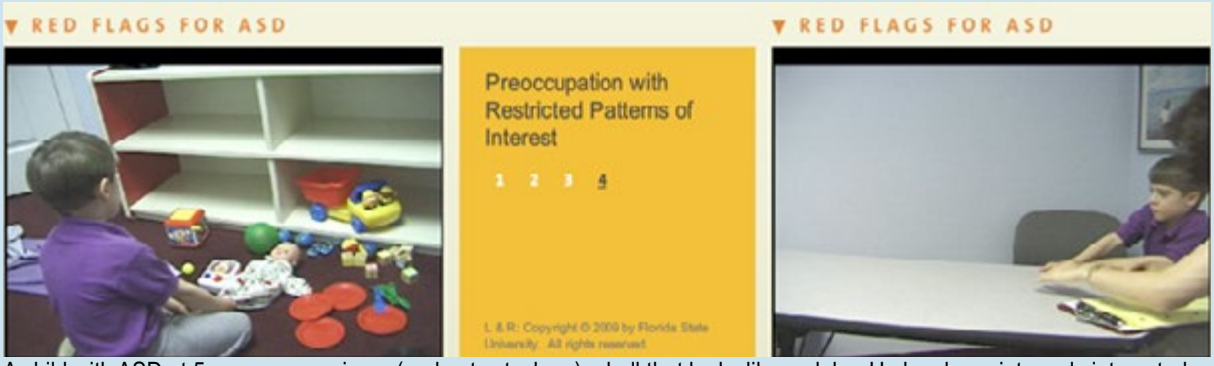
Many individuals show strong interests in some topics; they read extensively about them, collect items related to them, can talk on that subject for hours, and may proceed as young adults to join interest groups or societies dedicated to their interest. The difference between these normal behaviors and those of individuals with ASD can be explained in terms of narrowness of the focus, inflexibility, perseveration, and lack of social quality. Individuals with ASD can focus on a very specific part of the object of their interest, for example, only the number of teeth in dinosaurs. They can have problems in switching to other topics even when other people are clearly not interested in what they are talking about. They keep focusing on the topic when they are supposed to do other tasks and may become distressed or even agitated when they are interrupted. They may show less interest in sharing their hobby in social ways, like joining a club.

Inflexible adherence to specific, non-functional routines or rituals is also a typical symptom of ASDs. Difficulties with minor changes in personal routine and resistance to even small changes in the environment can cause significant problems

Figure C.2.5 Photographs illustrating "red flags"; video clips available at the Autism Speaks video glossary

A typical child at 20 months engages in make-believe play by offering "coffee" to everyone and scooping food for Big Bird and himself. A child with ASD at 20 months does not engage in make-believe play but instead explores objects by turning them over and rolling them.

A typical child at 15 months engages in make-believe play by hugging and feeding Big Bird with the bottle, and stirring, pouring, and blowing on food. He shifts his focus from one toy to another and from the toy to people. A child with ASD at 16 months does not engage in make-believe play but instead is very focused on wobbling the bowl and cup.



A child with ASD at 5 years zeroes in on (and gets stuck on) a ball that looks like a globe. He has been intensely interested in planets for a few years, so he was particularly drawn to the ball, to the exclusion of all the other toys. Same child with ASD at 5 years gets stuck on the camera. He has shown an interest in the camera and other mechanical or electronic things for a few years.

Click on the picture to access Autism Europe's "Persons with Autism Spectrum Disorders: Identification, Understanding, Intervention"

> – I said, 'Thank you for helping me with my investigation.'
> – And she said, 'You're Christopher, aren't you?'
> – I said, 'Yes I live at number 36.'
> – And she said, 'We haven't talked before, have we?'
> – I said, 'No I don't like talking to strangers. But I'm doing detective work.'
> – And she said, 'I see you every day, going to school.'
> – I didn't reply to this.
> – And she said, 'It's very nice of you to come and say hello.'
> – I didn't reply to this either because Mrs Alexander was doing what is called chatting where people say things to each other which aren't questions and answers and aren't connected.
> – Then she said, 'Even if it's only because you're doing detective work.'
> – And I said, 'Thank you,' again.
>
> Haddon M (2003) *The Curious Incident of the Dog in the Night-Time*. Jonathan Cape, p50.

in their and their families' daily lives (e.g., severe tantrums).

