Using imaging to understand the brain

We can image, or 'scan', the brain to examine its structure and function in living people and other animals. This can be done using various methods, such as computerised tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET), alone or in combination.

Researchers use these methods to try to understand how the healthy brain develops, performs its functions and changes as we get older, as well as to study the changes that occur in neurological conditions such as Alzheimer's disease and stroke. In the earliest stages of Alzheimer's disease, for example, the hippocampus begins to shrink, eventually leading to problems with memory. In stroke, damage to the grey matter and the white matter connecting different parts of the brain often affects a person's ability to speak and move. Doctors can image the brain to observe these changes to diagnose diseases more accurately. Brain imaging can also be used to monitor the progression of a disease, as well as the effects of therapy.

Magnetic resonance imaging (MRI) vs computerised tomography (CT)

	MRI	**CT**
Advantages	It is non-invasive It is very useful for producing images of soft tissues, such as the brain, eyes, ligaments and cartilage It can produce images in any plane (eg horizontal or vertical)	It is non-invasive It is very useful for imaging hard tissues such as bone It is quick – a scan can take as little as five minutes It produces highly detailed images It can be used on patients with metallic implants
Disadvantages	It is expensive It cannot be used on patients with artificial pacemakers or metallic implants It is not portable	It is not portable Some patients are allergic to the contrast dyes that are injected for some CT scans It exposes the patient to radiation

Volume changes in the brain can tell us about disease and ageing

Voxel-based morphometry (VBM) is a type of analysis applied to MRI images when researching certain neurological and psychiatric conditions. It can detect the reduction of hippocampus volume that occurs in Alzheimer's disease and depression, as well as the thinning of the cerebral cortex that occurs as a normal part of ageing.

Memory researchers in London have been investigating the changes that occur in taxi drivers' brains as a result of learning. To qualify for the job, London's taxi drivers have to learn 'the Knowledge' (every street name, landmark and direction of traffic flow in a six-mile radius of Charing Cross) so they can navigate the city effectively. Using VBM, the researchers found that those who qualified had an increased volume of grey matter in the hippocampus, a part of the brain known to be involved in generating maps and forming spatial memories. They have also found that the longer a person has been driving a taxi, the larger their hippocampus.

Imaging can be used to study neurotransmitters, too

Imaging can be used to measure the levels of a neurotransmitter, its receptors and its transporters (which remove neurotransmitters from the synapse after release). This is very useful because many neurological conditions involve the death of neurons that produce a specific neurotransmitter, or alterations in the activity or distribution of receptors or transporters within certain parts of the brain. The relationship between diseases and neurotransmitters is complex. For example, other neurotransmitters than those discussed below could also be involved in the conditions presented.

In Parkinson's disease, dopamine neurons in the midbrain die. Alzheimer's disease, depression and schizophrenia involve alterations in the transporter for the neurotransmitter serotonin. Attention deficit hyperactivity disorder (ADHD) has been associated with malfunctions of dopamine receptors and dopa decarboxylase, one of the enzymes needed for making dopamine, in the frontal cortex. ADHD, depression and schizophrenia can all involve disturbances in the function of receptors and transporters for the neurotransmitter noradrenaline.

The imaging methods used most often to measure neurotransmitter levels are positron emission tomography (PET) and single-photon emission computed tomography (SPECT). Both involve injecting a radioactive 'tracer' substance that binds to the molecule being studied. The scan reveals where the tracer binds, and the intensity of the radioactive signal in each brain area is related to the level of the molecule being studied.

Neurotransmitter receptors come in multiple forms, or subtypes, and each subtype has multiple variations. Some tracers bind to one particular subtype or more specifically to one variation of a subtype. To date, we know of at least five subtypes of receptor for dopamine – D1 to D5. Genetic mutations in the D4 subtype of the dopamine receptor (DRD4), for example, are linked to ADHD, Parkinson's disease and schizophrenia, as well as drug use and personality traits such as aggression and impulsiveness. PET and SPECT can be used to examine exactly how alterations in the DRD4 receptor are linked to these conditions and behaviours.

Imaging techniques that detect electrical activity

Electro-encephalography (EEG) and magneto-encephalography (MEG) are functional imaging methods used to measure brain activity directly and non-invasively (from outside the head). EEG detects synchronised electrical activity of large groups of neurons, whereas MEG detects the tiny changes in magnetic fields that this electrical activity is associated with. The images produced by EEG and MEG are not very localised, but they can monitor how electrical activity changes with time very precisely.

EEG requires electrodes to be attached to the scalp. It can be used to detect general patterns of electrical activity, such as the brain waves that occur during sleep. Researchers used EEG to compare the visual cortex activity of people who are born blind with those who are not blind, and they found that the visual cortex of blind people was active. EEG can also be used to detect electrical signals associated with specific sensory stimuli, thought processes or movements. Detecting and measuring these 'event-related potentials' can be done at a single electrode, but in practice, many are used. They are spread across the scalp, to help researchers pinpoint where in the brain the neurons responsible for the potentials are.

What does fMRI really measure?

The most common form of fMRI is blood-oxygenation-level-dependent (BOLD) fMRI.

