Structural brain imaging in biological psychiatry

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The application of X-ray CT and magnetic resonance imaging to the study of brain structure in psychiatry research is reviewed. In schizophrenia, CT showed minor enlargements of fluid spaces; MR has shown volume reductions in medial temporal lobe structures and, most recently, general cortical grey matter. In affective disorders, subcortical white matter lesions seem to characterise particular subgroups. In childhood autism, no clear consensus has emerged despite earlier claims for cerebellar pathology. In dementia, medial temporal changes can be detected reliably in Alzheimer’s disease and are of diagnostic and prognostic importance.

The advances made in in vivo structural brain imaging since the late 1970s have been central to the renaissance of biological psychiatry. The notion that ‘functional’ disorders, particularly the psychoses, might be underpinned by brain abnormalities was given crucial support by the demonstration, made possible by the new imaging technologies, that abnormalities of brain structure exist in some cases. In contrast to the organic psychoses, such as delirium and dementia, the functional psychoses had been seen essentially as disorders of mind rather than brain. If there were brain abnormalities, these were assumed to be a considerable way ‘downstream’, essentially comprising disturbances of software, rather than hardware.

Visual imaging of brain structure during life first became a possibility in the 1950s through the technique of pneumoencephalography. This essentially used the low electron density of air to act as an X-ray contrast medium, by introducing small volumes of air into the ventricles of the brain via a spinal tap. The procedure was lengthy, painful and hazardous. It was not until the second half of the 1970s that in vivo structural brain imaging using non-invasive, painless, relatively safe techniques became available. X-ray computed tomography owed its development in the main to the advent of fast computers, rather than any specifically radiological advances. CT imaging is based on the measurement of how different tissues differentially absorb X-rays, a property closely related to the electron density of the tissue. The resulting image of the brain distinguishes fluid from brain parenchyma and this led to the increasing use of quantitative image analysis methods to measure relative areas and volumes of brain and fluid spaces in psychiatric disease.
In research, magnetic resonance imaging has taken over from CT as the structural imaging technique of choice. Based on an entirely different set of transmission and emission principles, the images obtained are usually dependent on the proton density of tissues. Atomic nuclei comprise positively charged protons and neutral neutrons. Nuclei rotate and so, having both charge and spin, generate a magnetic field of finite strength and direction. When in an external magnetic field, interaction between the two fields induces a secondary 'wobbling' motion around the primary axis of spin: this is called 'precession'. Every isotope has its own frequency of precession within an external magnetic field of certain strength. Hydrogen, being very abundant in biological tissue, is the most important contributor to the magnetic resonance signal. Within a one Tesla magnetic field the hydrogen nucleus resonates at 42 MHz. What this means is that, if an external radio frequency signal is transmitted at this frequency, the spinning protons will be brought into phase. After the radio frequency pulse stops, the magnetization vector returns to its original direction by a process of ‘relaxation’. By convention, the time taken to relax back to the original state is determined by two time constants: $T_1$ and $T_2$. Energy emitted during various points of the relaxation process is picked up by detectors and used to create images ‘weighted’ to $T_1$ or $T_2$ parts of the relaxation curve. The different water content of grey and white matter can be used to generate excellent tissue differentiation. Other advantages of MR over CT are its safety and the relative ease of multiplanar imaging. Some artefacts of area and volume measurements applicable to CT are still constraints with MRI. In particular, the partial volume artefact can still be a difficulty especially when measuring small structures or convoluted surfaces. There is increasing use of very thin, contiguous slices down to 1–2 mm, as well as rapid image acquisition techniques which collect a complete 3D dataset, rather than a set of slices, allowing for resegmentation and reconstruction in other planes.

**Schizophrenia and affective disorders**

CT was central to schizophrenia research in confirming a biological focus for investigations into cause and mechanisms. As well the importance of structural imaging in redrawing the proper focus for investigation, the research findings have also been critical in generating hypotheses about the nature of brain abnormalities in schizophrenia.