Stereotyped and repetitive motor mannerisms and persistent preoccupation with parts of objects is more evident in younger children and individuals with intellectual disability. These include hand and finger flicking, rocking, toe walking, sniffing and licking non-food objects, spinning, and unusual visual gaze, among others. Persistent preoccupation with parts of objects can be seen, for example spinning wheels, flickering the eyes of dolls.

Stereotyped behaviors can be observed in several other conditions including Tourette's Disorder, Fragile X syndrome, Rett's disorder, obsessive compulsive disorder, deafness, blindness, schizophrenia and a variety of intellectual disabilities without ASD. It seems that the frequency but not the pattern – which is related to the developmental level – of the behavior is what is distinctive for ASDs (Bodfish et al, 2000).

Children with ASD show several atypical behaviors, probably due to sensory hypersensitivity, that can be observed in visual, auditory and tactile modalities and can be specific to certain stimuli (Baron-Cohen et al, 2009). Visual hypersensitivity may lead to lateral vision – staring at objects with pupils at the corner of the eyes (Mottron et al, 2006). Lateral vision has been interpreted as an attempt to limit excessive information or to focus on optimal information.

DIAGNOSIS

There is broad agreement that, once the presence of ASD is suspected, the child should be referred for a multi-disciplinary assessment in which all members of the team should have some ASD training and at least one team member should be trained in the assessment and diagnosis of ASD using standardized instruments. Also, it is recommended that the child should be ideally observed in different settings, both structured and unstructured. It needs to be recognized, however, that the vast majority of child and adolescent mental health services worldwide do not

have the state-of-the-art instruments such as the Autism Diagnosis Observation Schedule, the Autism Diagnostic Interview, the Diagnostic Interview for Social and Communication Disorder or the Developmental, Dimensional and Diagnostic Interview used in specialized clinics in wealthy countries. This highlights the need for dissemination, training and development of multi-cultural, multi-language, cheap, reality-oriented, user-friendly, instruments.

Click on the image to access "Diagnostic Instruments for ASD"

The NICE guideline is freely available and considers all the aspects of the ASD-specific diagnostic assessment, provides recommendations about its core elements, autism-specific diagnostic tools and how best to communicate to parents a diagnosis of autism for their child. In summary, the NICE guideline reiterates what has been established in other guidelines including a detailed enquiry into the specific concerns raised by families and teachers, medical history, home life, education and social care, and history and observation focusing on the developmental and behavioral features specified in ICD-10 and DSM-5. This core information is usually sufficient to establish a diagnosis of autism when diagnosis is straightforward. Beyond the diagnosis of ASD, a diagnostic assessment should also include a profile of strengths, needs, skills and impairments. The instruments needed for this will depend on the age of the patient and the developmental level, but should be capable of helping to identify:

- Intellectual ability and learning style
- Academic skills
- Speech, language and communication skills
- Fine and gross motor skills
- Adaptive (including self-help) skills
- Socialization skills
- Mental and emotional health including self-esteem, physical health and nutrition
- Sensory hyper- and hypo-sensitivities
- Behaviors likely to affect participation in life experiences, future support and management.

Physical examination

A thorough physical examination should also be undertaken. Findings from the physical examination may be useful to detect coexisting conditions or symptoms of disorders that may have a causative role or increase the suspicion of an ASD. Particular attention should be given to identifying skin stigmata of neurofibromatosis and tuberous sclerosis, as well as congenital abnormalities and dysmorphic features including micro and macrocephaly. The examination should also look for signs of physical injury, such as self-harm or maltreatment (Volkmar et al, 2014[p244]).

Differential diagnosis

Autistic disorder, when presenting in its typical form, is not difficult to recognize by a professional with some experience. However, clinicians should rule out medical, genetic, neurological or sensory dysfunctions or disorders. The situation is different for clinical pictures that do not fit the traditional descriptions

of the disorder, which are becoming more frequent due to the widening of the construct into the autistic spectrum and this can lead to diagnostic disagreement.

Click on the image to access the National Institute for Health and Clinical Excellence (UK) guideline on the recognition, referral, diagnosis and management of adults on the autism spectrum.

