Structural neuroimaging in learning disability

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Background Neuroimaging has proven useful in confirming diagnoses of certain neuropsychiatric conditions, but neuroimaging studies in learning disability are at an early stage.

Method A review of recent structural neuroimaging research in relation to learning disability was carried out.

Results Brain abnormalities can be detected in cases of idiopathic and non-idiopathic learning disability, but their significance is not clear due to discrepancies in study findings and the small cohorts involved.

Conclusion Although the role of structural neuroimaging in the assessment of people with learning disability is not clear, new magnetic resonance imaging technology holds great promise for future research.

Continuing developments in neuroimaging are making it possible to delineate both the structural and the functional anatomy of the human brain *in vivo* in greater and greater detail. Neuroimaging has proven useful in confirming the clinical diagnosis of certain neuropsychiatric conditions, and as an aid to understanding certain brain–behaviour relationships. Contemporary neuroimaging techniques could broadly be divided under two headings, namely structural neuroimaging, which includes techniques such as computed tomography (CT) and magnetic resonance imaging (MRI), and functional neuroimaging, which includes positron emission tomography and single photon emission computed tomography. In this article only structural neuroimaging findings in relation to learning disability will be discussed.

IDIOPATHIC LEARNING DISABILITY

Neuroimaging studies in learning disability are still in their early stages (Deb, 1995). How could one be certain that a particular neuroimaging finding is specific to a particular syndrome, and not merely associated with the severity of learning disability? In neuroimaging studies, as the approach has always been syndromic, and often there is no IQ-matched control group, the above question has remained unanswered. Whereas autopsy studies have demonstrated neuropathology in the majority of patients with severe learning disability it is estimated that in about 37% of cases, abnormalities could be detected using structural neuroimaging. This discrepancy could be partly explained by the fact that the so-called 'normal variants' in the MRI of subtle neurological abnormalities, such as macro cisterna magna, persistence of cavum septum pellucidum, hypoplasia of the corpus callosum, are subtle markers of cerebral dysgenesis (Schaefer & Bodensteiner, 1992). Cerebral dysgenesis associated with neuronal migration disorders (NMDs), was believed in the past to be consistent with profound learning disability and poor prognosis, but advanced structural neuroimaging has shown that NMDs are consistent with a mild degree of learning disability, epilepsy, normal life expectancy and mild to moderate localising neurological deficits (Palmini *et al*, 1991).

Homano *et al* (1990), using a volumetric measurement of sequential CT scans, showed an overall good correlation between head circumference and the total brain volume in both neurologically normal children and children with a learning disability. The proportion showing lower brain volume (less than 2 s.d. of the group mean of the normal children's brain volume) was even higher among children with learning disability who also had cerebral palsy (10 out of 15 children). Other abnormalities reported in cerebral palsy are dilated lateral ventricle and porencephalic cavities with occasional features such as agenesis of septum pellucidum and cerebral hemiatrophy (Süssová *et al*, 1990). However, in the majority of cases cerebral palsy was not associated with a learning disability.

Abnormalities of the corpus callosum are known to be associated with many learning disability syndromes. It is estimated that between 0.2 and 2.9% of children referred to specialist clinics for the diagnosis of developmental delays and/or learning disability, showed radiological evidence of absence or partial absence of corpus callosum. However, the significance of having a thin or small, but morphologically complete (hypoplastic) corpus callosum is not clear (Schaefer *et al*, 1991). Corpus callosal abnormalities are often shown to be associated with other brain anomalies, such as absent inferior cerebellar vermis and neuronal migration disorder; cingulate gyrus and limbic structures are also affected. Further support for an association between callosal abnormality and learning disability came from a retrospective series of case-reports (David *et al*, 1993).

Thus it appears from the literature that there is no specific neurostructural abnormality associated with idiopathic learning disability. Brain structure is often abnormal, and this abnormality could partly be revealed by *in vivo* neuroimaging studies. The type of abnormalities are often non-specific consisting of smaller brain volume (either due to cerebral atrophy or hypoplasia) which is associated with a dilated lateral ventricle. Specific abnormalities such as macrogyria, polymicrogyria and heterotopias are found in NMDs which are often

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associated with learning disability and epilepsy. On the other hand, cerebral abnormality such as dysgenesis of the corpus callosum and hypoplastic corpus callosum seem to be linked with learning disability. The severity of learning disability is directly related to the severity of cerebral abnormality, but not necessarily with a specific type of abnormality.

NON-IDIOPATHIC LEARNING DISABILITY

Computed tomography abnormalities such as diffuse cortical atrophy, ventricular dilatation, increased pneumatisation of the frontal sinuses, cerebellar and brain stem atrophy with thickening of the calcarial bones, have been demonstrated in patients with xeroderma pigmentosum (Mimaki *et al*, 1989). Not all patients, however, had a detectable learning disability at the time of the scan. Angelman syndrome is characterised by severe learning disability, microcephaly, 'puppet-like' ataxia, paroxysms of laughter and epilepsy. In a small case series, five out of seven children with Angelman syndrome showed evidence of cerebral atrophy (Dörries *et al*, 1988). Similarly, in Williams syndrome, over and above the general cerebral hypoplasia, a reduction in the volume of basal ganglia and thalamus was detected when compared with the cerebral volumes of control subjects (Jernigan *et al*, 1993). Cohort sizes were small in these studies, and the findings seem non-specific.

