

# 12 Imaging

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*Structural imaging • Functional imaging • Dementia • Affective disorders • Paraphrenia • Conclusion*

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## Structural imaging

Computerised tomography (CT), developed in the 1970s, allows a black and white image to be computed from multiple beams of X-rays. Magnetic resonance imaging (MRI) uses powerful magnets to alter the spin of hydrogen atoms. This allows mapping of their distribution. CT and MRI can be used to identify intracranial lesions such as tumours, abscesses, haematomas, haemorrhages, infarcts and normal pressure hydrocephalus. Quantification of changes in brain atrophy can be carried out using linear or area measurements of brain compartments. Computerised three dimensional displays of the brain allow the volumes of brain structures, like the hippocampus or temporal lobes, to be measured. Changes within the parenchyma of the brain, including white matter lesions, can be identified with MRI.

### **Box 12.1 Advantages and disadvantages of magnetic resonance imaging**

#### *Advantages*

- Distinguishes between temporal lobe and posterior fossa structures
- Gives a three dimensional display of the brain
- Sensitive to white matter lesions, distinguishes between grey and white matter
- Does not expose subjects to ionising radiation, particularly useful for repeated imaging

#### *Disadvantages*

- Some patients are unable to tolerate the claustrophobic scanners
- Magnets may displace pacemakers or metal in the body
- Calcified lesions are poorly visualised on MRI but clearly seen on CT
- MRI costs more than CT

## Functional imaging

Single photon emission computed tomography (SPECT) is a technique which involves intravenously injecting a radio-labelled tracer, and mapping its distribution in the brain. The radio-labelled compounds, depending on blood flow, are taken up and trapped by brain cells allowing a scanner to map their distribution. The scans can either be looked at, or quantities can be measured by comparing the radioactivity in different areas of the brain. Often the regions under study are compared with standards, such as 'total brain activity' or the activity of a 'neutral region', such as the occipital lobe in Alzheimer's disease. This gives a measure of regional cerebral blood flow (rCBF). Receptor populations can be mapped by injecting radio-labelled isotopes (radioligands) which bind to specific neurochemical receptors.

Positron emission tomography (PET) uses injected, radio-labelled material to measure blood flow, regional metabolism and receptor populations. The half-lives of the radio-labels used in PET are much shorter than in SPECT ( $^{15}\text{O}$  has a half-life of two minutes while  $^{18}\text{F}$  has a half-life of 110 minutes), and therefore need to be made on site, using a cyclotron. This makes PET extremely expensive and only available to a few centres. Using  $^{15}\text{O}$  labelled water, subjects can be imaged repeatedly in the same session, under different states. This allows brain activity to be measured in response to external sensory stimuli, voluntary movement, cognitive tasks and drugs.

Magnetic resonance spectroscopy (MRS) is a technique used to measure metabolites in the brain, giving the concentrations in the regions studied. It has the advantage of being a functional scanner which does not expose the subjects to radiation, so it is useful for repeated imaging. It has the disadvantage of being claustrophobic for some patients. At present it is exclusively a research tool.

### **Box 12.2 Advantages and disadvantages of positron emission tomography**

#### *Advantages*

Higher resolution and greater sensitivity than SPECT  
 Shorter half-life radio-labels allow more activation studies to be carried out in a session  
 More precisely quantified, whereas SPECT is used qualitatively or semi-quantitatively

#### *Disadvantages*

Very much more expensive than SPECT  
 Only available in a few specialist centres  
 Less patient friendly

**Table 12.1** Brain-imaging techniques and main uses

	Techniques	Main use
Computed tomography	Structural	Diagnosis
Magnetic resonance imaging	Structural	Diagnosis
Single photon emission computed tomography	Functional	Diagnosis and research
Positron emission tomography	Functional	Research
Magnetic resonance spectroscopy	Functional	Research

## Dementia

### Computerised tomography

The main value of CT in dementia is to exclude intracranial pathology. Space occupying lesions such as tumours, abscesses or haematomas, and lesions giving rise to altered ventricular size such as normal pressure hydrocephalus, can be identified. About 5% of patients with dementia have these lesions (Philpot & Burns, 1989).

