https://doi.org/10.1192/bjp.173.4.299 Published online by Cambridge University Press

Neuroimaging in autism

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Background Childhood autism is a developmental disorder with distinctive clinical features and characteristic cognitive deficits. Neuroimaging techniques have been extensively used in the study of autism and related disorders.

Method Recent important literature reported on structural and functional neuroimaging in autism was reviewed and discussed in the context of other neurobiological research findings.

Results Various abnormalities of brain structure and function have been proposed, but no focal defect has been reliably demonstrated. Important findings, so far, include increased brain volume, structural abnormality in frontal lobe and corpus callosum in a proportion of autistic individuals. Functional neuroimaging findings emphasised the imbalance in inter-regional and inter-hemispheric brain metabolism and blood flow as well as abnormality in the anterior cingulate gyrus.

Conclusion The research to date has been hindered by methodological difficulties. However, hypothesis-driven research, particularly involving activation studies and neurotransmitter/neuroreceptor activities, using functional neuroimaging will be very useful in unravelling the enigma associated with this intriguing and distressing condition.

Individuals with autism demonstrate characteristic symptoms which involve impairments of communication and of social reciprocity and in addition exhibit repetitive or ritualistic behaviours. In recent years a considerable body of literature has addressed the neurobiological mechanism underlying this intriguing neurobehavioural condition (Rapin & Katzman, 1998). At the same time, neuroimaging techniques have been used in an attempt to explain brain behaviour relationship in many neuropsychiatric conditions (Deb, 1997*a*). We discuss the recent important neuroimaging studies involving autistic individuals in this review. It is suggested that neurobehavioural findings of autism may be a common pathway for expression of many neurodevelopmental syndromes. As such its diagnosis as a homogeneous entity could be questioned. This conceptual controversy makes this review both difficult and interesting.

VENTRICULAR SYSTEM AND TEMPORAL LOBE

Hauser *et al* (1975) described dilatation of the left temporal horn of the lateral ventricle in a pneumo-encephalographic study of autistic individuals and hypothesised that medial temporal lobe dysfunction might be a major factor in the pathogenesis of the disorder. Several groups of investigators using computerised tomography subsequently reported abnormalities of the ventricular systems in their samples of people with autism (Damasio *et al*, 1980; Gillberg & Svendsen, 1983). However, the samples were rather heterogeneous and included individuals with known neurobiological disease. The ventricular abnormalities were not as specific as those reported by Hauser *et al*, and in addition a variety of other computerised tomography abnormalities were also seen.

However, despite the theoretical relevance of the limbic structures to autistic symptomatology together with autopsy data describing abnormalities in the limbic lobes in autism (Rapin & Katzman, 1998), studies seem to be rare in this area, so far. Whereas magnetic resonance imaging (MRI) studies in general failed to show abnormality in limbic structure in autism, a recent positron emission tomography (PET) study co-registered with MRI findings has shown abnormal structure and metabolism in the anterior cingulate gyrus of a small cohort of high functioning autistic subjects (Haznedar *et al*, 1997). They highlighted the significance of their findings in the light of the substantial difficulties that the subjects with autism had in expressing affect, decoding affect, and performing higher executive functions – activities which are modulated by the anterior cingulate gyrus. Similar abnormalities in the metabolism in the anterior cingulate gyrus in autism was also reported by others (Rumsey *et al*, 1985). Also Gillberg *et al* (1993) reported reduced hypoperfusion in temporal lobes in single photon emission tomography (SPET) in 31 children and adolescents with autism and autistic-like features.

CEREBELLUM AND POSTERIOR FOSSA

Courchesne *et al* (1987) reported abnormalities in the cerebellum of an individual with high functioning autism. Subsequently they compared a sample of 18 individuals with autism with a group of normal control subjects and reported a significant reduction in the size of vermal lobules VI–VII in the group with autism (Courchesne *et al*, 1988). Piven *et al* (1992) looked at a strictly defined sample of individuals with autism who were free of significant medical or neurological problems. They were compared with two separate control groups and after multivariate analysis adjusting for mid-sagittal brain area, age and IQ, no difference was detected in the size of the vermal lobules between the groups. Several other researchers have also failed to replicate Courchesne's original findings (Garber & Ritvo, 1992; Holttum *et al*, 1992).

Additionally, Courchesne suggests that there is a subgroup of individuals with autism who have cerebellar vermal hyperplasia (Courchesne *et al*, 1994) and that this could explain why other groups have

https://doi.org/10.1192/bjp.173.4.299 Published online by Cambridge University Press

failed to replicate his findings. However, Schafer *et al*'s (1996) recent findings suggest that hypoplasia of cerebellar vermal lobules VI–VII is a non-specific finding associated with many neurodevelopmental disorders. Also, Courchesne *et al*'s methodology has been criticised on the grounds of limited number of overlapping subjects being reported in multiple publications and lack of a control group matched for chronological and developmental age.

