Autism Spectrum Disorders

Understanding Brain Anatomy in Autism – Findings from Structural Neuroimaging

a report by
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Initially described by Leo Kanner in 1943, autism is a developmental disorder characterised by social and communication difficulties as well as a restricted, repetitive range of interests and activities. Although in his original case series Kanner stated that individuals with autism had an “innate inability to form the usual, biologically provided affective contact with people”, the psychodynamic zeitgeist meant that for many years autism was viewed as resulting from a lack of maternal warmth. Over the past 30 years this view has changed considerably, such that autism is now firmly regarded as a highly heritable disorder with its origins in early neurodevelopment. The precise pathophysiological mechanisms behind the expression of autism remain unclear; however, increasingly sophisticated investigative techniques are gradually shedding light on the neurobiological underpinnings of the condition.

Structural Magnetic Resonance Imaging
The development of computed tomography (CT) in the early 1970s was a major breakthrough in clinical brain science as it allowed, for the first time, researchers to use a non-invasive technique to gather in vivo information regarding brain structure. However, CT scanning has a number of disadvantages that limit its utility in brain research – most notably the use of ionising radiation but also the relatively limited resolution of many brain structures, particularly in areas in close proximity to the skull. The advent of magnetic resonance imaging (MRI) has allowed many of these difficulties to be overcome, leading to its widespread application in the study of neuropsychiatric disorders. MRI does not rely on the use of ionising radiation. Instead, a strong magnetic field is applied, causing protons – i.e. hydrogen ions contained within water molecules – to precess (spin) around the direction of the field (at a frequency determined by the strength of that field). A radiofrequency (RF) coil then emits a pulse that alters the alignment of the protons. In addition to the RF pulse, three smaller magnetic fields, set orthogonally to each other, are employed to locally alter the main magnetic field, so that only the protons contained within a specific slice, orientated in a particular plane, are affected for a given time-frame. When the RF pulse terminates, the protons relax back to precess around the direction of the main magnetic field, releasing energy – the MRI signal – as they do so. Since the rate of relaxation is different between different tissue types, it is possible to manipulate the imaging parameters according to the tissues that are of interest. This MRI signal is detected by the coil and transferred to a computer system, where the data are transformed to create the final image. Manual and automated analysis techniques can then be applied to the scans to quantify selected neuroanatomical characteristics, most commonly region volume. Diffusion tensor imaging (DTI) is an MRI modality that provides information regarding the movement of water in the brain. In areas of white matter that have tightly packed, highly myelinated and/or highly co-directional axons, water movement will tend to be anisotropic, i.e. constrained so that it moves in one particular direction. By measuring the level of anisotropy (called fractional anisotropy [FA]) in a particular region it is therefore possible to infer information about white matter microstructure.

Atypical Brain Growth
Recent research suggests that there is an acceleration in brain growth in individuals with autism, first detectable in infancy, which results in a greater mean brain volume, at least in younger individuals. Evidence for this atypical pattern of growth comes from a combination of head circumference studies prior to the clinical onset of autism and brain imaging studies thereafter. Head circumference is known to correlate strongly with brain volume in typically developing infants, hence its use as a proxy for brain volume in very young children in whom MRI studies would be difficult. A retrospective foetal ultrasound study of individuals who later went on to develop autism found no difference in foetal head circumference, although there was a trend towards a larger biparietal diameter. At birth, the mean head circumference of autistic individuals has been reported as being either smaller than or the same size as that of typically developing babies, whereas in the first year of life head circumference has been found to increase much faster than in typically developing infants. Interestingly, this pattern of early overgrowth has also been reported to be associated with the development of autistic symptoms in siblings of those with autism spectrum disorders, raising the possibility that it could be used as part of a predictive assessment for those with familial risk factors.

It is uncertain whether brain enlargements in autism persist throughout life or become less evident with increasing age. MRI studies of young children after the clinical onset of autism do appear to show greater enlargements in brain volume than are apparent in older individuals, although increased size of the adult brain has also been reported. A meta-analysis that combined post mortem MRI and head circumference estimates of brain size across many different age groups concluded that there is a rapid expansion in the first year of life, followed by a period of reduced growth, with a gradual normalisation in size occurring by adulthood. However, it is important to note that this conclusion is based on combining various cross-sectional studies; whether the same results would be seen in a longitudinal study of autism is not certain. Until such a study is available, any conclusions must be considered preliminary.

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Other than the developmental time-course, a number of questions remain regarding the nature of the brain enlargement in autism. Studies differ as to whether they have found enlargements that are generalised across the whole brain or confined to certain regions, and whether they affect grey matter, white matter or both. In addition, it is not known whether the extra brain volume reflects a quantitative difference from typical development or a more profound qualitative difference in the process of brain development. Proposed mechanisms include an increase in glial cell proliferation, an abnormal myelin maturational process and the development of smaller but more numerous cortical minicolumns (vertically orientated groups of cortical cells thought to represent functional units). The causes of brain enlargement in autism are also currently unknown, although there is some evidence that genetic factors may be important. A recent study identified an association between enlargements of the cerebral hemispheres and a low-activity variant of the promoter for the monoamine oxidase A gene (MAO-A) – an enzyme that breaks down catecholamines, including noradrenaline and serotonin – in individuals with autism. Increases in catecholamines, which could be caused by reduced MAO-A activity, have been associated with autism, and this low-activity variant has also been associated with more severe autistic symptomatology.