It is based on the idea that neurons require more energy when they fire and that increased blood flow to active parts of the brain supplies the oxygen required. This form of MRI measures changes in the concentration of oxygen in red blood cells.

The main limitation of fMRI is that it measures brain activity indirectly, using blood flow as an indication that neurons are active. In 2009, researchers in the USA published important work showing that parts of the brain that receive more oxygenated blood do not necessarily become more active. The researchers used fMRI to scan the brains of monkeys while they looked at pictures, and they found that the brain anticipates which of its parts will be activated over the next few seconds and pre-empts itself by sending more blood to them. Most areas that receive more blood are more active, but some areas that receive more blood do not become more active.

Other ways to image

Many different imaging methods are in use and development

One imaging technique that is now widely used by researchers is calcium imaging. When neurons fire, the concentration of calcium ions inside them increases. This can be detected in slices of brain tissue or in live animals, using fluorescent dyes that are sensitive to the concentration increases combined with two-photon microscopy (a type of microscopy used particularly to image living cells). This technique requires an operation to expose the brain and is not used in humans.

Near-infrared spectroscopy (NIRS) is a method that detects changes in blood flow around the brain. It works by transmitting light with a wavelength of 700–900 nanometres through the head; the light passes through skin, bones and brain tissue but is absorbed differently by oxygenated and deoxygenated blood. The person being scanned wears a cap containing lasers or light-emitting diodes; this allows people to do more things while their brain is examined because they are not enclosed in a scanner. NIRS is cheaper than fMRI and is particularly useful in small babies, whose skulls are thinner than those of children or adults and transmit the light used by NIRS better.

Other techniques include functional electrical impedance tomography by evoke response (fEITER). This uses electrodes attached to the head, which transmit electrical currents that are interrupted by the brain's electrical activity. Researchers recently used fEITER to image how brain activity changes when people lose consciousness under anaesthesia.

Positron emission tomography (PET)

PET can be used to detect brain abnormalities such as tumours, Alzheimer's disease and epilepsy, as well as to investigate conditions such as heart disease or atherosclerosis. One of the main uses of PET is to diagnose cancer and see how far it has spread or how well it is responding to treatment.

Radioactive

To have a PET scan, the patient either swallows or is injected with a radiotracer, a common chemical that has been altered by replacing one part of it with a radioactive atom. One common radiotracer is FDG (fludeoxyglucose), which is glucose with one oxygen atom replaced by a radioactive isotope of fluorine, fluorine-18.

FDG is processed in the body just as glucose would be: it gets broken down within cells for energy. Cancer cells use glucose much faster than normal cells, meaning the FDG is taken up by the cancer cells faster and, therefore, collects in the cancerous areas.

Throughout the 1950s and the 1960s, different kinds of tomography were being developed to study human diseases. In 1973 the first PET scanner was built, but without a radiotracer the technology couldn't be used to look at disease in humans. In 1976, when FDG had been developed, the first humans scans took place.

FDG works so well because fluorine-18 is a radioactive isotope that decays (breaks down) at a suitable rate. If it decayed too quickly we wouldn't be able to measure the energy, but if it took too long it would stay in our bodies for longer than we wanted. FDG decays to form positrons. Positrons are 'antielectrons' – particles similar to electrons but with the opposite charge. Once formed, they travel through the tissue until they collide with an electron and give out energy in the form of gamma rays.

From energy to image

To collect and measure the gamma ray energy, you have to lie down inside a machine that surrounds your body. Within it are multiple rings of detectors that record how many gamma rays are being emitted and from where.

Once a reading has been taken, the detectors convert the energy into an image of the inside of the brain (or other part of the body). If there were a tumour in the brain, the scan would detect the excess of FDG there, and so more gamma rays would be emitted from the tumour than from the healthy tissue.

The scan would show the location and, to some extent, the size of the cancer. But PET is less commonly used than magnetic resonance imaging (MRI) and computed tomography (CT), as there are only a handful of PET scanners in the UK.

On average, 40,000 PET scans take place each year, compared to more than 3.5 million CT scans and almost 2 million MRI scans. This is due to both the lack of availability of scanners and the difficulty of transporting the radiotracer long distances (in case it decays before it reaches the patient).

Why PET?

PET has many advantages over other types of imaging such as MRI or CT, including the ability to reveal the functional changes occurring in an organ or tissue on a cellular level. This is important because the early stages of many diseases involve functional changes in cells rather than structural changes. MRI and CT scans measure structural changes, which means that PET scans are able to diagnose certain diseases earlier than MRI or CT scans.

They can also detect smaller areas of disease that don't necessarily show up with other imaging techniques. In particular, they can be useful for finding out whether an unknown mass left over after treatment is scar tissue or an active tumour.

What's the problem?

A downside of measuring the metabolic changes in cells is that other differences in the body can give false results. For example, a patient with diabetes may have a different rate of processing glucose than a normal patient and this could skew the results slightly. In addition, PET scans are not so good at providing information about the size, shape and structure of tumours.

PET scanners are extremely expensive, which is why they are in limited supply. Even more expensive are the cyclotrons that produce the radioactive atoms used in the radiotracer.