The usual CT study of schizophrenia involved scanning a sample of schizophrenic patients, scanning a sample of non-schizophrenic controls, and comparing various parameters of the images obtained. However,
early on it became clear that any differences seen between patient and control groups were in the main quantitative rather than qualitative. Moreover, these changes were usually minor in degree, with considerable overlap between groups. Studies were soon seen to vary widely in the reported prevalence of abnormal findings and the most reasonable explanation of this lay in variation in the selection of patients, the choice of controls, and the methods of measurement\textsuperscript{1,2}. The ideal control group would seem to be healthy volunteers matched at least for age, parental social class, ethnicity and sex, prospectively scanned on the same machine during the same period. The most widely replicated finding was of slight enlargement of lateral ventricles in schizophrenia.

For most clinical variables mooted at one time or another to be related to ventricular enlargement on CT, there is little in the way of convincing replication. The appealing notion that negative symptoms and poor treatment response are characteristics of schizophrenia with ventricular enlargement does not have much objective support. The only associations that have more positive than negative replications are those of tardive dyskinesia and, most particularly, impaired performance on neuropsychological tests, although the specific areas of cognitive impairment tend to vary from study to study\textsuperscript{2}.

The lack of an association between length of illness and degree of lateral ventricular enlargement suggested that this enlargement is not progressive, either in the sense of reflecting a neurodegenerative disorder, or as being an artefact of continuing treatment or institutional care. This view received support from the demonstration of significant ventricular enlargement in young, first-episode patients. Direct evidence for the non-progressive nature of ventricular enlargement on CT is available from several follow-up studies which have rescanned patients after periods of up to seven years\textsuperscript{2}. The implication from the apparently non-progressive nature of the CT scan changes, was that they represent early neurodevelopmental abnormalities. This was reinforced by the increasing number of reports of congenital focal lesions.

There are several reports of gross focal brain lesions on CT and MRI in schizophrenia: for instance, aqueduct stenosis\textsuperscript{3}, arachnoid and septal cysts\textsuperscript{4,5} and agenesis of the corpus callosum\textsuperscript{6}. Three studies enable an estimate to be made of the prevalence of such focal lesions on brain imaging in schizophrenia. Owens \textit{et al}\textsuperscript{7}, in their series of 136 schizophrenic patients, found ‘unsuspected intracranial pathology’ as a focal finding on CT in 12 cases (9%), excluding lesions due to leucotomy. Five of these 12 were aged over 65. The study by Lewis and Reveley (in preparation) was an attempt to examine a geographically defined sample of RDC schizophrenic patients, ascertained as part of a large, multidisciplinary survey\textsuperscript{8}. In four (8%) of these 50 patients were found clinically unsuspected focal lesions: low density in the right caudate head;
a left occipitotemporal porencephalic cyst; low-density regions in the right parietal lobe; agenesis of the corpus callosum. None of 50 matched healthy volunteers showed focal pathology on CT. Using MRI, O'Callaghan and colleagues found definite focal neurodevelopmental lesions in 4 of 47 prospectively scanned cases of schizophrenia: one had partial agenesis of the corpus callosum. Given the differences in the nature of the patient samples, these three studies are in rough agreement about the prevalence of unexpected focal (usually neurodevelopmental) abnormalities on CT: between 6–9%.

As a technique, the inception of CT fuelled the renaissance of biological psychiatry in the 1970s. A torrent of early studies were more or less agreed that ventricular enlargement characterised a large proportion of patients with schizophrenia. Subsequently, there were reported several large, properly controlled studies which signalled caution about the initial enthusiasm. It is still fair to conclude that relative enlargement of third and lateral ventricles, and cortical sulci, is found in some schizophrenic patients, but the extent of these changes is probably not as marked as first thought. The failure of several rigorous studies to demonstrate these changes has yet to be explained. Variations in sampling methods of patients seems increasingly to be an important factor when appropriate control groups are used.

The first studies which applied structural MRI to schizophrenia essentially aimed to replicate the finding of enlarged fluid spaces, particularly lateral and third ventricles. The higher resolution structural imaging with MRI enabled lateral ventricular volume measurements to be made more easily. In a way reminiscent of the CT studies, the earlier studies noted a larger effect size than did the later studies. After initial studies replicating fluid space enlargement, several studies concentrated on measuring medial temporal lobe structures. Suddath et al reported a study of identical twins discordant for schizophrenia in which the affected twin consistently showed lateral and third ventricular enlargement compared to the unaffected co-twin, as well as reduced volume of temporal lobe grey matter including hippocampus. Reduced volume of the hippocampus-amygdala complex and parahippocampal gyrus is now a fairly well replicated finding in schizophrenia compared to healthy volunteer controls. Some studies have claimed that this reduction is more pronounced on the left than the right side in schizophrenia, but the balance of evidence suggests that the decrease is bilateral. Although decreased volumes in temporal lobe structures are probably bilateral in schizophrenia, correlates with clinical symptoms have been shown with decreased grey matter volume on the left. More or less intriguing associations have been reported between reduced superior temporal gyrus volume on the left with auditory hallucinations, and thought disorder.
Table 1  Is there decreased cerebral cortical volume in schizophrenia? MRI studies

