

Autistic-spectrum disorders: lessons from neuroimaging

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Summary Autistic-spectrum disorder is approximately half as common as schizophrenia but its cause remains unknown. Recent studies have begun to clarify the underlying neuroanatomical abnormalities and brain–behaviour relationships in autism. In the past decade, great advances have been made in our understanding of the neurobiological basis of autism.

Declaration of interest None.

Autistic-spectrum disorder, comprising the subtypes of ‘typical’ autism, high-functioning autism and Asperger syndrome, is characterised by pervasive developmental abnormalities in social and emotional behaviour and is associated with stereotyped and obsessional behaviours (World Health Organization, 1992; Wing, 1997; Gillberg, 1998). Qualitative impairments in reciprocal social interaction include inadequate appreciation of social–emotional cues (as shown by a lack of responses to others’ emotions), poor use of social signals and a lack of socio-emotional reciprocity.

Individuals with autism (Wing, 1997; Gillberg, 1998) also have delayed language development, and many have learning disability. However, around 20% are classified as high-functioning, because they have normal or superior general intellectual skills, despite having a history of early language delay. Individuals with Asperger syndrome have no history of language delay and have normal or superior intellectual abilities, but also show the characteristic impairments of reciprocal social interaction. Although by definition (ICD–10; World Health Organization, 1992) there is always a disparity between social understanding and cognitive skills in autism, this disparity is particularly marked in high-functioning individuals with autism/

Asperger syndrome. However, the biological associates of abnormal social behaviour in autism are poorly understood.

Prevalence rates of up to 60 per 10 000 for autistic-spectrum disorder are reported (Chakrabarti & Fombonne, 2001; Charman, 2002) for the broader phenotype – making it approximately half as common as schizophrenia. Controversially, some mental health services do not provide services for adults with autistic-spectrum disorder – arguing that it is not a ‘psychiatric’ disorder. This logic is at best flawed. Just like attention-deficit hyperactivity disorder and psychosis, autistic-spectrum disorder is a highly genetic neurodevelopmental disorder and is defined as a psychiatric disorder in both ICD–10 and DSM–IV (American Psychiatric Association, 1994); it is associated with significant comorbid mental health symptoms both in patients and in their families; and it responds to appropriate pharmacological, psychological and social interventions. There are currently few services for adults with autistic-spectrum disorder, and most child and adolescent services do not offer long-term follow-up when their young patients become adults.

The cause of autistic-spectrum disorder is unknown, but is most likely to be a complex interaction between genetic and environmental factors. It was still believed in the 1960s that cold, ‘refrigerator’-type parenting was responsible for the behavioural characteristics associated with this syndrome. One of the earliest indicators that it was in fact a neurobiological disorder was the high rate of epilepsy, which was found to affect approximately a third of autistic children. Twin studies have since shown autism to be among the most heritable of neuropsychiatric disorders (Bailey *et al*, 1995). Particularly poor science led to reports that autistic-spectrum disorder was caused by the measles, mumps and rubella vaccine, and this caused much alarm and a reduction in immunisation.

This is ironic, given that this vaccine protects against one of the established causes of autism – intrauterine exposure to rubella. The challenge therefore exists to define the biological determinants of autistic-spectrum disorder.

CONTRIBUTION OF NEUROIMAGING

The earliest report of abnormal brain development appears in the original description by Kanner (1943). In that report Kanner described 11 children and commented on the relative absence of substantial dysmorphism, apart from the presence of ‘large heads’ in five of the children. Following this, a variety of studies reported enlargement of brain volume based on head circumference measurements. Over the past 30 years, the explosion of neuroimaging technology has enabled the non-invasive study of the brain in individuals with autistic-spectrum disorder. To date, structural magnetic resonance imaging (MRI) results are inconsistent, partly owing to the heterogeneity of the disorder itself, and partly to the use of inappropriate control groups and the limitations of region-of-interest techniques. However, recent studies have begun to clarify the underlying neuroanatomical abnormalities and brain–behaviour relationships in autism.

Anatomical imaging

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). It has been proposed that people with autistic-spectrum disorder have an early period of accelerated brain growth followed by a period of decelerated development. It is also clear that in adulthood brain ageing is significantly different in people with autistic-spectrum disorder compared with controls (McAlonan *et al*, 2002). Thus, the biology of the disorder should not be seen as an initial ‘hit’ followed by a static disorder. Rather, the initial early biological differences most probably modify brain maturation across the lifespan.