Infants and toddlers

Differential diagnosis at this age should rule out disorders that interfere with normal development of language and social skills. Hearing loss can be suspected if the child has lost his babbling, shows poor vocalization or indifference to auditory stimuli. Routine exam in very young children who cannot be expected to cooperate include otoacoustic emissions and impedance audiometry. If they are normal, there is no need for further testing. If they are abnormal, the external ear should be examined and both tests should be repeated in two to three months. If the results are again abnormal, auditory evoked potentials should be studied.

Severe psychosocial deprivation

It is well known that severe emotional deprivation in childhood leads to serious psychological impairments including pseudo-autistic clinical pictures (Rutter et al, 1999). The autistic-like symptoms in these cases usually consist of a relative indifference to the environment, communication delay, restricted interests and repetitive behaviors. Unlike in ASD, social reciprocity is not completely abnormal – although bonding may be affected – and deficits can be reversed quickly in the majority of cases if environment improves.

Intellectual disability (formerly known as mental retardation)

It is often a difficult diagnosis to exclude in the early years of life because evaluation of cognitive functioning is more difficult (see Chapter C.1). Some symptoms (e.g., facial dysmorphy, microcephaly) may suggest the existence of genetic or neurological problems known to cause intellectual disability. It is also documented that severity of intellectual disability is positively correlated with social interaction deficits (Wing & Gould, 1979). Therefore, attributing communication and socialization defects, self-injurious or stereotypic behaviors to autism or severe intellectual disability can be challenging. This can be provisionally solved if there is evidence of an abnormal development in social, communication and imaginative skills discordant with the general level of intelligence (very difficult to clarify when mental age is below 18 months). It is important here to highlight that the association of ASD and intellectual disability is very common and that many known causes of intellectual disability, such as chromosomal abnormalities, often present with autistic symptoms (e.g., Fragile X syndrome, Prader-Willi syndrome) (see Chapter C.1).

It is important to highlight that the association of ASD and intellectual disability is very common and that many known causes of intellectual disability, such as chromosomal abnormalities, often present with autistic symptoms (e.g., Fragile X syndrome, Prader-Willi syndrome).

Rett's disorder

DSM-5 does not include this condition among the ASDs. Although patients often have autistic symptoms they are apparent only for a brief period during early childhood, so inclusion in the autism spectrum is not appropriate for most individuals. Rett's disorder is an X-linked neurodevelopmental condition that affects girls almost exclusively. Typically, there is normal development until 6–18 months of age, then development stops and a regression appears (loss of speech and of purposeful hand use) with specific hand stereotypies and social withdrawal, which mimic an autistic picture. Besides, there is a deceleration in head growth

Clay art by Santiago, an 11 year old with autism spectrum disorder. Photo: Lynn Albrink

leading to acquired microcephaly and seizures may appear. Research has led to the identification of a gene (MECP2) on the X chromosome (explaining the higher frequency in girls, but some male cases have been reported) (Amir et al, 1999).

Receptive-expressive language disorders

Expressive language disorders are very common in children and usually consist in a simple delay in mastering phonology, lexicon and syntax that looks very selective in the context of a typical development of social skills, non-verbal communication, cognitive skills and imagination. The situation is more challenging in a group of children previously diagnosed as 'pervasive developmental disorders not otherwise specified' that in DSM-5 are considered as not having ASD, but rather a social (pragmatic) communication disorder, a condition only differentiated from ASD by the absence of restricted/repetitive patterns of behavior, interests, or activities. The usefulness of this new diagnosis has been sharply questioned, since there are no studies supporting it as being an unrelated disorder. Also social (pragmatic) communication disorders constitute a significant proportion of cases participating in ASD treatment programs.

Landau–Kleffner syndrome

Acquired aphasia with epilepsy or Landau–Kleffner syndrome is characterized by a normal development until age three to four followed by a massive regression of receptive and later expressive language, typically in conjunction with the development of seizures or sleep electroencephalogram abnormalities. The regression may be associated with transient social withdrawal but a complete autistic picture is not observed. There is a sub-type of pervasive developmental disorder, *childhood disintegrative disorder*, where regression is evident, but the regression occurs earlier (18 to 24 months of age).

