1. Early identification and diagnosis

There are clearly recognised benefits to identifying and diagnosing autism spectrum disorder (ASD) as early as possible in a child’s life. The earlier it is established that a child has an ASD, the sooner tailored strategies and interventions can be put in place to optimise the child’s learning and development and minimise the impacts of ASD symptomatology in their future life course (Dissanayake, 2010). Early intervention may also assist in preventing the emergence of ‘secondary’ deficits such as preoccupations, compulsions and rituals (McEachin et al., 1993).

Historically, it has proven difficult for clinicians to establish a firm diagnosis of autism in children aged below 18 months. This is primarily because not all of the behavioural indicators currently used in diagnosis are apparent before the onset of language development; or they may be very subtly presented, with great variability between individual cases. Furthermore, many children will not be referred for diagnostic assessment at such a young age because their parents do not recognise the signs of atypical development (Ozonoff et al., 2010).

In view of these issues, there have been a number of recent research efforts directed at producing a screening tool that will effectively and consistently identify autism traits in very young children and infants. These instruments have met with varying levels of success when subject to reliability and validity testing. One of the recurring limitations of early-age diagnostic measures seems to be a low level of sensitivity (ability to accurately detect cases of autism vis-à-vis other disorders or no disorder) in non-clinical populations. However, a number of tools have yielded more rigorous evaluation outcomes and are summarised below.
The Early Screening of Autistic Traits Questionnaire (ESAT) (Dietz et al., 2006; Swinkels et al., 2006) contains 19 dichotomous response items and is administered by a clinician when a child is 14 months old. The ESAT retrospectively detected over 90 per cent of children with ASD in a general population sample and was able to discriminate well between typically developing infants and children with ASD. However, it also detected 19 per cent of children with ADHD. The remaining ‘false positives’ did not include any children who were typically developing, but included children who had language delay and developmental delay.

The First Year Inventory (FYI) (Reznick et al., 2007; Watson et al., 2007) is a parent-report instrument that aims to identify risk for a diagnosis of ASD at 12 months old. The 63 questions have a variety of response formats, including 46 items with a Likert scale, 14 items with multiple choice answers, and two open ended questions. The FYI was administered retrospectively to parents of pre-schoolers with ASD, pre-schoolers with generalised developmental delay, and a group of typically developing children. The children with ASD were rated by their parents as being at significantly higher risk than the children with developmental delay, who in turn were rated significantly higher at risk than the typically developing group.

The Autism Detection in Early Childhood (ADEC) tool, developed by Robyn Young and colleagues at Flinders University, clearly identifies and details autistic traits as manifested in preverbal children from 12 months of age. The ADEC has shown a high level of sensitivity and specificity, and has also been validated cross-culturally in a Spanish translation (Hedley et al., 2010). Research teams in China, Malaysia and Norway are continuing to investigate its use.

The ‘Q-CHAT’ (Quantitative Checklist for Autism in Toddlers) was developed by clinicians at the Autism Research Centre (ARC) at the University of Cambridge, UK. Q-CHAT replaces the conventional ‘Yes–No’ checklist format of diagnostic tools with ‘dimensional’ measures that have the sensitivity to capture earlier and more subtle manifestations of ASD.

An initial trial of Q-CHAT (Allison et al., 2008) found that it was able to reliably differentiate children aged 18 to 24 months with and without ASD. The measure also yielded normally distributed results, showed good test–retest reliability and adequate internal consistency. Subsequent research has indicated that Q-CHAT scores correlate with biological markers of autism in typically developing children, including foetal testosterone levels (Auyeung et al., 2010) and atypical electrophysiological response to social stimuli (Elsabbagh et al., 2010).

The ARC is currently undertaking a large-scale population study (n=4000) to further validate the Q-CHAT instrument. If successful, the tool may be used more widely in the future to identify autism and Asperger’s traits in toddlers and pre-schoolers.

See also: (2) DSM classification • (3) Autism and genetics • (4) Metabolic aetiology • (5) Neuroimaging and brain studies • (6) Prevalence rates and environmental factors
2. DSM classification

Significant revisions to the diagnostic criteria for ASD have been proposed for the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), due for publication in May 2013. Primarily, the existing classifications of Autistic Disorder, Asperger’s Disorder, and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) are to be collapsed into a single diagnostic category entitled ‘Autism Spectrum Disorders (ASD)’. A number of justifications have been advanced for making this change, namely:

- A single spectrum better reflects the overlapping pathology and symptoms of the three conditions.
- Separation of ASD from typical development is reliable and valid, while separation of disorders within the spectrum is variable and inconsistent.
- Individuals with autism, PDD-NOS or Asperger’s are often are diagnosed on the basis of severity, rather than by unique, separate criteria defining the three diagnoses.

