Pathophysiology of autism: evidence from brain imaging

Autism spectrum disorders involve pervasive developmental abnormalities in social communication, socio-emotional reciprocity, and restricted and repetitive interests. They are likely to be caused by abnormalities in multiple brain regions, including 'underconnectivity' between components of networks subserving a variety of cognitive functions.

Autism spectrum disorder (comprising the subtypes of 'typical' autism, high functioning autism and Asperger's syndrome) is characterized by a triad of pervasive developmental abnormalities in social communication, socio-emotional reciprocity, and restricted and repetitive interests, according to the *International Classification of Diseases* revision 10 diagnostic criteria (ICD-10; World Health Organization, 1993) and *Diagnostic and Statistical Manual of Mental Disorders* (4th edn) (DSM-IV; American Psychiatric Association, 1994).

Individuals with autism also have delayed language development, and many have a learning disability. Individuals with Asperger's syndrome have no history of language delay and have normal or superior intellectual abilities, but also show the characteristic impairments of social communication, reciprocal social interaction, and restricted and repetitive interests. Around 50% of individuals with an autism spectrum disorder are in the normal IQ range (Baird et al, 2006). Autism spectrum disorders are four times more common in males, and this excess increases with IQ (Baird et al, 2006). The disparity between general intellectual ability and social understanding is particularly marked in high functioning individuals with autism or Asperger's syndrome. However, the biological bases of abnormal social behaviour in autism are poorly understood.

Childhood autism was once considered rare, but studies have reported prevalence rates of 20–40 per 10 000 for autism (Fombonne, 2003) and 1% for the broader phenotype (Baird et al, 2006). The causes of autism spectrum disorders are unknown, but most likely involve a complex interaction between genetic and environmental factors. It was believed as recently as the 1960s that cold 'refrigerator' type parenting was responsible for the behavioural characteristics associated with this syndrome (Kanner, 1949). An early indication that it was a neurobiological disorder was the high rate of epilepsy found to affect approximately one third of autistic children. Twin studies have since shown autism to be among the most heritable of neuropsychiatric disorders, with estimates of 60–90% (Bailey et al, 1995).

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Genetic contributions to autistic traits

An important aetiological question concerns whether the triad of impairments comprising autism are highly correlated (implying shared causation), or are independently heritable (implying distinct causes). Attempting to investigate this in people with autism spectrum disorder begs the question of how the core impairments are related, because all three impairments must be present to receive the diagnosis. Hence, a population-based study of 3000 twin pairs assessed between the ages of 7 and 9 years was undertaken, which reported modest to low correlations between autistic-like behavioural traits in the three core areas of social impairment, communication difficulties and rigid and repetitive behaviours (Happe et al, 2006; Ronald et al, 2006). While each aspect of the triad is highly heritable, model-fitting analyses of cross-twin, cross-trait correlations indicate that more than half the genes that contribute to variation in one domain (e.g. social (dis)ability) are independent from those that contribute to variation in the other two domains (e.g. rigid and repetitive tendencies and communicative skills). Thus, separate genes contribute to social impairment, communicative difficulties and rigid and repetitive behaviour.

This evidence of behavioural fractionation of social impairment, communication difficulties and rigid and repetitive behaviours means that autism spectrum disorders are likely to be caused by abnormalities in multiple brain regions and networks, not single structures. A network perspective is central to current neuroimaging research into autism spectrum disorders, which focuses on abnormalities in structure and/or function of specific brain regions as parts of networks. For example, functional magnetic resonance imaging (fMRI) and positron emission tomography have been used to investigate differences between people with autism spectrum disorder and controls in the activity of distributed brain systems supporting a range of cognitive functions.

Brain activity in autism spectrum disorders

Face and emotion processing has been a major focus of research. Hypoactivation of the so-called 'face area' in the right fusiform gyrus has repeatedly been reported in adults and young people with autism spectrum disorder when viewing faces (Schultz, 2005). A study of neural responses to four primary emotional expressions (fearful, happy, sad, disgusted) at high and low intensities indicated that adult males with Asperger's syndrome showed fusiform-extrastriate cortical activation to all expression types, but generally to a lesser degree than healthy controls (Deeley et al, 2007). Relative hypoactivation of the fusiform gyrus in people with autism spectrum disorder may partly explain difficulties in recognizing and responding to the socio-emotional signals of others (Schultz, 2005).