Selective mutism and separation anxiety

Withdrawal, anxiety and communication problems are common. However, it can be easily distinguished from autism because of the existence of normal communication and social skills at home or in other familiar environments.

Older children

Differential diagnosis in typical autistic presentations is easier in older children, but it can be difficult in cases within the broader phenotype, cases in the 'periphery' of the spectrum, especially in high functioning children, or cases with a partial syndrome. Accurate medical and developmental histories, careful clinical examination, and reports from social situations are all essential..

Clinicians should consider childhood schizophrenia (see Chapter H.5). Confusion between this rare condition and ASD may arise from poor expression of emotions and negativism. However, hallucinations and delusions are specific to schizophrenia. Furthermore, most children with early onset schizophrenia do not show the language delay or abnormalities and the social deficits that are typical of ASDs.

Other psychiatric conditions to be excluded are *attention deficit hyperactivity disorder* (ADHD), especially as ADHD and ASD can now in DSM-5 coexist, and *obsessive compulsive disorder* (OCD), because of the rituals and selected interests seen in OCD, but the differential diagnosis can be made on the basis of the history and clinical presentation. It is of interest to highlight that some authors refer to a disorder not included in the current classifications: multiple complex developmental disorder (Towbin et al, 1993), which consists of impaired regulation of affective state with primitive anxieties, impaired social reciprocity and thought disorders, but failing to meet criteria for ASD.

PROGNOSIS AND ADULT OUTCOMES

ASDs are disorders that start in infancy; therefore, significant changes occur with development that will impact adult outcome. These changes should not be overlooked and require ongoing monitoring and individualized adaptation to optimize support programs. Baghdadli et al (2007) have stressed the high variability in short-term outcomes of pre-schoolers, emphasizing the importance of considering individual characteristics and adaptive strategies. They suggest that these differences may be due to certain initial characteristics like speaking skills and severity of autistic symptoms.

The more severe the comorbid intellectual disability the poorer is the outcome. It is generally accepted that speech before the age of six and a higher IQ are associated with better outcomes (Billstedt et al, 2011). However, there is limited research data about the whole spectrum across the life cycle. Therefore, clinicians must be cautious when predicting the distant future of their patients. ASDs are lifetime disorders and cannot be cured yet. Nevertheless, disability depends not only on the characteristics of the individual but also on the environment that is offered to that person, adapted or not, to minimize the disabilities.

Uncertainty arises from three sources. First, little research has been done about the role played by the supports provided. Second, there is a younger and less severely affected group of individuals now diagnosed with ASD in industrialized countries; their prognosis and response to treatment may be better than traditionally observed and some may even overcome some of their symptoms so that they no longer meet criteria for diagnosis later on. These optimal-outcome patients will still retain residual anomalies, such as in narrative performance (Feinn, 2013; Suh, 2014). Finally, there is limited epidemiological data on adults, particularly those with Asperger's disorder. Marriage and Wolverton (2009) showed that despite adequate academic achievement, work, living and mental health status can be poor in this population. Lehndardt et al (2011) estimate that the lifetime rate of psychiatric consultations for this group in Germany can be as high as 78%.

Overall, it can be said that the majority of children with ASD will continue to show deviance and difficulties in social interactions throughout their lives. It should be assumed that they will need support and help in many areas. However, their quality of life can be improved when adequate programs are available in their communities. Community based programs should be adapted to each individual, taking into consideration areas of difficulty and strengths, as well as the resources that the community has to offer. People with autism will need structure, clarity and predictability throughout their lives.

Three words summarize the treatment of individuals with ASD:

- Personalize
- Contextualize
- Empower.

Behavior and adaptive skills tend to improve with age. Nordin and Gillberg (1998) found that measures of flexibility and cognitive shifting abilities tend to be predictors of good social outcome. Unfortunately, more research is needed on the adult population, so that programs may be tailored to meet their needs as well as supporting transition into adulthood, which can be quite difficult.

Prognosis should be discussed with the family to avoid unrealistic expectations and focus all efforts on early intervention and on fostering family involvement and knowledge as well as community participation. It is important to underline that current efforts in treatments and the creation of services (non-existent in most countries), will shape the future functioning of the children diagnosed and treated now.