In addition to differences in volume of whole brain, however, some specific brain regions are particularly implicated, including the frontal, limbic, basal ganglia and cerebellar regions (for a review, see Sokol

& Edwards-Brown, 2004). For example, it was reported that people with Asperger syndrome had significantly less grey matter in frontostriatal and cerebellar regions than controls, and widespread differences in white matter (McAlonan *et al*, 2002). Furthermore, people with Asperger syndrome had significant differences in ageing of the cerebral hemispheres and caudate nuclei. These findings were also replicated in a study of a Chinese population of children with high-functioning autism (McAlonan *et al*, 2005), which found that they had significant differences in the volume and connectivity of frontostriatal networks. In another study (McAlonan *et al*, 2005) these authors found that children with autistic-spectrum disorder had a significant difference in the grey matter volumes of the ventral and superior temporal lobes, and the white matter volumes of the cerebellum, internal capsule and fornices (McAlonan *et al*, 2005). In summary, taken together these data suggest that people with autistic-spectrum disorder have abnormalities in the anatomy and connectivity of limbic-striatal brain systems and that this is true in samples from different countries, cultures and age groups.

Therefore, there is growing evidence that people with autistic-spectrum disorder have specific abnormalities in brain development and anatomy. However, it is unclear how variation in genetic systems which are important for brain growth and development relates to neurobiological differences.

Functional imaging

Functional magnetic resonance imaging (MRI) has allowed the investigation of the neural networks underlying cognitive impairments in autism, including face and emotion processing, which has been one of the most extensively explored areas. Hypo-activation of the so-called 'face area' in the right fusiform gyrus has repeatedly been reported in adults with autistic-spectrum disorder while looking at faces (Critchley *et al*, 2000). However, more recently it has been identified that this response can be modulated, depending on the familiarity and personal emotional content of the faces presented (Hadjikhani *et al*, 2004; Pierce *et al*, 2004).

The ability to attribute mental states to others (theory of mind) underpins many aspects of normal social interaction and is impaired in people with autism. Decreased

activation of medial prefrontal cortex and amygdala during 'mentalising' tasks has been reported in people with autistic-spectrum disorder, and suggests that these areas form a crucial component of the brain system that underlies the normal understanding of other minds (Happé *et al*, 1996; Castelli *et al*, 2002). Thus, people with autism also have functional differences in brain regions which are reported as anatomically abnormal and which are essential to normal social function.

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, respectively. This imaging technique has shown that people with autistic-spectrum disorder have significant abnormalities in prefrontal lobe neuronal integrity, and this is related to severity of clinical symptoms (Murphy *et al*, 2002). These results suggest that regional differences in neurodevelopment (programmed cell death) may underpin a proportion of the symptoms typical of the disorder.

Other neuroimaging techniques

Studies using positron emission tomography (PET) reported differences in the connectivity of cortico-cortical and cortical-basal ganglia circuits (Horwitz *et al*, 1988), and these findings are supported by the MRI studies noted above. Also, some studies reported significant differences in serotonin (5-hydroxytryptamine; 5-HT) synthesis (Chugani, 2004). The potential role of 5-HT in autistic-spectrum disorder is of importance, because 5-HT acts as a trophic or differentiation factor during brain development, and helps modulate social and repetitive behaviours. There is also growing evidence that some symptoms in people with autistic-spectrum disorder may benefit from medications that affect the 5-HT system (e.g. selective serotonin reuptake inhibitors and atypical antipsychotics).

In a recent edition of the *Journal* we were presented with a PET study of individuals with autism and savant abilities (Boddaert *et al*, 2005). On the basis of their findings, the investigators postulate that savant

capacities may be sustained by a memory-processing network involving the temporo-frontal regions (including the hippocampus). Structures in the medial temporal lobe are critical to normal memory functions, including acquisition of new information. Early abnormal development of this system is thought to result in abnormalities of long-term memory and lead to reliance on more habit-type memory processing. The preservation of the habit memory system also accounts for many characteristics typical of children with autism. It is consistent with Kanner's observations of an 'anxiously obsessive desire for the preservation of sameness', 'excellent rote memory' and 'limitation in the variety of spontaneous activity' in autism (Kanner, 1943). Boddaert *et al*'s study is of particular interest, as it has been suggested that as babies, all humans possess savant abilities, as can be seen in the rapid language acquisition at that age as well as the fact that absolute pitch and eidetic memory are much more commonly present in children and may reflect the reliance on habit memory processing in all humans at this stage.

FUTURE RESEARCH

The past decade has provided enormous advances in understanding the neurobiological basis of autism. However, more work is required using large, well-characterised samples to investigate the genetic and environmental determinants of neurobiological differences in brain systems and the potential role of neurotransmitters such as serotonin.

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