Neuroimaging and depression

Depression is a common mental health problem in older adults. Although there is a lot of overlap between depression in the elderly and younger age groups, elderly depressed patients are more likely to present with biological symptoms of depression, cognitive impairment and complain of physical symptoms. They are also more likely to suffer from depression due to organic problems and have physical health comorbidities. Studies have shown a wide range of brain structural and functional abnormalities in elderly depressed patients.

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Until the advent of computerised tomography (CT) scans in 1972, the living brain was not accessible for clinical or scientific investigation.\(^1\) Magnetic resonance imaging (MRI) scanners entered clinical practice a decade later and soon became the test of choice for imaging the central nervous system (CNS) due to the superior quality of their images and the fact that they did not expose the patient to harmful radiation.

MRI techniques were developed further to allow the study of the function of different areas of the brain through measuring the blood flow to those areas as well as studying a variety of metabolic processes in the brain. Other techniques which have developed more recently use radio-labelled material to study various biochemical processes and receptors of the brain. These techniques have been used in studies designed to understand pathological processes in the brain such as effects of the psychotherapeutic drugs on the brain receptors.\(^2\)

There is a substantial literature available on neuroimaging techniques, their applications and findings in old age depression.\(^3\) Various methods have been used to study the structural and functional abnormalities in the brains of people with depression compared with normal controls. They can also be used on the same patient to compare times of depression and periods of normality, in order to refine models of disease pathophysiology in mood disorders, better understanding the mechanisms of action of antidepressant medications and to help develop better treatments for these conditions.\(^4\)

Depression in the elderly

Old age depression is perhaps the most common cause of emotional suffering and poor quality of life in this age group.\(^5\) It has been identified as an independent risk factor for mortality in the elderly. There is an association between severity and chronicity of depression and an increased mortality rate among these patients.\(^6\) Recurrent major depressive disorder is a very strong risk factor for suicide among the elderly.\(^7\) This condition is also associated with a greater decline in physical ability,\(^8\) decreased cognitive and social functioning and greater self neglect.\(^9\)

Box 1 outlines a summary of the classification of mood disorders and box 2 presents the diagnostic criteria for an episode of depression from the
Box 1: ICD-10 classification of mood disorders

Manic episode: Single episode, with no previous history of mood disorder
Bipolar affective disorder: A disorder characterised by two or more episodes of significant disturbance in mood and activity level, consisting on some occasions of elevation of mood, increased activity and energy levels (mania or hypomania), and on others of depression
Depressive episode: Mild, moderate or severe depressive episodes (see Box 2)
Recurrent depressive disorder: A disorder characterised by repeated episodes of depression as described for depressive episode
Persistent mood (affective) disorders:
• Cyclothymia: persistent instability of mood involving numerous periods of depression and mild elation, none of which sufficiently severe or prolonged to justify a diagnosis of bipolar affective disorder
• Dysthymia: chronic depression of mood, lasting at least several years, not severe enough, or individual episodes long enough to justify a diagnosis of mild, moderate or severe depressive disorder
Other mood (affective) disorder: Any other mood disorder which cannot be classified to the above categories.

International Classification of Diseases, version 10. Although there is a lot of overlap between depression in younger and older people, older adults are less likely to complain of feeling sad or low in mood when they are depressed, and are more likely to present with somatic symptoms or disproportionate complaints associated with physical disorder, pain, behavioural problems, report insomnia, or present with psychotic symptoms.

A high proportion of depressed elderly patients present with psychomotor slowness or agitation. Delusional beliefs concerning poverty and physical illness are common among those with severe depression. They occasionally express nihilistic delusions, for example believing that their body is empty, not functioning or even non-existent (Cotard’s syndrome). Hallucinations of accusatory and obscene nature may also be present.

Some elderly depressed patients present with a syndrome called depressive pseudo-dementia. These patients mainly complain of difficulty concentrating and remembering things, but careful clinical examination shows that there is no major problem with their memory. Differentiating these patients from those with early stages of dementia (who could also suffer from depression at the same time) is important and can be difficult at times.

In patients with depressive pseudo-dementia the subjective complaint of memory problems may be greater than the informant’s account of problems with their memory and its effect on their day-to-day life. The onset of depressive symptoms in these patients often predate the memory difficulties and they may have a personal or family history of depression. Their engagement with psychological tests to evaluate their memory is often poor, typically replying “I don’t know” to questions and they may suffer from psychomotor retardation.