The ability to attribute mental states to others (theory of mind) is involved in many aspects of normal social interaction and is impaired in autistic individuals. fMRI studies suggest that mentalizing engages a network comprising: medial prefrontal cortex (supporting the representation of triadic relations, e.g. I, you, it); the right temporo-parietal junction (associated with the attribution to others of contentful mental states such as beliefs); posterior superior temporal sulcus (detection of goal-directed actions); and temporal poles (semantic knowledge) (Frith and Frith, 2006; Saxe, 2006). Hypoactivation of components of this network has been reported in a succession of studies using a variety of mentalizing tasks in people with autism spectrum disorder relative to controls (Happe et al, 1996; Baron-Cohen et al, 1999; Castelli et al, 2002).

The 'mirror neuron system' describes brain regions (such as inferior frontal gyrus and intraparietal sulcus) that are active during both the execution, and observation of actions (Iacoboni and Dapretto, 2006). It has been hypothesized that understanding the mental state of others is facilitated by rapid simulation of their actions or expressions via the mirror neuron system (Gallese and Goldman, 1998). For example, an fMRI study showed that activity in mirror neuron system (posterior inferior frontal gyrus, ventral premotor cortex, and rostral inferior parietal lobule) during observation and imitation of facial expressions in typically developing 10-year-old children correlated with empathy and interpersonal competence (Pfeifer et al, 2008).

Another fMRI study showed that compared to typically developing children, children with autism show reduced activity in frontal mirror neuron system (pars opercularis of inferior frontal gyrus), and this activity is inversely correlated with autism diagnostic observation schedule (ADOS) and autism diagnostic inventory revised (ADI-R) scores (Dapretto et al, 2006). An fMRI study in adolescent males with Asperger's syndrome showed reduced mirror neuron system activity during imitation of finger movements relative to controls (Williams et al, 2006). Hence, there is evidence that mirror neuron system activity is related to social competence, and that it is hypoactive in people with autism spectrum disorder.

Autism as a disorder of connectivity

In addition to evidence of hypoactivation of discrete components of networks supporting social cognition, there is also increasing evidence that autism spectrum disorders are characterized by 'underconnectivity' between components of networks. fMRI and positron emission tomography studies have been used to measure functional connectivity – the correlations between spatially remote brain activity during task or stimulus processing – to demonstrate underconnectivity across a range of neurocognitive networks in autism spectrum disorders.

For example, people with autism spectrum disorder showed reduced functional connectivity between frontal and parietal areas when undertaking a test of executive function (the Tower of London task), in association with a smaller cross-sectional area of regions of corpus callosum. There was also a correlation between the size of the genu of the corpus callosum with frontal-parietal functional connectivity in autism spectrum disorder, but not controls (Just et al, 2007).

Another study of executive function (inhibitory control) showed decreased activation and underconnectivity in inhibition networks (anterior cingulate gyrus, middle cingulate gyrus, and insula) and the right middle and inferior frontal and right inferior parietal regions (Kana et al, 2007). During a language task (sentence comprehension), people with autism spectrum disorder showed more activation than controls in Wernicke's (left laterosuperior temporal) area, and less activation in Broca's (left inferior frontal gyrus) area, plus reduced functional connectivity between the regions (Just et al, 2004).

In a test of social cognition (viewing animations that elicit mentalizing), people with autism spectrum disorder showed reduced functional connectivity of the superior temporal sulcus and visual cortex relative to controls (Castelli et al, 2002). Further, underconnectivity appears to be present not only during goal-directed cognitive activity, but also at rest. For example, one study reported reduced functional connectivity in anterior-posterior connections of the resting state (default) network in people with autism spectrum disorder relative to controls (Cherkassky et al, 2006).

Further evidence of underconnectivity has been provided by other measures of brain activity. For example, a magnetoencephalography study demonstrated that the temporal progression of activation in the mirror neuron system is delayed in adults with Asperger's syndrome, suggesting a deficit of connectivity between the inferior frontal gyrus and other mirror neuron system (Nishitani et al, 2004). Hence, there is increasing evidence from fMRI, positron emission tomography and other meas-

ures of brain activity that people with autism spectrum disorder show underconnectivity in distributed brain networks supporting a wide range of cognitive functions (executive, language, and social), as well as at rest.