The presence of infarcts has been used to differentiate vascular dementia from Alzheimer's disease. There are more white matter lesions in patients with Alzheimer's disease than in normal subjects, although this differentiation is not absolute and normal subjects often have vascular lesions.

In ageing and dementia, the brain atrophies (shrinks). Atrophy is identified by measuring the size of the ventricles and sulci in one of four ways: visually; linear changes on a standard section; area changes; and volume changes of the relevant spaces.

CT studies usually use linear or area measures, the latter being more sensitive. With ageing there is cortical atrophy and lateral ventricular enlargement. These tend to be greater after the age of 60, and correlate with age and cognitive impairment. In dementia, the third ventricle also enlarges and this correlates with cognitive impairment. Although measures of atrophy are greater in patients with dementia than controls, there is an overlap, and a diagnosis cannot be made on CT alone. However, follow-up CT scans, after a year, show that ventricular size increases much more rapidly in dementia than in normal ageing. A sensitivity and specificity of diagnosis approaching 100% can be made on serial scans (Luxenberg *et al.*, 1987).

Specific syndromes in Alzheimer's disease may be associated with regional atrophy, such as delusional misidentification and accentuated right frontal degeneration. In Creutzfeldt–Jakob disease, atrophy is found in around 80% of cases.

## **Magnetic resonance imaging**

MRI is more sensitive than CT at detecting white matter lesions. In Alzheimer's disease grey matter volumes are reduced, while white matter volumes are unchanged. This is particularly marked in the temporal lobe, which is consistent with the cortical cell loss found in pathological studies.

### *Hippocampal volumes*

MRI is used to measure the volumes of the hippocampus, amygdala and temporal lobe. These volumetric measurements, corrected for brain size, are smaller in disease, and have been shown to accurately distinguish Alzheimer's disease from normal ageing, without overlap (Kesslak *et al*, 1991). Furthermore, hippocampal volumes are smaller in patients with age associated memory impairment than in normal ageing, and are similar to patients with Alzheimer's disease.

Hippocampal atrophy also occurs in vascular dementia, Parkinson's disease with dementia, and to a lesser degree, in Parkinson's disease without dementia. Hippocampal volume correlates with memory scores in Alzheimer's disease and Parkinson's disease with dementia, but not in vascular dementia or Parkinson's disease without dementia. This may reflect the presence of Alzheimer's disease pathology, in dementia associated with Parkinson's disease (Laasko *et al*, 1996).

Apolipoprotein E4 alleles appear to predispose people to Alzheimer's disease. They are also associated with more severe neuropathological changes, particularly amyloid deposition. MRI studies have shown that Apo E4 alleles are associated with greater volume loss in the hippocampus and amygdala, but not the frontal lobes (Lehtovirta *et al*, 1996).

### *White matter lesions*

The image in MRI is compiled from measurements of proton behaviour following excitation by magnetic pulses. The behaviour of greatest interest is the 'relaxation time', which is the time taken for excited protons to return to their pre-stimulus positions. Relaxation time reflects the water content of tissue, and is altered in a number of diseases. In Alzheimer's disease it is prolonged in the hippocampus, although there is significant overlap with controls.

White matter lesions, associated with long relaxation times, are found more often in vascular dementia than Alzheimer's disease (Erkinjuntti *et al*, 1987). The lesions are more severe. White matter lesions in Alzheimer's disease tend to be associated with vascular risk factors, particularly hypertension, and are also found in normal ageing. Hypertension is itself associated with brain atrophy and white matter abnormalities. Furthermore, hypertensive patients, without severe white matter changes, have reduced cerebral metabolism, but normal neuropsychological

performance. The reduction in metabolism is small, and greatest in the vascular water-shed regions of the brain, a distribution different from the metabolic pattern seen in Alzheimer's disease. This evidence suggests that white matter lesions can be helpful in the diagnosis of dementia.

In Creutzfeldt–Jakob disease MRI shows diffuse cerebral atrophy and deep white matter lesions. There are bilateral, symmetrical, paired areas of increased signal in the lentiform nucleus. Regions of bilateral, increased relaxation times occur in hypoxic and ischaemic damage, such as carbon monoxide poisoning.