Older adults seem to be at a greater risk of developing depression due to biological compared with psychological and social factors than younger age groups. There is a strong association between depression and a variety of organic conditions such as stroke, Parkinson’s disease, Alzheimer’s disease, chronic pain, cardiac, respiratory and rheumatological diseases in the elderly. An increasing body of evidence also shows a complex and bidirectional relationship between late life depression and vascular disorders. There is a high prevalence of depression among patients with cardiovascular disorders, stroke and white matter ischaemic changes, and on the other hand, depression is believed to be a risk factor for cardiovascular disorders. A diagnosis of “vascular depression” is made in a subgroup of elderly depressed patients. This is conceptually different from post-stroke depression. Compared with non-vascular cases, patients with vascular depression present with milder depressive symptoms, more cognitive impairment,
Box 2. ICD-10 diagnostic criteria for depressive episode

The episode has been present for at least two weeks; there has been no history of a manic or hypomanic episode in the person’s life and the current symptoms are not attributable to psychoactive substance misuse or an organic mental illness.

A: At least two of the following three symptoms
- Depressed mood
- Loss of interest/pleasure
- Decreased energy or increased fatigability

B: Additional symptoms from the following list
- Loss of confidence or self-esteem
- Unreasonable and excessive feelings of self-blame or guilt
- Self-harming or suicidal thoughts or behaviours
- Poor concentration or indecisiveness
- Psycho-motor agitation or slowness
- Sleep disturbance of any type
- Changes in appetite (and/or weight)

Mild depressive episode: At least two of list A and one or more of list B (total of at least four symptoms)
Moderate: At least two of A and additional from list B (total of at least six)
Severe: All three from list A and additional symptoms from list B (a total number of at least eight symptoms).

Psychomotor slowing, poorer insight, higher level of disability, and higher rates of white matter or sub-cortical grey matter lesions in the brain.¹⁰

Structural brain imaging

Computerised tomography (CT) scans

CT scanners take a series of X-ray pictures of the head from all angles. The amount of radiation which passes through (ie. not absorbed by) the different tissues from each angle is then detected and the related data are fed into a computer, which will process and construct a set of two dimensional images. When viewed in sequence the CT scan images allow a mental reconstruction of the shape of the brain to be made.²

A CT scan provides a low resolution for anatomical structures of the brain but is good in discriminating between the brain and the surrounding cerebrospinal fluid or in the ventricular system.¹⁸ CT scanning is useful in detecting space occupying lesions, atrophy, changes in the ventricular volume and morphology and calcifications, for example in the basal ganglia.¹⁹%

This technique, however, has a number of limitations, such as exposing the patient to ionizing radiation, lower spatial resolution compared with MRI scans, and reduced sensitivity to distinguish between the grey and white matter in the brain.⁴ Certain tumours may also be invisible on a CT scan because they absorb as much radiation as the surrounding brain tissue, although intravenous injection of a contrast agent can be helpful in such cases.²

Although CT has been supplanted by MRI as the non-emergency structural neuroimaging of choice,² it is nevertheless still widely used, since it is readily available.¹⁹

Magnetic resonance imaging (MRI) scanning

MRI technique does not use X-rays to obtain images. It uses signals from protons, usually the hydrogen atoms in water molecules. This technique is based on nuclear magnetic resonance (NMR). It is thought that the nuclei of all atoms spin around an axis which is randomly oriented in the space.
When a strong enough external magnetic field is applied the axis of all odd-numbered nuclei align with the axis of the magnetic field. When a brief resonant radiofrequency pulse is applied to these atoms at a certain angle, their axis deviates briefly from the axis of the magnetic field and when the pulse ends they realign with the axis of the field. They emit their own radiofrequency signal during realignment. The signal emitted from these realigning nuclei is detected by the MRI machine sensors and processed by computer to produce two-dimensional images, which represent the brain. These images can be obtained in sagittal, axial or coronal planes.\(^3\)

MRI scanning is the structural brain imaging of choice due to its superior spatial resolution, lack of ionising radiation and improved soft tissue contrast, but has its own limitations. In particular patient movement can blur the image. MRI cannot be used for people with any kind of metallic implants, such as cardiac pacemakers, cerebral aneurism clips etc.\(^19\)

**Magnetic resonance spectroscopy (MRS)**

Routine MRI technique detects hydrogen atoms in order to picture the brain structures. MRS uses the same principles to detect several odd-numbered nuclei, such as Hydrogen (1H), Lithium (7Li), Carbon (13C), Nitrogen (14N), Oxygen (17O), Fluorine (19F) etc. The ability of this technique in detecting a range of biologically important atoms makes it possible to study many metabolic processes in vivo without the use of radioactive chemicals. The output of the MRS machine is usually in the form of a spectrum, although this could be converted into a pictorial representation of the brain.\(^2\)