TREATMENT

Treatment of ASDs depends on so many factors that it makes description of 'the treatment' difficult. Differences in age, degree of impairment, comorbid disorders, family and social situation, level of resources and community development, provision of education (or lack of it), health and welfare assistance, opportunities for sheltered employment, and availability of inclusive living in the community in adult life will make a huge difference to sufferers' outcome and quality of life. If there are three words that summarize what should be done for people with ASDs, they are *to personalize*, *to contextualize* and *to empower*.

Despite accepting these common sense ideas, many families and clinicians search for a *cure* for ASD, as if there was a single cause, a unique mechanism, and a single condition underlying the syndrome that, if identified, would lead to a cure for all ASDs. The Internet allows families and professionals to hear about many 'treatments' – some based on current knowledge but others based on false beliefs or

'To assess Theory of Mind, researchers use the Sally-Ann test to see if children can understand how other people think. This test uses a story format with two girls, Sally and Ann. Sally has a ball, which she puts in a basket, and then she leaves the room. While she is gone, her tricky friend Ann removes the ball from the basket and places it in a box instead. Children are then asked to guess where Sally will look for the ball when she returns. Those who understand Sally's thinking will choose the basket, knowing that's where Sally thinks she left the ball. Those who lack Theory of Mind will choose the box because that's where they know the ball has been placed. Typically children with autism believe that Sally knows the ball is in the box because they know it's there; they don't stop to consider that Sally is unaware that the ball has been moved while she was gone.

Since Alex has never been tested for Theory of Mind as far as I know, I was curious to see how he would do with the Sally-Ann test. When I gave him the test this morning, he immediately gave me the right answer, confidently telling me that Sally would look for her ball in the basket. Was this a lucky guess, or does Alex truly possess Theory of Mind? From recent progress we have seen in Alex, I believe that he has developed some understanding of the way other people think.

As the article in Science magazine points out, little research has been done to determine what helps develop Theory of Mind. With Alex, I think that behavioral therapy has helped him to understand better how his actions impact others. Through social stories and scripts his behavioral therapist has developed, Alex recites the rules for interacting with other people. For example, in his script "I Need to Keep My Hands to Myself," he reminds himself that he needs to stop when he wants to touch someone or their belongings. The last line of this script explains the outcome when he follows the guidelines: "EVERYONE is happy when I keep my hands to myself." In addition, his behavioral therapist discusses with Alex the potential consequences of impulsive behaviors, asking him what can happen if he would throw something or grab someone. He knows that those are bad behaviors and can verbalize that he doesn't want to break things or hurt people. He will sometimes add, "That would be sad."'

Pam Byrne. *One Autism Mom's Notes* (with permission)

even superstition – with the result that many are confused about what to do. The worst aspect is that families (and often professionals) feel there is something else they should be doing and by not doing it, they are not providing the best treatment for their loved one with ASD. In the same line, very often there is a disregard for local limitations and resources. Thus, programs developed over the years in wealthy countries are copied or applied in completely different areas of the world without regard for the local circumstances, opportunities and future maintenance of the program.

Click on the image to watch the administration of the Sally-Anne test

While there is no cure for ASDs, there is strong evidence that appropriate, lifelong educational approaches, support for families and professionals, and provision of high quality community services can dramatically improve the lives of persons with ASD and their families. There are up to date practice guidelines in many countries such as Spain (Fuentes-Biggi et al, 2006) and the UK (NICE, 2011) that have reviewed the available evidence for a large variety of treatments advocated for ASD. The UK departments for Education and Skills and for Health have also produced guidelines for the education of students with ASDs. Much has been learned about practices that are supported by evidence and those that are not, and about which programs make a real difference to the lives of individuals with ASD. Unfortunately, this knowledge has not yet been incorporated into clinical practice around the world, even in some affluent societies. Thus, there remains a gap between knowledge and opportunity; it is evident that very few people with ASDs receive state-of-the-art support.