Other structures within the posterior fossa have also come under scrutiny. Gaffney *et al* (1987) reported an increase of fourth ventricular size in a rather heterogeneous group of individuals with autism compared with medical control. Hashimoto *et al* (1995) performed MRI scans on a large sample of individuals with autism and controls. Both samples were divided into nine different age groups. The range of intellectual functioning in the group with autism was from normal (IQ>80) to severe learning disability (IQ<29). The control group was of normal intelligence and included a proportion of 'medical controls'. They concluded that while the brain stem and cerebellum increased in size with development, these structures were significantly smaller in the patients with autism than in controls and that this was suggestive of an early developmental insult and hypoplasia rather than a degenerative process. However, the posterior fossa abnormality in autism was not a universal finding (Hsu *et al*, 1991).

INCREASED BRAIN VOLUME

Recently it has been reported that head circumference is increased in autism, with about 25% of such individuals having a circumference above the 97th percentile (Bailey *et al*, 1995). In 1992, Piven *et al* (1992) in their study of structures within the posterior fossa described that the subjects with autism had a significantly larger mid-sagittal brain area than either control group. Piven *et al* have since published a study which measured brain volume in a group of 22 males with autism compared with 20 normal male control subjects (Piven *et al*, 1995). They reported that after controlling for height and performance IQ, the group with autism had significantly greater total brain, total tissue and total lateral ventricular volumes. Similar findings concerning brain size have been reported by Filipek *et al* (1992) who found brain volume in a sample with autism to be increased when compared with normal control subjects, a group of individuals with disabilities and a group suffering developmental language disorders.

CORPUS CALLOSUM

One other brain area which has drawn researchers' attention in autism is the corpus callosum. The corpus callosum is the largest and most prominent axonal pathway in human brain, and as such has become the paradigm for the study of inter-hemispheric transfer of information, an activity which is shown to be impaired in autism (Ellis *et al*, 1994). A recent quantitative MRI study of 35 subjects with autism (mean age 18 years) and 36 control subjects detected significantly smaller size of the body and posterior sub-regions of the corpus callosum in autistic individuals (Piven *et al*, 1997).

FRONTAL LOBE

Piven *et al*'s (1995) finding of the increased brain volume in subjects with autism affected particularly the posterior regions, namely parietal, temporal and occipital lobes but not frontal lobes. Looking at it from a different angle, in comparison with the findings in the control group, it is the frontal lobe which seems abnormal in autism. This finding is important as Ozonoff (1995) proposed that autism is a consequence of impaired 'executive function' associated with impaired frontal lobe activity. Piven *et al* (1995) argued that the finding of hypofrontality and the corpus callosal abnormality are synchronous. This study is important not only because they used a quantitative MRI technique, a reasonable number of cohorts, and a case control methodology, but also the analysis of the region of interest was based on a known neuropsychological hypothesis. Other studies have also supported this finding of abnormality in frontal lobe structure in autism (Damasio *et al*, 1980; Zilbovicius *et al*, 1995).

'THEORY OF MIND'

An area where activation studies have been employed is the investigation of 'mentalising' abilities or 'theory of mind' skills which have enriched our understanding of the difficulties which autistic individuals encounter in social interactions. In a two-part experiment Baron-Cohen *et al* (1994) first established that subjects with autism performed significantly worse in recognising mental state terms when compared with normal control subjects and then went on to investigate regional cerebral blood flow (rCBF) in normal volunteers using SPET. They demonstrated an increased rCBF in the orbito-frontal cortex relative to an adjacent area of the parieto-frontal cortex in the volunteers while performing the mental state recognition task. They suggest that the orbito-frontal cortex is the region of the brain employed in such cognitive tasks.

GLOBAL BRAIN METABOLISM

In contrast most investigators have concentrated on functional imaging under resting conditions. Rumsey *et al* (1985) measured resting cerebral glucose utilisation rates using PET in 10 adult men with a history of childhood autism compared with 15 normal control subjects and reported significantly elevated glucose utilisation globally in the brains of the autistic group members. This finding may indirectly support the neurostructural finding of increased brain volume in autism. Horwitz *et al* (1988) also reported increased cerebral metabolism in autism but others have failed to replicate this finding (Herold *et al*, 1988).

INTER-REGIONAL AND INTER-HEMISPHERIC BRAIN FUNCTION

Abnormalities in regional brain glucose metabolism in autism, was not always a consistent finding, particularly when a control group was used (De Volder *et al*, 1987). Others (Buchsbaum *et al*, 1992) reported decreased relative metabolic activity in PET between a control group and a group with autism in the subcortical areas, including right putamen and right posterior thalamus. They also demonstrated nearly equal metabolic rates in right and left hemisphere when compared with controls who showed greater metabolic rates in the right than the left cerebral cortex. Small cohort size of six subjects with autism was an obvious drawback of this study. While most studies concentrated on discrete regional abnormalities in the brain of autistic subjects, some assessed relative imbalance

https://doi.org/10.1192/bjp.173.4.299 Published online by Cambridge University Press

of inter-regional activities. For example, Horwitz *et al* (1988) using PET showed discrepancy in activities between frontal and parietal lobes and the striatum and thalamus in 14 children with autism when compared with a matched control group. In the absence of a definite hypothesis for an inter-regional discrepancy in autism, it is difficult to interpret these findings.