In addition, to better reflect the symptomatology and clinical presentation of ASD, the diagnostic criteria relating to social communication and social interaction deficits, which are currently considered separately, will be reworked into a single domain. The fixated interests/repetitive behaviours axis will remain as a standalone category, but will include a new area of symptom manifestation, namely: “Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment”.

To improve the clarity and specificity of diagnostic decisions, each deficit area will be defined along a continuum of three severity levels. In addition, examples will be provided under each heading to describe symptom presentations at various ages, developmental stages and levels of cognitive functioning.

With regard to the diagnostic process itself, a significant change under DSM-5 is that a person meeting the criteria for ASD must display a total of five symptoms out of a possible seven, including all three of the specified social/communication deficits and at least two of the fixated interest/repetitive behaviour manifestations. The current DSM-IV requirements for ASD diagnosis are six symptoms out of a possible 12.

These revisions have prompted debate about the impacts they will have on the diagnosis of ASD in the future. In particular, concerns have been raised that some people who meet the current DSM-IV diagnostic criteria for ASD would not qualify for a diagnosis under the new system and hence be ineligible for autism-related services.

A recent study carried out by the Diagnostic Assessment Service team at Autism Spectrum Australia (Aspect) explored these issues by conducting ‘double diagnoses’ on 132 incoming clients (Gibbs et al., 2012). The team collected normal diagnostic data for each participant (background information, standardised ASD diagnostic assessments, naturalistic observations, and/or consultation with other professionals) and evaluated each dataset twice, using first the existing DSM-IV criteria and then the proposed new criteria for DSM-5.
This process revealed a sharp discrepancy between the proportions of clients classified with ASD in each case: 84 per cent met the criteria for ASD according to DSM-IV, in contrast to 64 per cent according to DSM-5. The majority of those who ‘missed out’ on an ASD diagnosis under DSM-5 had been identified as having PDD-NOS using DSM-IV criteria. In total, half of the initial PDD-NOS group failed to qualify for an ASD diagnosis according to DSM-5. The most common reason for this was that they did not display the stipulated two (out of four) manifestations of fixated interests/repetitive behaviours.

In addition to its revisions to the ASD classification system (among others), DSM-5 is introducing a new diagnostic category of Social Communication Disorder, defined by “persistent difficulties in pragmatics or the social uses of verbal and nonverbal communication in naturalistic contexts” and “persistent difficulties in the acquisition and use of spoken language, written language, and other modalities of language for narrative, expository and conversational discourse”. Because of the overlap with ASD symptomatology, DSM-5 guidelines specify that ASD must be ruled out before a diagnosis of Social Communication Disorder is given. In practice, this is likely to mean that many people currently meeting the diagnostic criteria for PDD-NOS, who do not display significant fixated interests/repetitive behaviours, will be classified as having Social Communication Disorder under DSM-5.

**See also:** (11) The female profile of autism
3. Autism and genetics

The results of twin and family studies indicate that there is almost certainly a genetic component to autism. Whilst no single ‘causal’ gene for the disorder has been identified – and may well not exist – there is growing evidence that particular genetic variations, passed through families, can increase the risk of a child being born with ASD.

The Autism Genome Project (AGP) is a large-scale, collaborative genetics research project designed to map the human genome in a search for the genes responsible for the inherited risk for autism. The AGP is the largest research consortium ever to focus on the genetics of autism and includes more than 170 of the world’s leading genetic researchers from over 50 academic and research institutions throughout the United States, Canada, the United Kingdom, France, Sweden, Denmark and Germany. The project includes approximately 2,300 multiplex families (two children with autism spectrum disorders and their parents) and over 1,000 control families from all over the world.

To date, the AGP has reported findings that show individuals with autism tend to carry more sub-microscopic insertions and deletions, called copy number variants (CNVs), in their genome than control participants (Anney et al., 2012). Some of these CNVs appeared to be inherited, while others are found only in affected offspring and not in their parents. Taken together, more CNVs are found on genes previously implicated in intellectual disability than would be expected by chance. Although each identifiable CNV may only explain a small fraction of cases of autism, collectively these variations are starting to account for a greater percentage of individuals in the autism community, as well as providing insights into possible common pathogenic mechanisms.