## **Single photon emission computed tomography**

### *Alzheimer's disease*

Regional cerebral blood flow reflects the severity of dementia. In Alzheimer's disease there is a characteristic picture of reduced rCBF in the temporal and posterior parietal lobes. This is consistent with neuropathological changes and neuropsychological testing (Burns *et al*, 1989). In early Alzheimer's disease these changes may be undetectable, or confined to the temporal lobes. As the disease progresses reduced rCBF is seen in the temporal and posterior parietal cortex, then more globally. In more severe Alzheimer's disease reduced rCBF is found in the frontal cortex.

Reduced rCBF correlates with deficits on neuropsychological testing. In the early stages, the most profound correlations involve temporal and posterior parietal rCBF, and global scores of dementia, praxis and language (Burns *et al*, 1989). As the disease progresses, reduced frontal rCBF correlates with neuropsychology (Brown *et al*, 1996). Using clinical criteria the rate of accurate diagnosis of Alzheimer's disease is around 75%. With SPECT this increases to over 90% (Read *et al*, 1995).

Physostigmine (a short acting acetylcholinesterase inhibitor) increases performance in some memory tasks in Alzheimer's disease. SPECT studies have shown that it is associated with increased left cortical and frontal rCBF. Tacrine (another acetylcholinesterase inhibitor) increases right temporal rCBF in Alzheimer patients whose performance improves on memory tasks (O'Brien, 1996). These studies suggest SPECT can play an important role in providing objective evidence of improvement with the new acetylcholinesterase inhibitors, such as donepezil.

Patients with Alzheimer's disease and delusions, have reduced temporal rCBF compared to non-delusional patients with the same severity of disease. Patients with hallucinations have relatively increased parietal rCBF (Kotrla *et al*, 1995).

### *Age associated memory impairment*

In age associated memory impairment there are perfusion deficits between those of Alzheimer's disease and controls. The reduced rCBF correlates

with global cognitive impairment. This finding, together with the finding that hippocampal volumes are similar to Alzheimer's disease, suggests that the two conditions are on a continuum rather than being distinct entities (Parnetti *et al*, 1996).

### *Vascular dementia*

Multi-infarct dementia is associated with focal deficits of rCBF, corresponding to ischaemic lesions. The contrast between the temporal and parietal reduced rCBF found in Alzheimer's disease, and the irregular perfusion deficits found in vascular dementia, mean that SPECT can play a role in the differentiation between these two conditions.

### *Lewy body dementia*

Lewy body dementia is a relatively new type of dementia characterised by a fluctuating cognitive impairment, visual hallucinations and marked sensitivity to the extrapyramidal side-effects of neuroleptics. Preliminary data suggest that patients with Lewy body dementia show reduced temporal and parietal rCBF, in a similar picture to Alzheimer's disease (Read *et al*, 1995).

### *Frontotemporal dementia*

Frontotemporal dementia accounts for around 15% of primary degenerative dementia. It is characterised by behavioural changes and frontal lobe neuropsychological deficits. Patients with this condition have reduced frontal or frontotemporal rCBF. Post-mortem pathology demonstrates an absence of plaques and tangles, but marked frontal gliosis and neuronal loss. Pick bodies are found in a quarter to a half of cases. In Creutzfeldt–Jakob disease, irregular dispersed mottled deficits are found.

## **Positron emission tomography**

### *Coupling*

PET allows CBF and cerebral metabolic rates for oxygen and glucose to be measured. Generally speaking, CBF and cerebral metabolism change together (i.e. they are coupled). However, in ageing (which is associated with declining blood flow and metabolism), the blood flow declines faster. This is because neurones relatively increase their oxygen extraction from the blood. Uncoupling can also occur in certain pathological processes, the principal one being vascular disease.

CBF and oxygen metabolism decline in Alzheimer's disease and vascular dementia, and this decline is more severe as the dementia advances. In vascular dementia, oxygen extraction increases in order to meet the oxygen

requirements of active tissue, in the presence of a declining blood supply. In Alzheimer's disease reduction in the metabolic requirements of the ailing neurones means that lower blood flow adequately meets the oxygen demand.