**Dysconnectivity**

Given the multifaceted nature of human behaviours, it is not surprising that the brain functions that subserve them are not carried out by specific areas of the brain in isolation, but rather require the temporally co-ordinated integration of multiple brain regions. The complex nature of the behaviours central to the autism phenotype brings into focus dysconnectivity between distributed brain regions as a putative contributing factor. Electro-physiological and functional MRI studies have demonstrated alterations in connectivity in the autistic brain during a variety of tasks, while the strongest neuroanatomical evidence for dysconnectivity comes from MRI studies of white matter. The corpus callosum is the largest white matter tract in the human brain and connects homotopic areas of the contralateral cerebral cortices. A reduction in the mid-sagittal area of the corpus callosum was the first white matter abnormality to be identified in autism, and has been consistently replicated. More recently, several DTI studies have reported reduced FA in the corpus callosum, which is consistent with the volumetric findings and indicative of interhemispheric dysconnectivity.

In addition to reports of interhemispheric dysconnectivity, other patterns of reduced FA have been identified in autism, including in brain regions involved in social cognition such as the anterior cingulate, orbitofrontal cortex, superior temporal sulcus and areas approaching the amygdala and fusiform gyrus. Other DTI studies have found reductions in FA in the internal capsule, superior temporal gyrus and temporal stem and the short association fibres of the prefrontal lobe. The last of these studies also found that people with autism have a fibre distribution skewed towards long association fibres, and these fibres were also found to be longer than expected in typically developing controls. Other neuroanatomical evidence of dysconnectivity comes indirectly from reports of disturbances to prefrontal cortical folding and greater sulcal depth in autism, both of which may be related to changes in the underlying innervation of a region.

**The Social Brain**

Deficits in social cognition are well documented in autism and include impairments in mentalising ability (attributing mental states to others) and the recognition of the emotional content of a variety of stimuli, particularly facial expressions. In typically developing individuals there are several connected brain regions that are known to be involved in social cognition. These include the fusiform face area, the superior temporal sulcus (STS) and the amygdala, which are covered below, and the frontal–thalamo–striatal networks, which are dealt with in a separate section. The fusiform face area is located on the ventral surface of the temporal lobe and is known to play an important role in the processing of facial stimuli. Although differences in the amount of fusiform grey matter have been observed between individuals with autism and controls, these are inconsistent, with both increases and decreases identified. However, a recent post mortem study did find a reduction in neuronal number and size in the fusiform face area, and functional imaging studies have reported that people with autism show abnormal activation patterns in the fusiform gyrus when viewing faces compared with unaffected individuals. The regions around the superior temporal sulcus are proposed to be involved in auditory perception as well as the initial analysis of more complex social stimuli derived from biological motion. There are several MRI studies of autism that have found reductions in grey matter around the superior temporal sulcus. Cortical thinning has also been found in this region, the degree of which was associated with overall symptom severity. In addition, anterior shifting of the relative position of the superior temporal sulcus within the brain has been reported in autism (along with displacements of other major frontal and temporal sulci).

The amygdala is a collection of nuclei that lie in the medial temporal lobe. It is involved in many aspects of social cognition, including the mediation of fear and arousal and the attribution of emotional valence to stimuli. It has been found to be increased in size in younger individuals with autism, but is normal or reduced in volume in adults. This is particularly notable when considered in the light of findings that early amygdala damage has significant effects on social cognition, whereas later damage does not. In addition, in children with autism a large amygdala has been associated with increased anxiety levels, whereas in adolescents and adults a small amygdala was found to be associated with social impairment. These findings suggest that it is not just the initial enlargement of the amygdala, but also the extent of the volume reduction that affects the clinical severity of autism. As with the findings for the whole brain volume, it must be emphasised that longitudinal studies are required to definitively establish the temporal pattern of amygdala enlargement in autism. In addition to the traditional network of social brain regions described above, recent studies have suggested that there is a further system that is important in social cognition: the mirror neuron system. Located in the inferior frontal and inferior parietal cortices, mirror neurons are activated both when an individual performs an action and when he or she views an action carried out by another person. This mental representation is proposed to be...
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important in imitating and understanding the actions of others and hence in the development of social cognitive skills. Much of the evidence for an abnormality of the mirror neuron system in autism spectrum disorders comes from electrophysiological and functional MRI data. However, individuals with autism have also been reported to show reductions in grey matter and cortical thinning in areas relevant to the mirror neuron system, suggesting that anatomical abnormalities underlie these functional deficits. Significant converging evidence therefore implicates neuroanatomical abnormalities in brain regions associated with social cognitive skills in autism. It is important to note that changes to FA have been found in white matter close to several important social brain regions, including the superior temporal sulcus, amygdala, fusiform gyrus and the orbitofrontal cortex. It therefore seems likely that dysfunction of the social brain is associated with changes to key structures themselves, as well as the degree of connectivity between them. Which of these (if either) is the primary problem is unknown.