The AGP study has also succeeded in identifying a number of new autism susceptibility genes. Some of these genes determine synaptic connections in the brain, while others are involved in cell growth, division and movement, as well as communication between cells. In the future, these areas may form focal points for the development of new treatments.

A further area of investigation within the AGP has suggested that there may exist distinct genetic architecture across IQ-related subtypes of ASD (Vieland et al., 2011). It appears that the presentation of autism with lower IQ may reflect major gene effects (defined as a gene having a consistent effect on the phenotype, regardless of how this effect is modified by other genes), whilst autism in the absence of any intellectual impairment potentially involves more common alleles with lower penetrances.

See also: (5) Neuroimaging and brain studies • (7) Parental age
4. Metabolic aetiology

Medical evidence suggests that children with ASD may have severely abnormal metabolic profiles (James, 2005). Accordingly, research is intensifying into a possible metabolic basis for autism and related conditions. The ‘metabolic hypothesis’ offers flexibility to account for differences in levels of functioning in ASD and allows for the possibility that external as well as intrinsic causal factors may be involved (Shattock, 1998).

Recent research by scientists at Imperial College London and at the University of South Australia (Yap et al., 2010) has shown that it is possible to distinguish between children with and without autism by looking at the by-products of gut bacteria and the body’s metabolic processes in the children’s urine. Subsequent studies by Ming et al. (2012) and Williams et al. (2012), the latter of which examined direct intestinal biopsy samples, have demonstrated similar outcomes. If it can be ascertained that there is a distinctive metabolic fingerprint for autism, then this is anticipated to form the basis of a non-invasive urine test to help diagnose the condition earlier.

One specific hypothesis surrounding the metabolic aetiology of autism is that children with ASD have an enzyme deficiency that renders them unable to digest the proteins gluten and casein, leading to a build-up of peptides in the gut and bloodstream. These peptides are thought to have an opiate-like effect that may account for some ‘typical’ autistic traits such as high pain tolerance, repetitive behaviours and lack of concentration. Consequently, diets that eliminate gluten and casein are gaining popularity amongst parents of children with ASD and in online media.

Despite their widespread anecdotal endorsement, research evidence for the effectiveness of gluten- and casein-free diets remains limited and inconclusive (Millward et al., 2008). However, one clinical trial (‘ScanBrit’) currently underway in Scandinavia has so far yielded findings suggesting that specialised dietary interventions do improve developmental outcomes in at least some children with autism (Whiteley et al., 2010). This work is continuing with the aim of ascertaining what, if anything, predisposes ‘dietary responders’ to positive changes to their symptoms.

See also: (6) Prevalence rates and environmental factors
5. Neuroimaging and brain studies

Advanced brain imaging techniques, such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) have lately provided evidence of some important, albeit subtle, functional and/or micro-structural changes in the brains of children and adults with ASD. Specifically, when comparing subjects with and without autism, these studies have highlighted:

- differential activation in areas related to the three core domains of autistic dysfunction – social interaction, verbal and non-verbal communication and repetitive or stereotypic behaviours – in children with autism (Verhoeven et al., 2010);
- reduced connectivity between brain regions, especially those associated with language processing, in children with autism (Duffy & Als, 2012).

The second of these two studies is being regarded as a particular milestone in neuroimaging research because of its large sample size (430 children with autism and 554 controls) and the fact that it involved children as young as two years. The authors argue that their findings could form the basis for an objective diagnostic test of autism, particularly at younger ages. Their next goal is to repeat their study with children with Asperger's syndrome and investigate if their EEG patterns are similar to or different from those associated with autism.

These findings have been reinforced by the first ‘diffusion tensor imaging’ studies. This recent development in MRI technology allows a more direct view on white matter structure and organisation. For subjects on the autism spectrum, these studies have demonstrated white matter alterations in important communication pathways, especially those allowing long distance communication and integration of the two brain hemispheres (Anderson et al., 2011); mechanisms that are essential for the efficient completion of higher cognitive functions such as executive control, theory of mind tasks and social cognition.

Early neurological studies of autism tended to focus on isolated indicators only, but recent research has highlighted that the presence of the condition is reflected in multiple aspects of the cerebral anatomy, including cortical thickness, cortical surface area, degree of convexity or concavity, mean curvature, and degree of cortical folding (Ecker et al., 2010).