In other words, the decline is coupled in Alzheimer's disease, but uncoupled in vascular dementia. This is useful in differentiating the two conditions. It also demonstrates the complex relationship between blood flow, metabolism and disease.

### *Alzheimer's disease*

In Alzheimer's disease the cerebral metabolic rate for glucose is reduced by 20 to 30%. The reduction correlates with cognitive impairment. The pattern of impairment in glucose and oxygen metabolism mirrors that of cerebral blood flow (i.e. reductions occur in the temporal and posterior parietal lobes). Deficits in early dementia may be asymmetrical. Longitudinal studies, one to two years apart, show that in mild to moderate dementia, metabolism in the parietal cortex decreases faster than in the frontal cortex. In the severely demented, metabolism in the frontal cortex falls faster (Jagust, 1988).

Patients with familial Alzheimer's disease show no difference in regional glucose metabolism from sporadic cases. However, patients with early-onset Alzheimer's disease show different patterns of regional glucose metabolism to late-onset Alzheimer's disease. Metabolic impairment is found mainly in the frontal and parietotemporal cortices in the early-onset group, whereas there are more global reductions in the late-onset group (Guze *et al*, 1992).

Extrapyramidal signs, particularly rigidity and tremor, are found in some patients with Alzheimer's dementia. Dopamine receptor imaging, using 18-fluorodopa, shows no difference in basal ganglia uptake between normal controls and rigid, and non-rigid, patients with Alzheimer's disease. In contrast, patients with Parkinson's disease show a marked reduction in 18-fluorodopa uptake in the basal ganglia, demonstrating that the extrapyramidal syndrome in Alzheimer's disease may have a different pathogenesis to Parkinson's disease (Tyrrel *et al*, 1990). In Creutzfeldt-Jakob disease, areas of diffuse hypometabolism occur, corresponding to spongiform changes.

### **Magnetic resonance spectroscopy**

MRS allows a number of brain metabolites to be measured. Proton spectroscopy and phosphorus spectroscopy are the two most commonly used techniques.

#### *Proton spectroscopy*

Proton spectroscopy is used to measure N-acetylaspartate, which is a marker of neuronal damage and the most commonly studied metabolite.

### Box 12.3 Imaging in Alzheimer's disease

CT: trophy, including third ventricle, correlates with cognitive impairment, increases rapidly  
 MRI: reduced grey matter, hippocampus, amygdala and temporal lobes volumes  
 SPECT: characteristic reduction in blood flow in temporal and parietal regions  
 PET: reduced blood flow and metabolism in temporal and parietal regions  
 MRS: abnormal synthesis of membrane phospholipids early in the disease

N-acetylaspartate is reduced in patients with Alzheimer's disease and this correlates with the number of senile plaques and neurofibrillary tangles. N-acetylaspartate is also reduced in Creutzfeldt-Jakob disease.

### *Phosphorus spectroscopy*

Phosphorus spectroscopy allows the direct measurement, *in vivo*, of brain membrane phospholipid metabolism. Phosphomonoesters reflect the rate of synthesis of membrane phospholipids, and phosphodiester reflect the rate of degeneration of membrane phospholipids. In ageing, phosphomonoesters decrease while phosphodiesters increase. In Alzheimer's disease, phosphomonoesters increase early in the course of the disease. Later, phosphomonoester levels correlate negatively, and phosphodiester levels correlate positively, with the number of senile plaques (Pettegrew *et al*, 1988). This suggests that abnormalities in the synthesis of membrane phospholipids occur early in Alzheimer's disease. This technique may help to differentiate Alzheimer's disease and vascular dementia.

### Box 12.4 Imaging in vascular dementia

CT: increased number of infarcts  
 MRI: white matter lesions are more numerous and severe than in Alzheimer's disease  
 SPECT: irregular perfusion deficits  
 PET: cerebral blood flow and metabolism reduced and uncoupled  
 MRS: absence of phospholipid changes allow differentiation from Alzheimer's disease

## Affective disorders

### **Computerised tomography**

Late-onset depression is associated with cortical atrophy and ventricular enlargement. The CT scan appearances are closer to subjects with dementia than controls. Cortical CT density is reduced, while caudate density is increased. Patients with greater cortical atrophy have a reduced life expectancy. Patients with depressive pseudo-dementia have increased lateral ventricular size and decreased tissue density counts.