### Structural brain abnormalities in depression

Several studies have consistently reported structural brain abnormalities among patients with depression.\(^4,20\) Jacoby and Levy (1980) used CT scanning for first time to compare the brain morphology in depressed and normal individuals. They found a higher prevalence of ventricular enlargement in a cohort of 41 elderly depressed patients, compared with a group of 50 healthy controls (who were matched for age, sex and social class with the depressed group). They identified a subgroup of depressed patients with ventricular enlargement who had a higher age of onset of depression, and showed more “endogenous” symptoms of depression than other patients.\(^21\)

In a follow-up study they found a significantly higher (two year) mortality rate among the depressed patients who had previously displayed ventricular enlargement on CT.\(^22\)

Later volumetric studies using MRI have reported structural abnormalities in areas of the brain implicated in the regulation and expression of emotions.\(^4\) A meta-analysis of studies using MRI to assess the hippocampal volume showed smaller hippocampal volumes in depressed patients compared with normal individuals.\(^23\) Another meta-analysis performed slightly later also found that despite heterogeneity of studies in terms of age, gender, average number of episodes and responsiveness to treatment, the effect of depression was significant in both hemispheres for patients with unipolar depression. This study found an average reduction of hippocampal volume of 8% in the left and 9% in the right side. It also found that the total number of depressive episodes was significantly correlated with hippocampal volume reduction on the right, but not on the left side.\(^24\)

Although the amygdala is important in the processing and interpretation of the emotions, studies assessing changes in the amygdala in depression have provided more inconsistent results. This could be due to the fact that the amygdala consists of multiple nuclei with difficult to define borders.\(^20\)

Studies have also showed cortical grey matter volume reduction in subgenual prefrontal cortex, orbital frontal cortex and anterior cingulate cortex, mainly in patients with unipolar depression.\(^20\)

There is evidence showing a bidirectional association between depression and vascular disease.\(^15,25\) Periventricular and deep subcortical white matter lesions are a common incidental finding in the brain MRI scans of the elderly. These are often due to vascular changes and ischaemia of the brain tissue.\(^26\) These lesions have been found to be associated with worse prognosis\(^27,28\) and poorer response to treatment with antidepressant medications\(^29,30\) or ECT.\(^21,32\)
Functional brain imaging

Functional magnetic resonance imaging (fMRI)

Neuronal activity in the brain causes an increase in the local blood flow to the functionally active areas (and therefore an increase in the level of oxygenated haemoglobin in these areas). The difference in the level of oxygenated haemoglobin can be detected by the MRI machine to produce images of the areas of the brain which are activated whilst performing different tasks, or at rest. This forms the basis of the blood oxygen level dependent (BOLD) fMRI. Another fMRI technique called arterial spin labelling (ASL fMRI) uses magnetically tagged water as a source of signal to identify the activated areas.

fMRI offers a dynamic composite of brain activity in contrast to the structural imaging techniques, which only give a snapshot of the neuroanatomical regions of the brain. Sensitivity and spatial resolution of the fMRI images are low compared with structural techniques. Acquisition of images can take much longer than the structural MRI (between 20 minutes to three hours). The subject’s head must remain in exactly the same position during this time.

Single photon emission computed tomography (SPECT) scanning

SPECT uses manufactured compounds labelled with single photon-emitting isotopes of elements such as Iodine-123, Technetium-99m and Xenon-133 to study regional differences in the blood flow of the brain. This is a high resolution imaging technique, which records the pattern of single photon emission in various areas of the brain to provide a representation of regional blood flow and thereby regional activity level. SPECT images are sometimes superimposed on an MRI or CT scan image obtained before SPECT, in order to improve the accuracy of the anatomical location for the functional information.

In addition to measuring blood flow, radiolabelled compounds with affinity for muscarinic, dopaminergic and serotonergic receptors (ligands) can also be used to study receptors with SPECT technology.

Positron emission tomography (PET) scanning

PET uses radio-isotopes, which are unstable, have an excess of proton and emit positrons when they decay. Positrons travel a distance of 1–3mm before colliding with an electron. This collision produces two photons (gamma rays) which travel at 180 degrees from each other. These gamma rays are then detected by a range of radiation detectors placed around the head to produce images of the areas of brain containing various amounts of the radio isotope. The most commonly used isotopes are Fluorine-18 (18F), Nitrogen-13 (13N) and Oxygen-15 (15O). These atoms are usually bound to another molecule (with the exception of 15O), such as [18F] fluoroexyoglucose (FDG), which is used as an analogue of glucose that the brain picks up but cannot metabolise, or molecules which act as ligands with an affinity for the various receptors etc.