Click on the image to view a lecture by Connie Kasari (University of California Los Angeles, US) about "**Treatment of ASD in early childhood**" (available in English, Basque, Spanish, and French); from the International Society for Autism Research (INSAR) meeting at Donostia/San Sebastian (Spain) in 2013. (33:36)

Recent reviews of the evidence conclude that relatively few treatments meet the necessary criteria when assessing the value of interventions. Nevertheless,

evidence is improving, with growing numbers of well-conducted studies. Randomized control trials are also increasing in number. However, even when outcome is positive, most research still focuses on very short-term goals and on a limited number of outcome measures. There is little attempt to address questions such as whether treatment succeeds in maximizing the long-term potential of the individuals involved or if it truly improves their quality of life. Such issues may require different research strategies such as audits and reviews, systematic analysis of problems, and measures of satisfaction. It is also crucial to collect the views of individuals with ASD themselves.

Click on the image to view a lecture by Patricia Howlin (Institute of Psychiatry, London, UK) about "**Treatment of ASD during the life cycle**" (available in English, Basque, Spanish, and French); from the International Society for Autism Research (INSAR) meeting at Donostia/San Sebastian (Spain) in 2013. (40:09)

To date, programs involving behaviourally-based interventions, those designed to improve parent-child interactions, and those with an emphasis on developing social and communication skills appear to have the strongest supporting evidence, at least in the short term. As Autism Europe states, there are many other elements that are essential to improve longer-term outcome:

- *Education*, as early as possible, with special attention to social, communication, academic and behavioral development, provided in the least restrictive environment by staff who have knowledge and understanding of both autism and the individual student.
- *Accessible community support,* in terms of appropriate, well-informed, multi-agency services that will help each individual to realize their potential and life-time goals (either chosen by the individuals themselves, or those who know, love and legally represent them).
- *Access to the full range of psychological and medical treatments* (adapted as necessary to meet the needs of individuals with ASD) that are available to the general population.

The use of *psychotropic medication* in this population calls for caution and sound knowledge. In summary, medication is currently justified only to treat comorbid conditions (e.g., ADHD), not for the core symptoms of ASD, and in the management of challenging behaviors (e.g., aggression, self-harm) that do not respond to other approaches. There is good evidence that risperidone can be helpful for the latter (see presentation by Andres Martin in side box). Sung et al (2014) have reviewed drugs in development for ASD.

There are a variety of strategies that can augment autistic children's communication ability. New technologies are expanding greatly the capacity and sophistication of these communication aids. One example is "e-Mintza", a free application to generate a personal communication board on a computer or tablet (currently available in the Basque, Spanish, English and Frech). To view a short video about e-Mintza (in Basque and Spanish), click on the picture above. Click **here** to download the application in any of the four languages.

According to Autism Europe, interventions that are best supported by evidence and are examples of good practice include four principles:

- *Individualization*. There is not a single treatment that is equally effective for all persons with ASD. Variations in the manifestations of this spectrum as well as sufferers' skills, interests, life vision and circumstances mandate personalization.
- *Structure*. That is, adapting the environment to maximize each individual's participation by offering varying degrees of predictability and stability, more effective means of communication, establishing clear short and long-term goals, defining the ways in which these goals can be met, and monitoring outcomes.
- *Intensity and generalization*. The interventions used should not be sporadic or short term, but applied in a systematic manner on a daily basis, across different settings, and by all those living and working with the person with ASD. This will ensure that the skills acquired in more structured settings can be maintained in real life situations. Those

Table C.2.3 Treatments for autism spectrum disorders, evidence supporting their effectiveness and recommendation about their use

Effectiveness	Intervention	Recommendation
Not supported by evidence	• Doman-Delacato therapy • Irlen lenses • Facilitated communication • Psychodynamic psychotherapy • Secretine • Antimycotic therapy • Chelation • Immunotherapy • Craniosacral therapy • Animal assisted therapies	**Not recommended**
Weakly supported by evidence	• Auditory integration • Sensory integration • Expressive psychotherapies (art and music) • Vitamins and dietetic supplements • Gluten and/or casein free diets	**Recommended only in controlled research studies**
	• Social skills programs • Augmentative / alternative communications systems • TEACCH (Treatment and Education of Autistic and Related Communication-Handicapped CHildren) program • Cognitive behavioral therapy • SSRIs in adults with ASDs (if comorbid with obsessive compulsive disorder) • Stimulants in persons with ASD and comorbid ADHD	**Recommended**
Supported by evidence	• Behavioral interventions • Risperidone (for comorbid severe irritability or challenging behaviors)	

Source: Fuentes-Biggi et al (2006)

responsible for carrying out the interventions should also have access to appropriate support and guidance from professionals with expertise in ASDs.