<table>
<thead>
<tr>
<th>No of subjects (patients:controls)</th>
<th>Analysis controlled for</th>
<th>Cortical volumes patient vs controls: mean (SD); mls</th>
<th>% reduction in cortical grey; significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zipursky et al (1992) 22:20</td>
<td>Age, height, sex (all male) handedness, ethnicity</td>
<td>z-scores quoted</td>
<td>1.15 of 1 SD P &lt; 0.01</td>
</tr>
<tr>
<td>Harvey et al (1993) 48:34:26 BP</td>
<td>Age, sex, ethnicity, family SES, height, intracranial volume</td>
<td>Men 275 vs 264 normals, women 235 vs 225</td>
<td>Women 4.4%, men 4.0% P = 0.03</td>
</tr>
<tr>
<td>Schlaepfer et al (1994) 46:60:27 BP</td>
<td>Age, sex, family SES</td>
<td>688(97) vs 722 (73) normals vs 700 (90) BP</td>
<td>4.7% P = 0.07</td>
</tr>
<tr>
<td>Bäder et al (1994) 53:45 (first episode)</td>
<td>Age, height</td>
<td>Men 999 (114) vs 1038 (70), women 894 (85) vs 919 (90) BP</td>
<td>Men 3.8% NS</td>
</tr>
<tr>
<td>Pieri et al (1995) 17:15 (first episode)</td>
<td>Age, sex, ethnicity, family SES</td>
<td>704 (87) vs 746 (122)</td>
<td>5.6% P &lt; 0.01</td>
</tr>
<tr>
<td>Lim et al (1995) 29:53 (first episode)</td>
<td>Intracranial volume</td>
<td>z scores quoted</td>
<td>0.63 of 1 SD P &lt; 0.05</td>
</tr>
<tr>
<td>Lauriello et al (1995) 19:20</td>
<td>Age, sex (all female)</td>
<td>z scores quoted</td>
<td>1.2 of 1 SD P &lt; 0.01</td>
</tr>
</tbody>
</table>

The question remains whether the decreases in temporal lobe grey matter are truly limited to the temporal lobe in schizophrenia. Theoretical considerations have focused attention on this area, but recent MRI volumetric studies have suggested that more widespread volumetric decreases in grey matter are present. Harvey et al controlled for a variety of anthropometric and demographic variables, including height, parental social class, age and gender, and showed a small (6%) but significant reduction in diffuse cerebral cortical grey matter volume, but not white matter volume, in schizophrenic patients compared to controls. Zipursky and colleagues in a careful study reported the same finding. Importantly, the findings seem to be specific to schizophrenia rather than psychosis in general: two studies have found grey matter volume reduction in schizophrenic patients, but not in bipolar patients, compared to controls. In the Schlaepfer study, volumes of association cortex in dorsolateral prefrontal cortex, superior temporal gyrus and inferior parietal lobule, were particularly reduced, leading to the interpretation that heteromodal association cortex was principally affected. Table 1 reviews findings from all studies published to date which have examined cerebral cortical volume in schizophrenia. All have found a reduction of at least 4% compared to healthy controls, although this was not statistically significant in two studies.

These most recent findings with structural MRI in schizophrenia support a hypothesis that it involves a disorder of development of cerebral cortex, perhaps particularly association cortex, arising largely out of genetic factors. The cells that make up the central nervous system descend from ectodermally-derived neural tube cells. With a few exceptions, such as the cerebellum, cell proliferation occurs in a germinal, periventricular zone containing a growing area of post-mitotic cells. Neurogenesis is driven by gene products intrinsic to cells and by extrinsic factors such as growth factors. A cascade of gene-environment...
interactions controls cell migration to and within the cortex, thalamocortical axon development, apoptosis (cell death) and a series of further events. The cerebral cortical dysgenesis which seems to have been demonstrated by brain imaging in schizophrenia will be shown to have its origins in the genetic and epigenetic events controlling brain development.