Brain anatomy and connectivity

In addition to fMRI evidence of underconnectivity, structural MRI has provided evidence of widespread differences in the anatomy and developmental trajectory of components of distributed brain systems in people with autism spectrum disorder relative to controls. The most consistent finding to date is the replication of Kanner's original observation of increased brain volume (megalencephaly) in autism and there is some evidence that this may be age dependent (Courchesne, 2002, 2004). Further, autism spectrum disorder is a developmental disorder, possibly characterized by grey and white matter overgrowth in very young children and reduced volumes in later childhood (Courchesne, 2002, 2004). It is also clear that in adulthood brain aging is significantly different in people with autism spectrum disorder as compared to controls (McAlonan et al, 2002). These developmental differences in brain anatomy may reflect abnormalities of brain growth associated with abnormal neuronal loss and synaptic pruning (Muller, 2007), providing a potential basis for the reduced functional connectivity in distributed brain systems reported in fMRI studies.

In addition to differences in volume of whole brain, however, some specific brain regions and networks are particularly implicated. For example, there is evidence of involvement of frontotemporal, frontolimbic, frontoparietal and interhemispheric connections (Courchesne and Pierce, 2005; Minshew and Williams, 2007), accompanied by widespread abnormalities in white matter development (Herbert et al, 2004). It has also been hypothesized that people with autism spectrum disorder have local overconnectivity but reduced long range (global) connectivity (Courchesne and Pierce, 2005).

Further, it has been proposed that autism spectrum disorder may be 'exponentially distributed', meaning that early brain abnormalities in autism spectrum disorder increasingly affect additional regions and functional systems throughout development, partly as a consequence of the cumulative impact of abnormal experiences as a result of the core deficits (Muller, 2007). If correct, this suggests that differences in brain anatomy and function would become more severe as the brain matures into adulthood, underlining the importance of studying brain anatomy and function across the lifespan of people with autism spectrum disorder, as well as the normal population (Deeley et al, 2008).

Diffusion tensor magnetic resonance imaging

Grey matter regions that comprise the 'nodes' of neurocognitive networks are connected by white matter tracts (Catani et al, 2002). Hence, abnormalities of the microstructural organization or integrity of white matter tracts may reduce the efficiency and speed of communication between nodes, so contributing to the pathophysiology of underconnectivity in autism spectrum disorders.

Diffusion tensor magnetic resonance imaging (DT-MRI) can be used to examine the orientation and integrity of white matter tracts. This is achieved by measuring the amount and direction of water diffusion, which can be isotropic (the same amount in every direction) or anisotropic. Diffusion of water molecules in white matter tends to be greater along the direction of white matter tracts and thus predominantly anisotropic, with the degree of anisotropy in particular tissues often being quantified through its fractional anisotropy value (Basser et al, 1994). The degree of anisotropy depends on a number of factors, such as myelination, fibre diameter and density. A lower fractional anisotropy may be indicative of altered microstructural integrity or organization of the fibres (Basser, 1995).

Three-dimensional trajectories of specific white matter tracts in vivo can be explored with DT-MRI tractography. For example, one study reported that adults with Asperger's syndrome have significantly lower fractional anisotropy in the short intracerebellar fibres and right superior cerebellar (output) peduncle compared to controls, but no difference in the input tracts (Catani et al, 2008). These findings suggest a vulnerability of specific cerebellar neural pathways in people with Asperger's syndrome. Also the localized abnormalities in the main cerebellar outflow pathway may reduce cerebellar feedback inputs to the cerebral cortex, which are necessary for adaptive social behaviour. However, whole brain multivoxel techniques are required to investigate large-scale anatomical connectivity of brain systems implicated in autism spectrum disorder.

A previous whole brain DT-MRI study included seven children with autism and nine controls (Barnea-Goraly et al, 2004). They reported that the children with autism had a significant reduction in fractional anisotropy of white matter adjacent to the ventromedial prefrontal cortices, anterior cingulate gyri, temporoparietal junctions, and in the corpus callosum. Subsequently, others investigated mixed samples of children and adults with autism. They reported that people with autism have a significant reduction in fractional anisotropy of areas within (or near) the corpus callosum (Alexander et al, 2007; Keller et al, 2007), right external capsule (Keller et al, 2007) and the superior temporal gyrus and temporal stem (Lee et al, 2007). Hence, there is evidence of widespread reduction in the microstructural integrity of white matter tracts in autism spectrum disorder.