- *Family participation*. Throughout childhood and beyond, parents must be recognized and valued as the key elements of any intervention. Information, training and support, always within the context of family values and culture, should be the common denominator of any professional intervention. Other important sources of support, such as babysitting, respite care, short breaks, or tax benefits should be available to avoid the discrimination that many of these families face. Adequate support for social, medical and educational services is necessary to ensure that these families are able to enjoy the same quality of life as everyone else. A recent study in the US (Lavelle et al, 2014) concluded that, even in a high income country, the economic burden associated with ASDs is substantial and can be measured across multiple sectors. Previous analyses that focused on health care underestimated

Medication treatment

Click on the picture to view a lecture by Andrés Martin (Yale Child Study Center, US) discussing in detail the evidence for pharmacological intervention in autism (52:15).

this economic burden, particularly for schools. Given the increasing incidence of ASD, these high costs may not be sustainable. Therefore cost-effective intervention in the low and middle income countries context is critical.

Globally, given that the vast majority of people with ASDs are not receiving specialized treatment – more often than not, they are not receiving what could be considered adequate generic treatment – child mental health professionals should be devoting their efforts to the development of resources in the community where they practice and to support these children's families. Regardless of their age, most people with ASDs around the world live with their families. It is of these families that one needs to ask how they want to be supported, what are their priorities, what are their dreams, what life project they would like for their child. The person with ASD should participate in this dialogue, directly or helped trough interpersonal support and augmentative communication means; in the minority (at least 25%) that cannot express themselves at all, by delegation, from people who know them well. Families are the essential support network that cannot be replaced by government; their role should be gratefully recognized – our task being to maximize their potential in their own terms. We are talking not only about a health goal but also about fighting ignorance and discrimination.

Click on the image to view a presentation by Joaquín Fuentes (Policlinica Gipuzkoa, San Sebastian, Spain) about "**ASD: support and community development**" (available in English, Basque, Spanish, and French); from the International Society for Autism Research (INSAR) meeting at Donostia/San Sebastian (Spain) in 2013. (40:09)

- Do you have questions?
- Comments?

Click here to go to the Textbook's Facebook page to share your views about the chapter with other readers, question the authors or editor and make comments.

PLEASE GO TO APPENDIX C.2.1 FOR SELF-DIRECTED LEARNING EXERCISES AND SELF-ASSESSMENT QUESTIONS

Clay art by Santiago, an 11 year old with autism spectrum disorder. Photo: Lynn Albrink

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Clay art by Santiago, an 11 year old with autism spectrum disorder. Photo: Lynn Albrink

Appendix C.2.1

SELF-DIRECTED LEARNING EXERCISES AND SELF-ASSESSMENT

- Administer, score and write a brief report after you have administered the MCHAT-R to the parents of three children, 2½-4 years of age (we suggest you choose one child with possible ASD, one normal developing child, and one with intellectual or communication problems)

  Click on the picture on page 8 to access the M-CHAT website and see if your local language version is available. If not, use the English version and contact the authors (contact address available in their website). They will probably be interested in collaborating with you in making a (non-commercial) translation to your language.

- Administer, score and write a brief report after you administer the CAST to the parents of two children aged 5 to 7 years (we suggest you choose one child with social/communication difficulties and a normally developing child)

  Click on the picture on page 8 to access the website of the Autism Research Centre of the University of Cambridge, find the CAST instrument, and see if there is a version in your local language. If not, use the English version and contact the authors (contact address available in their website). They will probably be interested in collaborating with you in making a (non-commercial) translation to your language.

- Prepare three PowerPoint slides illustrating the causes of autism spectrum disorder for a talk to be delivered to an audience of parents and representatives from your community,

  Please review pp. 10 to 13. If you want to make a comprehensive presentation, access also the embedded links and consider them in your talk.

- Write a one-page essay summarizing the ideas you want to highlight after studying this chapter. Please, consider sending this essay – with the linking reference – to your colleagues.