A further study (Spencer et al., 2011) has pointed to the first neuroimaging biomarkers of familial risk for autism. The research identified differences in the neural response to facial expression of emotion between unaffected siblings of individuals with autism, and healthy controls with no family history of ASD. Specifically, the fMRI response to happy versus neutral faces was significantly reduced in unaffected siblings compared with controls within a number of brain areas implicated in empathy and face processing. Moreover, the response in unaffected siblings did not differ significantly from the response in autism. Further investigation suggested that, within the context of this study, an atypical response specifically to happy faces, rather than to faces in general, accounted for the observed sibling versus controls difference and is a clear biomarker of familial risk. Overall, the findings suggest that an atypical implicit response to facial
expression of emotion may form the basis of impaired emotional reactivity in autism and in the broader autism phenotype in relatives.

In a similar vein, the British Autism Study of Infant Siblings (BASIS) is using newly developed techniques to investigate whether there are any differences in brain and behavioural development between infants who have brothers or sisters with autism and those who do not. In the long term, this will help identify the early signs of the disorder, allowing for earlier and more effective intervention.

A recently published longitudinal study by the BASIS team (Elsabbagh et al., 2012) investigated neural responses to social stimuli in 104 infants aged six to ten months, examining whether differences in brain activity on this task could predict a later diagnosis of autism. The infants watched an image of an adult face that switched from looking away from them to directly at them and away again. On average, infants who went on to receive an autism diagnosis at age three showed significantly less neural activity in response to these simulated eye-gaze shifts than those who were not subsequently diagnosed with autism. This finding is consistent with existing evidence that atypical eye contact is a characteristic feature of ASD, and points to a possible early diagnostic marker of autism that is worthy of further exploration.

A less well developed method used to study the neurology of autism is post-mortem brain tissue analysis. Progress in this area of research is generally slow and limited because of the reliance on brain donation by deceased individuals and their families. The Autism Tissue Program (ATP), a clinical branch of the US organisation Autism Speaks, is the most well established body dedicated to acquiring, processing and distributing donated brain tissue for the purposes of autism research. The ATP works directly with the Harvard Brain Tissue Resource Center (HBTRC) in Boston, Massachusetts, to serve as its tissue repository.

In 2011, ATP scientists conducted a small, preliminary post-mortem study comparing anatomical features of the brains of seven boys with autism and six without (Courchesne et al., 2011). The researchers found that the children with autism had around two-thirds more neurones in the prefrontal cortex – the region of the brain implicated in executive functioning, emotion, personality expression, decision making and socially appropriate behaviour – than the typically developing children. In addition, the brains of the children with autism weighed more than those of the control group children and in relation to age-adjusted norms.

With such a small number of brains examined in the study, few definitive conclusions have been drawn from the findings. One thing that is known is that no new neurones are generated after birth. This implies that the increased number of neurones in the brains of children with autism was due either to above average production in utero, or below average death of these cells after birth. However, it remains unclear at this stage whether brain overgrowth is typical of children with autism or a chance finding of the research. Further studies will be needed in order to see whether the same patterns are found in larger samples, and to start exploring in more depth why the phenomenon might occur.
In May 2012, a major freezer unit failure occurred at the HBTRC, with the result that over 50 brain tissue samples set aside for the ATP were damaged. The full impact of this event on the future of ATP’s research has not yet been determined.

**See also:** (11) The female profile of autism
6. Prevalence rates and environmental factors

Several research reviews have noted a substantial increase in diagnosis rates for autism spectrum disorders since the earliest prevalence studies were conducted in the 1960s. This finding is often attributed to a heightened awareness of ASD amongst parents and professionals; the gradual broadening of the diagnostic criteria; the now more frequent identification of children with mental retardation as also having autism; and a growth in early-age diagnosis (Weintraub, 2011).

Latterly, however, there has been a resurgence of interest in the possibility that there may exist environmental risk factors for ASD that should be taken into account when considering changes in diagnosis rates (Rutter, 2005). The likely nature of these factors depends in part on whether the increase in recognised cases of autism reflects a genuine rise in prevalence (suggesting that new environmental risks have emerged over the last half-century), or is an artefact of diagnostic and social factors (which would imply that the risks have ‘always’ been present).

Within the USA in particular, new research efforts are being made to delineate the genetic, environmental and social contributors to the surge in autism diagnoses over recent decades, and to hypothesise more reliably as to what form any environmental risk factors might take.

Over the last few years, sociologists at Columbia University in New York have examined nearly five million Californian birth records, alongside 20,000 records from the state’s Department of Developmental Services, to produce a rich picture of the demographics and life history of individuals with autism; in turn providing clues to the social factors that influence diagnosis (King et al., 2009; King & Bearman, 2009, 2011). The researchers claim to be able to attribute 25 per cent of the increase in autism identification to ‘diagnostic accretion’ (that is, the greater likelihood of children with mental retardation now being concurrently diagnosed with autism); 15 per cent to improved awareness of the condition; four per cent to ‘geographic clustering’ (concentrations of diagnoses within particular areas that reflect localised community awareness and availability of diagnostic and support services); and ten per cent to a rise in the average age of childbearing, considered by some to be a risk factor for autism.