In affective disorder, structural imaging studies have produced less of a consensus, although particular subgroups have yielded important findings. In late life depression, appearances of atrophy as well as an increased rate of subcortical white matter lesions have been shown\(^{20,21}\). Ventricular enlargement in depression seems to be more apparent in chronic samples, and has been correlated to psychotic symptoms. Krishnan et al.\(^22\) reported reduced basal ganglia volumes in depression and basal ganglia hyperintensities have also been reported. Increased rates of subcortical hyperintensities have been found in several studies of bipolar disorder, compared to controls\(^{23,24}\).

### Childhood autism

Once classified as a psychosis in childhood, autism is a developmental disorder whose cardinal features involve deficits in social communication and repetitive behaviour. The pure syndrome is rare compared to schizophrenia or affective psychosis and interpretation of structural brain changes made difficult by the varying degrees of mental impairment which accompany it. In a similar way to schizophrenia, several small series have shown a variety of neurodevelopmental lesions including porencephalic cysts, grey matter heterotopias and gangliogliomas\(^25\). Studies using CT to estimate ventricular size were largely inconclusive. In 1988, Courchesne and colleagues reported hypoplasia of the cerebellar vermis (lobules 6–7) in 18 patients compared to normal controls\(^26\). Despite wide publicity, these findings have been difficult for other groups to replicate and at least 4 negative studies now exist\(^27\). Most recently, the finding of increased brain size in a proportion of autistic subjects has been reported on MRI and by measuring head size\(^28\).

### Dementia

The clearest clinical application for structural brain imaging in psychiatry is in the diagnosis and assessment of dementias and focal organic brain syndromes. Either CT or MRI examination is mandatory in the clinical assessment of presenile dementia and many would argue that senile dementias presenting between the ages of 65–75 years also deserve
routine structural brain imaging. The purpose is firstly to rule out treatable although rare causes of dementia such as slow growing tumours, chronic subdural haemorrhage and normal pressure hydrocephalus. In Alzheimer’s disease, findings on CT are of progressive enlargement of lateral and third ventricles and cortical sulci which is earliest and most marked in medial temporal lobe regions. The appearances of cerebral atrophy are supportive of a diagnosis of dementia in the presence of clinical features and alongside other investigations such as neuropsychological evaluation and EEG. However, normal ageing is accompanied by reduction of brain volume by 5–10% by the age of 80, with enlargement of lateral and third ventricles and cortical cerebral sulci. Thus, the presence of cerebral atrophy on CT or MRI alone in diagnosing the presence of dementia is not a definitive diagnostic sign. Follow up rescanning, looking for progressive change, makes for a more accurate diagnostic test. Furthermore, high resolution MRI with quantitative measures of hippocampal atrophy appears to be a promising and sensitive marker for SDAT, successfully distinguishing cases from elderly controls or depressives in about 90% of instances.

On MRI, small areas of high signal subcortically, known as white matter hyperintensities, appear in about a third of healthy elderly subjects. Multi-infarct dementia similarly shows the appearance of generalised cortical atrophy, along with radiological evidence of deep lacunar infarcts in about 70% of cases. There is a large overlap with Alzheimer’s disease appearances. In Huntington’s disease, there is progressive atrophy of the caudate nuclei. Basal ganglia volumes have been noted to be decreased in presymptomatic individuals who are gene marker positive, although this is insufficiently sensitive to be of practical value. In HIV disease, structural imaging can be used firstly to exclude intracranial opportunistic infections such as cytomegalovirus, and lymphomas, and also to disclose the cerebral atrophy and periventricular white matter changes seen in the AIDS-dementia complex. Magnetic resonance imaging is useful in particular neurological disorders which may have psychiatric consequences: it is the method of choice to show the plaques of demyelinating disorders such as multiple sclerosis. Recent research suggests that MR of the hippocampus may become a more useful diagnostic tool in complex partial epilepsy of temporal lobe origin than is conventional EEG. Hippocampal atrophy in comparison to the unaffected side can usually be demonstrated with careful measurement.

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