MCQ C.2.1 Which of the statements listed below apply to the definition of ASD in DSM-5?

1. Asperger disorder remains a separate diagnosis
2. ASD is classified under the heading of pervasive developmental disorders
3. Hyper- or hypo-reactivity to sensory stimuli are included in the diagnosis
4. It does not consider “specifiers”
5. Social (pragmatic) communication disorder is considered part of ASD

MCQ C.2.2 When examining babies-at-risk (those born after an older sibling who suffers from ASD), it has been found that frequently younger siblings showed non-specific motor delays which in about one quarter of them preceded the development of ASD. These motor problems can be seen at about the age of…

1. Six months
2. Twelve months
3. Eighteen months
4. Twenty four months
5. Thirty months

MCQ C.2.3 Which of these conditions are associated with ASD more often than expected?…

1. A Diabetes mellitus type 1 (formerly insulin dependent diabetes)
2. Nephrotic syndrome
3. Ewing sarcoma
4. Cystic fibrosis
5. Tuberous sclerosis

MCQ C.2.4 Risperidone has been studied as a potentially useful treatment for comorbid severe irritability and challenging behavior in children with ASD. According to the Research Units on Pediatric Psychopharmacology Autism Network Study, the size of the effect of risperidone compared with placebo in relation to irritability (measured with the Aberrant Behavior Checklist) after eight weeks of treatment was…

1. Nil
2. Marginal (<0.2)
3. Moderate (0.6)
4. Large (1.2)
5. Very large (1.8)

MCQ C.2.5 Many treatments have been proposed for ASD and families find a bewildering array of therapies in the Internet, most without any supporting evidence. Trustworthy guidelines, using evidence-based data and bearing in mind patients' safety, highlight that for the treatment of the core symptoms of ASD it is recommended to…

1. Implement facilitated communication
2. Administer behavioral interventions
3. Use chelation in order to remove potential toxic compounds
4. Provide psychodynamic psychotherapy
5. Administer secretine

ANSWERS TO MCQS

- **MCQ C.2.1** Answer: 3 (hyper- or hypo-reactivity to sensory stimuli are included in the diagnosis

  See page 5 as well as the video clips of Susan Swedo, Andrés Martin and Temple Grandin

- **MCQ C.2.2** Answer: 1 (six months)

  The Baby Sibs studies (systematic developmental surveys of babies born after an older sibling was diagnosed of ASD) show a prospective view of the unfolding of autism, which is different from what we had expected: no symptoms appear before six months, just non-specific motor delays. In the following 12 months many social and communication symptoms start to appear. Autism unfolds with development and the "peak" of symptom onset in the most disabled children is before 24 months. Nevertheless, some siblings do not show any difficulties at that age, but eventually show the ASD symptoms at 36 months of age. Please review pages 6 and 7 and the video clips from Drs Landa and Zwaigenbaum (embedded in the text in these pages).

- **MCQ C.2.3** Answer: 5 (tuberous sclerosis)

  24-60% of patients with tuberous sclerosis also have ASD. Thus, when any of these two conditions are diagnosed, clinicians should screen for the other one. Please see page 13. If you want to review the risk factors identified for ASD, please click on page 12 on the image of the 2011 NICE Guideline embedded there.

- **MCQ C.2.4** Answer: 3 (large (1.2))

  The effect size of risperidone on irritability was large: 1.2 (Aberrant Behavior Checklist irritability score). When general improvement observed by blinded researchers was considered, risperidone was quite effective, to the point that one needs to treat just two patients to observe a significant improvement in one (number needed to treat). It needs to be emphasized that no effect was seen in the social and communication aspects of ASD. If you want to know more, please review the lecture by Andres Martin embedded in page 28.

- **MCQ C.2.5** Answer: 2 (administer behavioral interventions)

  Please review Table C.2.3 (page 28). You may also wish to view the video clip by Patricia Howlin (page 27) for a review of these treatments. The video clip by Connie Kasari on page 26 offers full details about early treatment. If you want to know even more information about treatment, click the NICE link on page 22, and you be able to learn about the reasons for the rejection of many therapies that, sadly, are still advocated by some lay people (and even some professionals) in many countries.