Two other federally funded research trials currently underway in the USA are the Study to Explore Early Development (SEED), an initiative of the Centers for Disease Control and Prevention (CDC), and the Early Autism Risk Longitudinal Investigation (EARLI) study. Both are seeking to examine the interplay between genetic susceptibility and environmental factors that might contribute to a child being diagnosed with autism, and will involve the collection of a range of biological and developmental data from participating families over a number of years.

See also: (7) Parental age • (8) Low birth weight and autism • (9) The Autism Phenome Project
7. Parental age

Separate to theories surrounding an identifiable ‘genome’ for autism, research suggests that some cases of ASD may arise from isolated, spontaneous changes to DNA sequences that occur at the cell formation stage. At least 50 per cent of active genes play a role in neural development, meaning that randomised genetic anomalies are more likely to affect the brain than other organs. Sebat et al. (2007) propose that these rare ‘de novo’ mutations account for around one in ten of all people diagnosed with ASD; most notably in cases where there is no family history of the disorder.

It is well known that older mothers are at greater risk of giving birth to babies with genetic abnormalities, such as the extra chromosome that causes Down Syndrome. In line with this, some commentators have suggested that there may be a link between the rise in autism diagnosis rates in recent decades and the growing trend for women to delay having children until their late 30s and early 40s.

The relationship of maternal age to autism was explored in a Swedish study by Santin et al. (2012). Reviewing 16 epidemiological reports that together represented 25,687 cases of ASD and over 8.6 million control subjects, the researchers compared the risk of autism for children born of mothers aged under 20, 24-29, 30-34, and 35-plus. They found that children whose mothers were aged 35 and over at the time of their birth had a 30 per cent increased risk of autism, while children of mothers aged under 20 had the lowest risk. The association between maternal age and autism was stronger for male offspring and children diagnosed in more recent years. The authors point to several potential explanations for this link that fit with the ‘genetic mutation’ hypothesis, including increased occurrence of gene alteration during the ageing process and the effects of exposure to environmental toxins over time.

However, within a few months of the publication of this research, another study was reported that, for the first time, implicated the increasing average age of fathers in the numbers of children being born with complex developmental and psychiatric disorders, including autism (Kong et al., 2012). The investigation, led by the Icelandic company Decode Genetics, analysed the genetic material of 78 trios of a father, mother and child, searching for mutations in the child’s DNA that were not present in either parent and that therefore must have arisen spontaneously in the sperm, egg or embryo.

When these genetic anomalies were traced, it was found that fathers passed on nearly four times as many new mutations as mothers. Furthermore, paternal age accounted for almost all the variation in the number of new mutations in a child’s genome, and the number of new mutations being passed on rose exponentially with the age of the father. The average child born to a 20-year-old father had 25 random mutations that could be traced to paternal genetic material. The number increased steadily by two mutations a year, reaching 65 mutations for children of 40-year-old men.
These findings add weight to those of three recent studies (Sanders et al., 2012; O’Roak et al., 2012; Neale et al., 2012) that together identified dozens of new genetic mutations implicated in autism and found that these mutations were four times more likely to originate on the father’s side than the mother’s.

In discussing their study findings, Kong et al. (2012) stress that the overall risk of an older man fathering a child with a developmental or psychiatric disorder caused by a genetic mutation remains very low, at below one per cent for a man in his 40s.
8. Low birth weight and autism

Research has historically linked low birth weight to a range of motor and cognitive problems, including cerebral palsy, behavioural disorders, poor school performance and psychiatric conditions. Last year, for the first time, findings from a longitudinal study conducted at the University of Pennsylvania specifically suggested that babies born weighing less than 4.5lb (1.8kg) may have a greater chance of developing autism than children born at normal weight (Pinto-Martin et al., 2011).

The research followed 623 New Jersey children of low birth weight from 0 to 16 years of age, at which point they were screened for risk of an autism spectrum disorder. Of the 117 screen-positive participants, 70 were assessed again at the age of 21 using clinical diagnostic criteria, with eleven being classified as having an ASD. From these results, the researchers calculated an estimated prevalence rate for ASD of five per cent for the original sample – notably higher than the 1-2 per cent prevalence found within the general population. Within a subgroup of participants who were born weighing less than 3lb 5oz, the prevalence of ASD rose to 11 per cent.