AUTISTIC DISORDER

There is an association between autism and learning disability in that two-thirds of autistic children are known to have learning disabilities and 14.3% of children with a learning disability also show DSM–III–R autistic disorder (Deb & Prasad, 1994). Earlier CT studies showed no consistent neuroimaging findings specific to autistic disorder. Some reported abnormalities such as ventricular enlargement, asymmetry between right and left parieto-occipital regions and reduced radiodensity in the caudate nuclei were found, but when a control group was used no significant difference in neuroimaging findings was detected (Creasey *et al*, 1986).

The most striking finding so far in MRI studies of autistic subjects is that of Courchesne *et al* (1988), who demonstrated specific cerebellar vermal abnormality affecting lobules VI and VII with a largely intact anterior section (lobules I to V). Initially they reported smaller cerebellar vermal lobules VI and VII in autistic subjects, but later reported a subgroup with hyperplastic vermal lobules VI and VII. Attempts to replicate their findings have drawn inconclusive results (Filipek, 1996). It should be emphasised that patients with an autistic disorder are neurobiologically a mixed group, some of whom suffer from epilepsy, some have associated learning disabilities and some suffer from specific syndromes related to learning disability (Deb, 1997). It is thus perhaps not surprising that different groups have found different neuroimaging abnormalities in autistic subjects. It is also possible that there is a subgroup of autistic subjects who show a specific cerebellar abnormality, although if so the characteristic of that subgroup is yet to be described. A handful of autopsy studies of autistic subjects also showed Purkinje cell abnormality in the cerebellum (Ritvo *et al*, 1986). In a recent report Schaefer *et al* (1996) concluded "that hypoplasia of cerebellar vermal lobules VI and VII is a non-specific finding that even occurs in several conditions with autistic behaviour". This conclusion was based on neuroimaging findings of 125 normal individuals with a broad age range, and 102 patients with a variety of neurological abnormalities. While the controversy regarding a specific cerebellar abnormality in autism continues, some recent MRI studies have drawn our attention to cerebral cortical abnormality, particularly in the parietal lobes, along with evidence of cerebral dysgenesis among autistic subjects (Piven *et al*, 1995). Although these studies are case-controlled, the reporting of MRI was qualitative rather than quantitative.

FRAGILE X SYNDROME

While Courchense *et al*'s (1988) observation of cerebellar vermal defect in autistic individuals received some publicity, similar brain abnormalities have recently been reported in patients with fragile X syndrome (Reiss *et al*, 1991*a*,*b*). Wisniewski *et al*'s (1991) earlier CT findings of mild brain atrophy associated with ventricular enlargement in eight out of 21 fragile X cases, may have been non-specific changes associated with learning disability rather than the fragile X syndrome *per se*. By using quantitative analysis of MRI, Reiss *et al* (1994) revealed right and left hippocampal volume to be significantly larger in the fragile X group. The fragile X subjects also showed an age-related increase in hippocampal volume and an age-related decrease in volume of the superior temporal gyrus. It is difficult to understand the significance of these findings. Although case-controlled, the cohort sizes in all three studies were small. No correlation was drawn between the length of the fragile X gene, the severity of learning disability and the type of abnormality in neuroimaging.

DOWN'S SYNDROME

Earlier CT studies of people with Down's syndrome showed smaller brains and intracranial volume along with basal ganglia calcification when compared with non-Down's syndrome controls (Schapiro *et al*, 1989); although after normalisation, the volume of cerebrospinal fluid, ventricles, and brain parenchyma did not differ in Down's syndrome subjects when compared with the controls. The age-related decline in cognitive performance was often reflected in the neuroimaging finding of increased cerebral atrophy with an increasing age in Down's syndrome subjects. By using a different quantitative method of mesial temporal CT measures to calculate the *suprasellar* cistern ratio (SSCR) (presumed to measure mesial temporal lobe atrophy or hypoplasias), Pearlson *et al* (1990) showed a correlation between SSCR and severity of cognitive impairment, even when age effects were removed, and predicted dementia status with an accuracy greater than 75%. A recent MRI study on an 18-month-old translocation Down's syndrome girl with epilepsy showed a significant delay in myelination in the white matter of the occipital, frontal, temporal, and parietal lobes, and branching of subcortical white matter was not demonstrated (Koo *et al*, 1992). The myelination seen in this patient was that expected in an 11-month-old infant. Delayed myelination has been shown in a number of conditions, including hypoxic ischaemia of the brain, delayed development, and migrational disorder. The degree of delayed myelination correlates well with the extent of developmental delay in children, and it is particularly important in relation to Down's syndrome as this finding was supported by autopsy studies. In Down's syndrome subjects structural neuroimaging findings correlate well with autopsy findings, and the age-related decline in cognition reported in the literature.

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CONCLUSION

The role of structural neuroimaging in the assessment of people with a learning disability is far from clear at present. Research should aim to include a well defined patient population in adequate numbers (if necessary by venturing into a multi-centre study) selected randomly from a general population to avoid a selection bias. A meta-analytic approach of pooled data may be a partial solution to overcome the problem of small cohort size used in many studies. Adequate control groups should be included, selected in the same way as experimental groups. In this context it makes sense to have both IQ-matched, and an average-IQ control group. Most importantly various centres have to collaborate to standardise and validate the quantitative techniques for structural neuroimaging. New MRI technology like functional MRI and magnetic resonance spectroscopy also hold great promise for future research in this field.

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