SEROTONIN METABOLISM

To date we have been able to find only one report of PET being used to investigate neurotransmitter metabolism. Chugani *et al* (1997) investigated serotonin synthesis using alpha-(11C) methyl-L-tryptophan and found altered synthesis in the dentato-thalamo-cortical pathway in a small sample of children with autism when compared with their siblings without autism. This is an interesting finding as several authors have previously suggested that abnormalities of serotonergic function are implicated in autism (Anderson *et al*, 1990). Unfortunately, this particular paper suffers methodological shortcomings and the significance of the results remain unclear.

DISCUSSION

What is known

The recent surge of interest in neuroimaging research in autism has produced evidence of structural and functional abnormality in the brains of subjects with autism. This finding is not unexpected given the fact that autism is often associated with learning disability which could be caused by brain damage, and the fact that autistic features are manifested in many neurodevelopmental conditions. However, the important question is, how specific and sensitive are these findings in relation to autism? Some findings such as abnormality in parietal lobe structure and caudate nucleus and neuroimaging evidence of cerebral dysgenesis have not been reported in this review because of their questionable significance. Also, excitement surrounding the findings of abnormal cerebellar and other posterior fossa structures seem to have faded lately. Currently more emphasis is placed on findings such as increased brain volume, abnormalities in the structure of corpus callosum, frontal lobe and some limbic structures. Functional neuroimaging studies have also emphasised the imbalance in inter-regional and inter-hemispheric brain function.

Methodological critique

It is not surprising to see such inconsistency in neuroimaging findings in autism considering the methodological problems these studies had to face. To start with, the definition and detection criteria for autism have changed over the past two decades, so different groups ended up studying different types of autism. As autistic features are seen in many genetic and non-genetic syndromes (Deb, 1997*b*), it is sometimes therefore unclear whether the researchers studied: (a) autistic spectrum disorder; (b) subgroups of people with autism; or (c) a heterogeneous group of people with autism. Many of these studies are case reports and often the number of subjects included in these reports are small. As many variables such as age, gender, level of cognitive abilities, specific neuropsychological deficits (particularly language abnormality) and associated neurological conditions (epilepsy) can effect neuroimaging findings, unless control groups are used to appropriately match for these variables, proper interpretation of data remains difficult. Also, there is an urgent need for various centres involved in neuroimaging studies to standardise their methods for quantification of both structural and functional neuroimaging data.

Clinical implications

Beyond the academic interest of using 'high-tech' methods for their own sake how can neuroimaging findings influence clinical practice in autism? Neuroimaging could be used to exclude or include other diagnoses associated with autism. Similarly, neuroimaging findings can shed light on the prognosis of autism in an individual case. Outcome of any treatment becoming available could also be monitored by using these techniques. At a more fundamental level, neuroimaging has the potential to highlight the neurobiological mechanisms underlying this condition. This in turn should lead to more rational therapeutic approach.

What needs to be done

Obviously lessons could be learned from past mistakes. It is important to study subjects with pure autism who do not have other associated neurological or neurodevelopmental conditions. This will exclude contamination from confounding factors. It is also important to define the autistic group in terms of aetiology and symptomatology so that the others are able to replicate the study. It is important to avoid selection bias by randomly recruiting subjects from a population-based sample where possible. Adequate numbers of subjects should be included in the study to provide adequate statistical power, if necessary by conducting multicentre trials. The importance of including a properly matched control group of adequate number could not be emphasised more. Finally, it is time to stop relying on serendipity and instead to carry out hypothesis-driven research.

In this context, functional imaging studies involving SPET, PET and functional MRI will be more useful in future than the straightforward structural neuroimaging studies at a resting state. In structural neuroimaging studies careful volumetric analysis of data may reveal valuable information. Both activation studies and neurotransmitter/neuroreceptor studies also hold great promise and future potential in this field.

ACKNOWLEDGEMENT

We thank Mrs J. Wheeler for patiently typing the manuscript.

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CLINICAL IMPLICATIONS

- Neuroimaging studies have revealed inconsistently many structural and functional brain abnormalities in autism.
- Some recent important structural neuroimaging findings are; increased brain volume, abnormalities in frontal lobe and corpus callosum.
- Some functional neuroimaging studies have shown imbalance in inter-regional and inter-hemispheric brain function as well as abnormal metabolism in the anterior cingulate gyrus.

LIMITATIONS

- Data should be interpreted with care as many methodological problems exist, particularly often the lack of a properly matched control group.
- Specificity and sensitivity of findings in relation to autism are unclear.
- Often research in this area has not been hypothesis-driven.

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(First received 16 February 1998, final revision 10 June 1998, accepted 11 June 1998)

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