In another population-based case-control study conducted in Finland (Lampi et al., 2012), researchers examined the birth records of 4,713 children, adolescents and young adults with an ASD, together with four times the number of control cases, to determine whether birth weight, gestational age, and SGA (small for gestational age) predicted ASD. The findings showed that very low and moderately low birth weight, very low gestational age (less than 32 weeks), and SGA were associated with an increased risk of childhood autism and PDD-NOS, but not Asperger’s Disorder. Risk levels remained the same after controlling for potential confounding variables, namely maternal age, parity, smoking during pregnancy and psychiatric history, as well as any major congenital anomalies in the infant.

These studies have contributed to debate as to whether factors directly related to preterm and underweight births – such as brain haemorrhaging and bruising – might, in some cases, contribute to the development of autism. An alternative possibility is that the medical interventions used to keep these babies alive have a role to play in triggering the disorder. The next stage of the University of Pennsylvania research will involve examining brain scans of the low birth weight participants in the study to determine the rate of brain injury in the entire cohort.

In another ongoing investigation, Lisa Croen, an epidemiologist at the Kaiser Permanente institute in California, is analysing the records of 180,000 babies born in the Kaiser health system over eight years. Croen will study the medical problems and interventions experienced by the smallest babies in neonatal intensive care units, as well as the health of their mothers (including use of antibiotics) during pregnancy.
9. The Autism Phenome Project

One of the major obstacles to understanding the causes of and finding effective interventions for autism is that it has extremely diverse outcomes. The heterogeneity of the condition raises the possibility that there are several types of autism with a variety of causes.

The Autism Phenome Project (APP), based at the UC Davis MIND Institute in California, is the largest and most comprehensive assessment of children with autism ever attempted. The project, which has been in the design phase for two years, will ultimately include 1,800 children at multiple sites across the country and, potentially, internationally.

Data gathered from children with autism will be compared to that from children with typical development. The APP is a longitudinal study, with families returning for follow-up evaluations for several years. During the first year of the project, each participating child is involved in the following research areas:

- medical evaluations
- environmental toxin exposures/epidemiology
- behaviour and neuropsychology assessments
- genetic profiling
- brain development, structure and function
- immune system function.

The ultimate goal of the APP is to distinguish recognised subgroups or phenotypes of autism, based on biomedical and behavioural characteristics. This in turn could lead to greater clarity in the diagnostic process and more individualised and appropriate intervention strategies for children (and adults) with ASD.

So far, APP researchers have studied the brain growth, environmental exposure and genetic make-up of 350 children aged between two and three and a half years, and believe they have identified two biologically distinct subtypes of autistic brain development. One group of children – all boys – had enlarged brains and most had regressed into autism after 18 months of age; another group appeared to have immune systems that were not functioning properly.

Other key findings from this stage of the research include:

- Total cerebral volume is highly variable in ASD, but appears to be on average higher in boys with autism than in control subjects.
- There are various types of onset in autism: early onset, plateau, and regression.
- Subjects who exhibit regressive loss of skills have enlarged brains, with head circumferences beginning to diverge at about four to six months (a potential early warning sign before regression itself is evident).
10. Oxytocin therapy

The neuropeptide oxytocin has been identified as playing a crucial role in the development of social memory and attachment, maternal behaviour and human bonding (Lee et al., 2009). There are suggestions that abnormalities in the neural pathways for oxytocin may account for the social deficits characteristic of autism spectrum disorders (Modahl et al., 1998; Insel et al., 1999). Oxytocin has also been implicated in other key features of ASD such as early onset, repetitive behaviours, cognitive impairment, alterations in neural development, and male predominance of the condition.

Research in this area is currently limited, but a small number of clinical trials have been conducted for the therapeutic use of oxytocin in the management of ASD.

Hollander et al. (2003) demonstrated a significant reduction in six repetitive behaviour types in adults with autism or Asperger’s Syndrome following an intravenous oxytocin infusion treatment, relative to a placebo.

Guastella et al. (2010) found that in comparison to a non-intervention condition, administration of an oxytocin nasal spray led to improved scores on the Reading the Mind in the Eyes Task (RMET), a widely used and reliable test of emotion recognition, for teenage males with an ASD diagnosis.

Andari et al. (2010) assessed cooperation skills and attentiveness to social signals in individuals with high-functioning autism or Asperger’s Syndrome. Performance in both domains was enhanced following inhalation of oxytocin.