### **Magnetic resonance imaging**

MRI shows elderly depressed patients to have more atrophy than controls. Changes include: sulcal atrophy; larger Sylvian fissures; larger ventricles; more basal ganglia lesions; smaller caudate nuclei, putamen and hippocampal volumes; and more subcortical hyperintensities.

Hippocampal atrophy increases with age in Alzheimer's disease and depression (O'Brien *et al*, 1994). Using visual semi-quantitative measures of hippocampal atrophy it is possible to differentiate up to 90% of patients with Alzheimer's disease from major depression. Depressed patients with delusions do not differ from those without delusions on any MRI measure (Rabins *et al*, 1991).

### ***White matter lesions***

There are two types of white matter lesions: those adjacent to the ventricular system, periventricular white matter lesions, and those separate from the ventricles, in deep white matter.

Periventricular white matter lesions and deep white matter lesions are both more common in depression. However, periventricular white matter lesions occur more frequently in Alzheimer's disease than depression, and deep white matter lesions are found in a number of conditions including multi-infarct dementia, multiple sclerosis, hydrocephalus and Binswanger's disease

In depression, deep white matter lesions tend to occur in the left basal ganglia and, to a lesser extent, the right frontal area. They are associated with sporadic, late-onset depression, psychomotor retardation and poor prognosis (O'Brien *et al*, 1996). Deep white matter lesions may represent a biological factor predisposing the elderly to depression.

Some studies have linked deep white matter lesions with cognitive impairment, but this is not a universal finding. Deep white matter lesions are significantly increased in late-onset mania. Lesions occur in equal frequency in both hemispheres. Otherwise, there is no difference from controls in terms of ventricular size or the presence of periventricular white matter lesions.

**Box 12.5 Imaging in depression**

CT: cortical atrophy and ventricular enlargement

MRI: atrophy, ventricular enlargement, basal ganglia and white matter lesions

SPECT: reduced rCBF, sparing the posterior parietal cortex

**Single photon emission computed tomography**

SPECT studies in elderly patients with depression have found reduced global blood flow and reduced rCBF in the anterior cingulate, frontal and temporal areas, but no reduction in the posterior parietal cortex. This may be helpful in distinguishing patients with depression from Alzheimer's disease (Curran *et al*, 1993). Depressed patients who have larger areas of white matter intensity on MRI have lower rCBF.

**Paraphrenia****Computerised tomography**

CT studies have found that in paraphrenia there is dilation of the lateral ventricles, but the degree of cortical atrophy is normal for the patient's age. People with paraphrenia with Schneiderian first rank symptoms have more cerebral atrophy, particularly in the left frontal lobe (Howard *et al*, 1992).

**Magnetic resonance imaging**

Patients with paraphrenia have greater lateral and third ventricular volumes than controls. When patients are subdivided into schizophrenia or delusional disorder, enlargement is slightly more marked in the delusional disorder group. Temporal lobe volumes were smaller in patients with delusional disorder than with schizophrenia, or controls (Howard *et al*, 1994).

White matter lesions are not found more frequently in paraphrenia. Periventricular white matter and subcortical grey matter hyperintensities are associated with raised blood pressure. Furthermore, these lesions and deep white matter lesions are associated with increasing age (Howard *et al*, 1995).

**Conclusion**

The role of imaging is shifting from predominantly research, to clinical investigation and diagnosis. Structural imaging remains of greatest clinical

value in identifying brain lesions in the elderly such as tumours, infarcts, vascular malformations and hydrocephalus. CT and MRI are also useful at measuring focal and global atrophy and the volumes of specific brain regions. This is particularly informative when done serially. Functional imaging offers the promise of a greater understanding of the physiological processes in mental illnesses in the elderly. SPECT is the most widely available technique and can offer information to aid diagnosis and treatment plans. Imaging is increasingly becoming part of a full, clinical assessment in old age psychiatry.

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