PET scanning can be used for a variety of functional assessments, such as cerebral blood flow (CBF), oxygen extraction fraction (OEF), cerebral glucose metabolic rate (CMRglu), receptor binding and occupancy and a range of metabolic processes.

Diffusion tensor imaging

This is an imaging technique based on magnetic resonance technology to study the diffusion of water in the tissues. It is ideal for studying the brain white matter and the integrity of the neural tracts.

Functional brain abnormalities in depression

Functional neuroimaging techniques have shown a range of perfusion, metabolic and cell surface abnormalities in limbic and prefrontal structures of the brain in patients with mood disorders.

In a recent study Staffen et al compared regional cerebral perfusion, using HMPAO-SPECT scan in 127 patients with depression and cognitive impairment (DCI), 149 with a diagnosis of mild cognitive impairment (MCI), 131 with dementia of Alzheimer’s type (DAT) and 123 controls without any cognitive impairment. DCI patients showed a hypoperfusion of the thalamus, lentiform nucleus and medial temporal cortex compared with the control group. Patients with MCI showed a different perfusion pattern compared with the control group in both hemispheric temporal and parietal areas and posterior part of the cingulate cortex in the right side. DAT patients showed a more...
extensive reduction in global and regional forebrain perfusion which discriminated them from all other groups.

Kenny et al (2010) used resting-state fMRI to compare brain connectivity (as measured by spatial synchrony of spontaneous low-frequency fluctuations in blood oxygenation level between the areas) in patients with late life depression (LLD) and normal controls. They found a different pattern of functional connectivity between the head of caudate nucleus in both sides and other areas of the brain in depressed and non-depressed people. Areas of significant functional connectivity with the head of the caudate nucleus in the non-depressed subjects were predominantly frontal, whereas in LLD patients significant connectivity was observed to a much wider area in the brain.35

Low metabolic ratios of N-acetyl-aspartate/Creatine (Cr), choline/Cr and myo-inositol/Cr, as well as high absolute concentration of creatine has been found in the frontal brain of depressed patients compared with controls, using MRS scanning.36

A follow up study of depressed patients who were treated with the antidepressant medication sertraline found an increase in functional connectivity between the anterior cingulate cortex and limbic regions after six weeks of treatment, using fMRI technique.37 Significant metabolic changes have been reported in brains of patients whose depression improved following a course of CBT. PET scan showed an increase in glucose metabolism in the hippocampus and dorsal cingulate and a decrease in the same parameter in dorsal, medial and ventral frontal cortical areas.38 Elderly depressed patients who fail to respond to treatment with antidepressant medications have been found to have lower fractional anisotropy (due to white matter microstructural abnormalities) in multiple frontal limbic areas such as anterior cingulate, dorsolateral prefrontal cortex, genu of the corpus callosum, white matter near hippocampus, multiple posterior cingulate cortex regions and insular white matter, compared with those who do respond to these medications.39 Such studies aim to shed light on the neural systems needed for antidepressant response and thereby help the researchers and clinicians to develop a system to enable them to predict response to antidepressant medications through selection of the appropriate neuropsychological tests of the involved neural pathways.40

**Conclusion**

Neuroimaging techniques have been widely used in the last three decades by scientists and clinicians to study brain structure and function and to help understand the normal and abnormal states of the mind. Numerous studies have been designed, using different research methods and imaging techniques to explore the way in which abnormalities in the structure and function of the brain cause abnormal mental states.

A wide range of structural and functional abnormalities have been reported in various areas of the brain in patients with depression, particularly the limbic system and related areas, which are involved in the processing of emotions. Ischaemic deep white matter lesions, volumetric changes in the hippocampus, amygdala and different cortical areas, perfusion changes, abnormalities in glucose metabolism, abnormal connectivity between the areas involved in the generation and processing of emotions and white matter microstructural abnormalities have been widely reported in elderly depressed patients.

Although studies have provided impressive results, to show the existence of brain abnormalities in depressed patients, and hold considerable promise for demystifying the biological processes underlying mood disorders, their findings to date are more helpful when studying groups of patients rather than individuals and therefore the clinical indications of most of the neuroimaging techniques discussed in individual patients in routine clinical practice are limited.

Structural neuroimaging techniques are indicated when there is suspicion of an organic pathology in a depressed patient, but there are no clinical indications for the routine use of functional neuroimaging techniques at present.41 Neuroimaging techniques are currently extensively used in the development of psychotropic drugs. These techniques enable the clinicians to determine whether the potential target for a medication is abnormal in a psychiatric disorder and whether its occupancy (with that medication) will lead to clinical improvement.41

**Conflict of interest:** none

**References are included in online version at www.gmjournal.co.uk**