Gordon et al. (2012), from the Yale School of Medicine, are performing a double blind, crossover, randomised controlled study, in which 40 children and adolescents (aged eight to 17) with ASD are randomly assigned to oxytocin and placebo nasal sprays on two consecutive visits. Participants are then assessed for their ability to detect biological motion and read others’ emotions using the RMET. Functional magnetic resonance imaging (fMRI) was employed to observe the effects at a neural level. This is believed to be the first ever intranasal oxytocin study using fMRI with such a young age group.

Preliminary data from this study have indicated that intranasal administration of oxytocin results in enhanced activation of the superior temporal sulcus (STS) region during perception of biological motion compared to placebo. Oxytocin also appears to improve participants’ ability to accurately define and describe other’s mental states, as well as enhance brain activation in the brain regions previously implicated in social perception and cognition, mentalising, and theory of mind abilities.

Together, the results of these studies suggest that the administration of oxytocin may allow individuals with ASD to adjust to their social context by identifying the differing behaviours displayed by those around them and reacting accordingly. Oxytocin may also play a role in reducing the fear of others and promoting closer social relations.
Andari and colleagues will be continuing their work to study the long-term effects of oxytocin on improving the everyday living challenges of people with autism, as well as its efficacy at an early stage of the condition. Meanwhile, the Yale researchers have highlighted the need for a more in-depth exploration of the mechanisms underlying oxytocin's effects using fMRI techniques.
11. The female profile of autism

One of the most striking features of autism is the fact that it is diagnosed much more frequently in boys than girls. Estimations based on epidemiological data put the male–female diagnostic ratio at around 4:1 (Whiteley et al., 2010), though with proportionally more males at the higher functioning end of the spectrum, and more females in the moderate-to-severe intellectual disability range (Fombonne, 2009).

A number of researchers have explored possible biological bases for the male preponderance in ASD, including foetal testosterone and X chromosome theories (Baron-Cohen et al., 2011). Recently, however, attention has turned to the possibility that one of the reasons ASD is diagnosed less often in girls than boys is because the female presentation of the condition is less well researched, differentially and more subtly expressed, and therefore more likely to be overlooked.

One way to examine this issue is to study groups of children with ‘autistic-like traits’ who are presented for diagnostic assessment, and ascertain what, if anything, systematically differentiates those children who are subsequently given an ASD diagnosis from those who are not. Specifically, the question may be asked: what are the factors unique to girls with autistic-like traits that affect diagnostic decisions made about them?

One such study attempting to address this question was conducted by Dworzynski et al. (2012), who analysed data from a large population-based sample of children in the UK. Girls and boys aged 10 to 12 years who met diagnostic criteria for ASD were compared with those who failed to meet diagnostic criteria despite scoring highly on the Childhood Autism Spectrum Test (CAST), a validated screening instrument for autism traits. Teacher reports of behavioural difficulties and early estimates of intellectual functioning formed the key comparison variables.

The results of the study showed that girls, but not boys, meeting the clinical criteria for ASD demonstrated lower intellectual ability and more challenging behaviours than peers with similarly high CAST scores who were not given an ASD diagnosis. This suggests that, in the absence of additional intellectual or behavioural problems, girls with autistic-like traits are more likely than boys to be ‘passed over’ in the diagnostic process.

Dworzynski et al. (2012) suggest two possible lines of reasoning for this finding:

1. That current diagnostic criteria, concepts or practices are biased towards the ‘conventional’ male presentation of ASD.
2. That girls are better able to adapt to, or compensate for, aspects of ASD symptomatology than are boys.

The latter of these two hypotheses formed the subject of a paper by Gould & Ashton-Smith (2011), who reviewed the literature to identify some of the ways in which girls and women may seek to overcome limitations in social understanding, social
communication and social imagination so as to (intentionally or otherwise) ‘mask’ an underlying ASD. Some examples cited in the review include:

- Girls are more able to follow social actions through observation and delayed imitation. They may be quicker to apologise and appease when they make a social error, increasing the likelihood of their anomalous behaviour being overlooked or forgotten by others (Attwood, 2007).
- Girls are often more socially aware and socially driven, and so more likely to seek out play and interaction opportunities (whilst often being ‘led’ by peers rather than initiating activities themselves). They may have one special friend with whom they share an intense, sometimes dependent, relationship.
- As they grow in self-awareness and recognition of their ‘differences’, girls may take greater pains to avoid drawing attention to themselves, for example by being quiet, well behaved and compliant at school (Attwood, 2011).
- The intense special interests of girls with ASD (such as animals, celebrities and fiction franchises) may more closely align with the ‘mainstream’ than the corresponding interests of boys with ASD.