### Language Regions

Language areas of the human brain include Broca’s area in the inferior frontal gyrus, Wernicke’s area in the temporo-parietal regions and the superior temporal sulcus. Despite the core role of communication in autism, there are surprisingly few studies that have specifically examined the neuroanatomy of these regions in the autistic brain. Two studies have found a reversal in the normal pattern of asymmetry in Broca’s area and surrounding regions, suggesting that an interference in the process of cerebral lateralisation may be important. Some studies have found a change to the asymmetry of the structures that make up Wernicke’s area; however, conflicting findings as to the direction of this change are reported. Superior temporal sulcus abnormalities have, as already described, also been identified in autism.

### The Fronto-striatal Networks

There are five fronto-striatal networks in the human brain: the motor circuit; the oculomotor circuit; the dorsolateral prefrontal circuit, which is involved in executive functions; the orbitofrontal circuit, which receives input from the social brain areas discussed earlier; and damage to which is characteristically associated with behavioural disinhibition and emotional lability; and the anterior cingulate circuit, which is involved in motivation. Each of these circuits begins in the area after which it is named and passes to the frontal cortex via the thalamus.

The caudate nucleus, a component of the striatum, has been found to be consistently enlarged in autism, and the degree of enlargement has been associated with the severity of restricted and repetitive behaviours. Changes to thalamic volume are less well established, although several studies have found a dissociation between the size of the thalamus and that of the total brain, which is not seen in typically developing individuals. There is some evidence that orbitofrontal size differences exist in autism, with children and adolescents reported to have reduced volume of the right lateral region, while the opposite result was seen in adults. However, more research is required before any definitive conclusions can be drawn. The size of the orbitofrontal cortex has been found to be positively associated with the presence of circumscribed interests in individuals with autism. This, along with the similar relationship identified for the caudate, suggests that dysfunction in the orbitofrontal-striatal network may account for the stereotyped behaviour seen in autism. Interestingly, orbitofrontal-striatal dysfunction has also been associated with obsessive-compulsive disorder, a syndrome that is also characterised by repetitive patterns of behaviour.

### The Cerebellum

Until relatively recently the cerebellum was regarded as being solely involved in motor function; however, there is a growing body of evidence that it has a broader role in cognition and emotional regulation. It is richly connected to both motor and non-motor regions of the brain, leading to suggestions that it plays a similar regulatory role for the cognitive and emotional domains to the role it plays in motor function. A disturbance to this regulation in individuals with autism has been proposed to lead to some of the cognitive and clinical features of autism, such as deficits in switching attention and difficulty following and interpreting social situations. Postmortem studies have consistently identified microstructural abnormalities of the cerebellum in autism, and a reduction in the midsagittal area of lobules VI and VII of the cerebellar vermis was the first quantitative neuroanatomical abnormality to be reported using structural MRI. While this finding has been replicated, it appears to be accounted for, at least in part, by differences in intelligence quotient (IQ) between case and control groups rather than by autism per se. It has also been suggested that the growth of this part of the vermis is atypical in autism, being initially smaller than in controls but subsequently accelerating in growth until a normalisation in size occurs, in a manner opposite to that proposed for the whole brain volume. While this appears paradoxical, supporting evidence includes a reciprocal relationship between the size of the frontal lobe and that of lobules VI and VII of the vermis. The implication is that while younger individuals with autism may show reductions in these lobules, these findings may simply not exist in older individuals. Less controversy exists over the size of the cerebellar hemispheres, which are generally accepted to be enlarged in people with autism; whether they show a similar gradual normalisation in size as proposed for the whole brain volume is unknown.

### Conclusion and Future Directions

Over the last 20 years the use of structural MRI has considerably advanced our understanding of the neuroanatomy of autism. There is an increasing consensus that autism is associated with an enlarged brain, disordered inter-regional connectivity and changes to specific brain structures involved in social behaviour. The evidence to date also suggests that changes to brain structure pre-date the onset of behavioural features and may continue to evolve for some time afterwards, although longitudinal studies are needed to validate this. Despite this increase in knowledge, there remains significant work to be done before the neuroanatomy of autism can be fully unravelled. Advances in imaging technology, of which DTI is one, and an increase in the number and size of post mortem studies are required to determine precisely the neuroanatomical disruptions and pathological processes underlying the features observed using MRI. Further attempts to link putative aetiological factors, particularly polymorphisms in known genetic risk variants, and brain structural and functional changes are also likely to prove fruitful. Finally, and crucially, the heterogeneous nature of the autism spectrum demands a comprehensive clinical assessment and a tight definition of the behavioural phenotype under examination as key components of any future research.