Future studies will relate measures of fractional anisotropy to functional connectivity to determine to what extent underconnectivity across neurocognitive net-

works in people with autism spectrum disorder is explained by reduced microstructural integrity of white matter tracts.

Proton magnetic resonance spectroscopy

Proton magnetic resonance spectroscopy can be used to measure concentrations and ratios of N-acetylaspartate, creatine and phosphocreatine, and choline, which act as indicators of neuronal density and mitochondrial metabolism, phosphate metabolism and membrane turnover. Proton magnetic resonance spectroscopy has shown that people with autism spectrum disorder have significant abnormalities in prefrontal lobe neuronal integrity, and that this is related to severity of clinical symptoms (Murphy et al, 2002). Moreover, there is preliminary evidence that people with autism spectrum disorder have an abnormal amygdala glutamate metabolism (Page et al, 2006). These results suggest regional differences in neurodevelopment (programmed cell death) may underlie a proportion of the symptoms typical of the disorder, and that some symptoms of autism may be partially explained by differences in glutamate.

The role of 5-hydroxytryptamine

5-hydroxytryptamine (5-HT) is potentially important in autism spectrum disorder because 5-HT acts as a trophic or differentiation factor during brain development, and helps modulate social and repetitive behaviours (Chugani, 2004). There is also growing evidence that some symptoms in people with autism spectrum disorder may benefit from medications (e.g. selective serotonin-reuptake inhibitors and atypical antipsychotics) that affect the 5-HT system. Initial positron emission tomography studies suggest that neural serotonin synthesis differs between children with autism spectrum disorder and controls (Chugani, 2004). Also, people with autism spectrum disorder are significantly different to controls in brain 5-HT-2A receptor density (Murphy et al, 2006). Future studies will use fMRI and methods of altering brain levels of 5-HT (such as tryptophan depletion) to investigate the modulatory effects of 5-HT in social cognitive function in autism spectrum disorder, and the normal population.

Conclusions

Evidence of behavioural fractionation of social impairment, communication difficulties and rigid and repetitive behaviours suggest that autism spectrum disorders are likely to be caused by abnormalities in multiple brain regions and networks, not single structures. Hence, current brain imaging studies of autism spectrum disorders focus on relationships between abnormalities in structure and function of specific brain regions as parts of networks (e.g. subserving executive function, social cognition, and language processing).

In keeping with this approach, there is increasing evidence from a range of neuroimaging methods that autism spectrum disorder is a disorder of underconnectivity between nodes in neurocognitive networks. For example, reduced functional connectivity across a wide range of tasks, and at rest, has been demonstrated in people with autism spectrum disorder compared to controls. Also, there are widespread differences in structure and developmental trajectory in both grey and white matter regions in people with autism spectrum disorder relative to controls. In addition, DTI investigations have revealed reduced microstructual integrity of white matter tracts in people with autism spectrum disorder, providing a potential pathophysiological basis for reduced functional connectivity. Findings from proton magnetic resonance spectroscopy suggest regional differences in neurodevelopment (programmed cell death), which may relate to abnormalities of grey and white matter in autism spectrum disorder (Murphy et al, 2002).

KEY POINTS

- Autism spectrum disorders are likely to be caused by abnormalities in multiple brain regions and networks, not single structures.
- Autism spectrum disorders are characterized by underconnectivity between components of networks subserving a variety of functions (e.g. executive function, facial emotion processing, theory of mind, and language processing).
- Structural brain imaging has revealed widespread differences in structure and developmental trajectory in both grey and white matter regions in people with autism spectrum disorder relative to controls.
- Diffusion tensor imaging investigations show reduced microstructural integrity of white matter tracts in people with autism spectrum disorder, providing a potential pathophysiological basis for reduced functional connectivity.
- Findings from proton magnetic resonance spectroscopy suggest regional differences in neurodevelopment (programmed cell death), which may relate to abnormalities of grey and white matter in autism spectrum disorders.
- Future research will focus on improved understanding of genetic and environmental determinants of brain structure and function in typical and atypical development; the relation between brain function and structure at both macro and micro levels; and relations between brain, cognition, symptomatology and behaviour.

The past decade has provided enormous advances in understanding the neurobiological basis of autism. However, more work is required (in large well-described samples) to investigate the genetic and environmental determinants of neurobiological differences in brain systems. This will involve improved understanding of the relation between brain function and structure at both macro and micro levels, and also of relations between the brain, cognition, symptomatology and behaviour. **BJHM**

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