Echoing Dworzynski et al. (2012), Gould & Ashton-Smith (2011) note that the diagnostic criterion of restricted and repetitive behaviours, which often includes the manifestation of intense special interests, “is a crucial area in which the male stereotype of autism has clouded the issue in diagnosing girls and women”. They go on to argue that diagnosticians must “ask the right questions”, examine developmental histories, and conduct observations in a variety of settings when assessing girls and women who present with autistic-like traits. This way, they may better ascertain when an individual “has adopted a social role which is based on intellect rather than social intuition”.

The authors further observe that the effort involved in perpetual social mimicry and repression of integral ‘autistic’ behaviour can be mentally and emotionally exhausting and lead to a high incidence of mental health problems for girls and women with ASD.

The National Autistic Society in the UK is currently leading a two-year international research program, ‘Autism in Pink’, to investigate issues surrounding misdiagnosis, stress, social exclusion and vulnerability of women with ASD.

Meanwhile, the first comparative neuroimaging study of men and women with ASD is entering its final analysis stages at Kings College London’s Institute of Psychiatry, partnering with the Autism Research Centre at the University of Cambridge. Results are expected early in 2013.
12. Bullying

A number of recent research studies have put a spotlight on the issue of bullying of children and adolescents with ASD, questioning whether this population is at greater risk of being victimised by their peers than typically developing young people.

A survey by the US-based Interactive Autism Network (IAN) explored in some depth the bullying experiences of over 1,000 children aged six to 15 with ASD, as part of which comparisons were drawn with the experiences of their typically developing siblings. Thirty-nine per cent of children with ASD were reported by their parents to have been bullied within the preceding month, in contrast to 12 per cent of unaffected siblings. Overall, 63 per cent of children with ASD had been bullied at some time in their lives. Common modes of bullying included teasing and mockery, name-calling, being ignored or excluded from social activities, and – to a lesser degree – physical intimidation or violence. Instances were also recorded of bully victims seemingly being deliberately provoked to aggression or a meltdown by their attackers.

A similar study by Sterzing et al. (2012), based on interviews with 1,100 parents of students with ASD and a survey of school staff, reported that these young people were four times more likely to be bullied than those without an ASD, but no more likely to be bullies. A caveat to be applied to this research and its findings is that ‘bullying’ was not defined to respondents and is open to subjective interpretation. In addition, no measures of frequency or duration of bullying behaviour were obtained.

The IAN survey identified the risk of bullying to be higher for children with Asperger’s Disorder than for those with Autistic Disorder, suggesting that bullies may be less inclined to victimise peers who show obvious signs of a disability, and instead target those who merely present as a little ‘different’ or ‘odd’.

The first large-scale survey of adults with Asperger’s Disorder and high functioning autism conducted in Australia, entitled ‘We Belong’ and led by Autism Spectrum Australia (Aspect), gathered retrospective data on bullying experiences in education settings and looked for associations with outcomes in adult life. Nearly three-quarters of the 313 study participants reported negative social experiences at school, college or university, with many making direct reference to bullying. The incidence of these reports was consistent between genders and across age groups.

Further analysis showed that respondents who had experienced bullying in education settings were more likely than their fellow respondents to express ongoing support needs in areas relating to interpersonal and social interaction, including improving their social skills, accessing community leisure activities, and dating. They were also more likely to say that they were currently dissatisfied with their social life.
References


Dissanayake C (2010), ‘Working in partnership to promote the early identification of infants and toddlers with an autism spectrum disorder’, paper presented at the Early Childhood Education Conference


Links

- Autism Phenome Project
  http://www.ucdmc.ucdavis.edu/mindinstitute/research/app

- Autism Research Centre (University of Cambridge, UK)
  http://www.autismresearchcentre.com

- Autism Tissue Program (ATP)
  http://www.autismtissueprogram.org

- British Autism Study of Infant Siblings (BASIS)
  http://www.basisnetwork.org

- Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)
  http://www.dsm5.org

- Early Autism Risk Longitudinal Investigation (EARLI) study
  http://www.earlistudy.org

- Interactive Autism Network (IAN)
  http://www.iancommunity.org

- King’s College London Institute of Psychiatry
  www.kcl.ac.uk/iop

- ScanBrit trial
  http://www.espa-research.org.uk/scanbrit.html

- Study to Explore Early Development (SEED)
  http://www.cdc.gov/ncbddd/autism/seed.html

- ‘We Belong’ study (Autism Spectrum Australia)