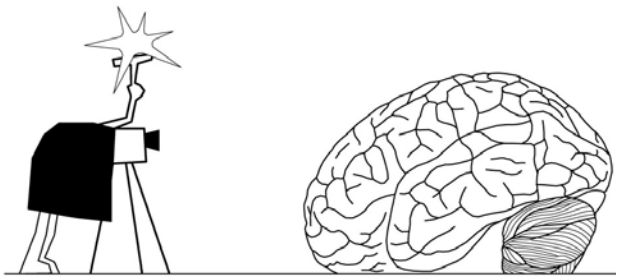
Brain Imaging



Phrenologists thought they could understand the brain by examining the bumps on the surface of the skull. If this seems far-fetched now, their ambition to understand the brain by looking at it from outside the skull has fascinated many throughout the ages. Now we really can do this – through the advent of modern brain imaging techniques. Modern scanners use a variety of means to give us wonderful images of neuronal and fibre pathway structure, of blood flow and energy metabolism in the brain, and of the changes in neural activity that occur when we do different things.

The walkway to modern techniques

In attempts to relate structure to function, a great deal has been learned by neurologists and neuropsychologists who correlate any oddities of mind or behaviour with measurements of brain structure at postmortem. It was in this way that the speech areas of the brain were identified by Broca. This approach has had many successes, but it also has limitations. One cannot make the simple assumption that the loss of a function due to damage to a region of the brain represents the normal function of that region. For instance, a deficit might occur because that region is cut-off or disconnected from other regions with which it normally communicates. It is also possible that brain areas that are undamaged may take over some functions that are performed by the damaged area under normal circumstances; this is known as plasticity. Finally, very few pathological lesions are confined to a precise functional area. And there may be long delay between the study of a patient when they are alive and the later analysis of their brain.

Structural brain imaging techniques began to be developed about 30 years ago. The recent development of functional imaging methods by medical physicists has attracted particular attention. These enable us – literally - to see inside the skull and so peer into the human brain - as it thinks, learns or dreams.

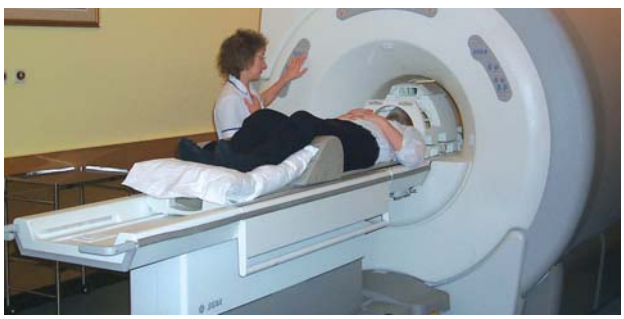
How it all works

Electrophysiological techniques for monitoring neuronal activity are based on changes in the membrane potential of activated neurons. Brain scanning techniques work by monitoring changes in energy metabolism required by activate neurons.

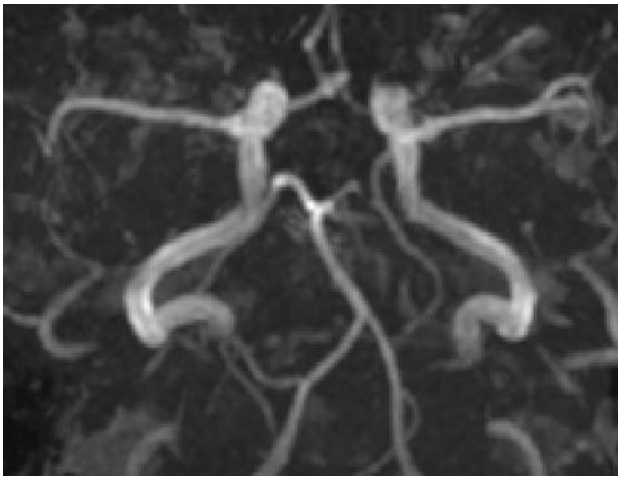
The electrochemical gradients that move charged ions in and out of neurons (that underlie synaptic and action potentials) require energy for their operation. The source of this energy is oxidation of glucose. Glucose and oxygen are delivered to the brain by the cerebral circulation. By virtue of the **neurovascular link**, there is a local increase in cerebral blood flow in active areas. This occurs very quickly. Modern neuroimaging devices measure these changes in local cerebral blood flow and use them as an index of neural activity.

The first functional technique to be developed was called **Positron Emission Tomography (PET)**. This procedure involves the injection, into the humansubjects, of radioactive tracers that are attached to compounds of biological interest (such as drugs that bind to neurotransmitter receptors). Rings of detectors around the subject's head record the timing and position of gamma particles emitted by the nuclear isotope as it traverses the brain and decays. PET can be used to produce maps of changes in local cerebral blood flow (CBF). Such measurements have led to the localisation in the human brain of sensory, motor and cognitive brain functions. There are several disadvantages of PET, the major one being that it requires the injection of radioactive tracers. This means that many people cannot have a PET scan, such as children and women of child-bearing age, and the number of measures taken during a scan are limited.

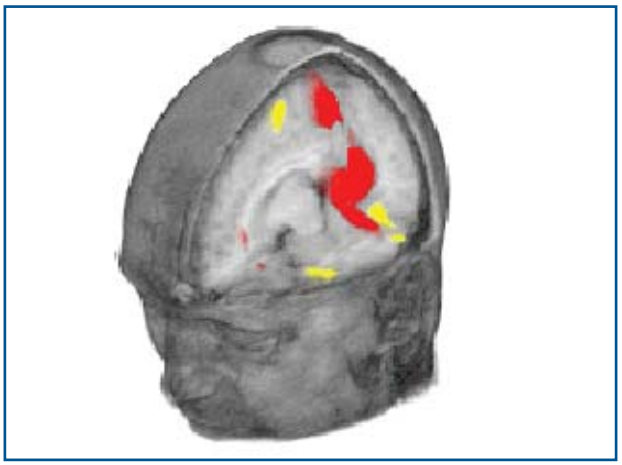
A different technique, called **Magnetic Resonance Imaging (MRI)**, was developed that is non-invasive and does not



Left: The profits made by E.M.I. from the sale of records by 'The Beatles' helped to pay for the development of the first brain scanners. These and later machines have enabled neuroscientists to look into the brain in new ways.
Right: A modern MRI scanner. The subject lies on a table that is moved into the ring of magnets for the scan that may take anything from 30 min to 1 hour.



Images of blood vessels in the brain. Changes in blood flow can be detected and serve as an index of neural activity.



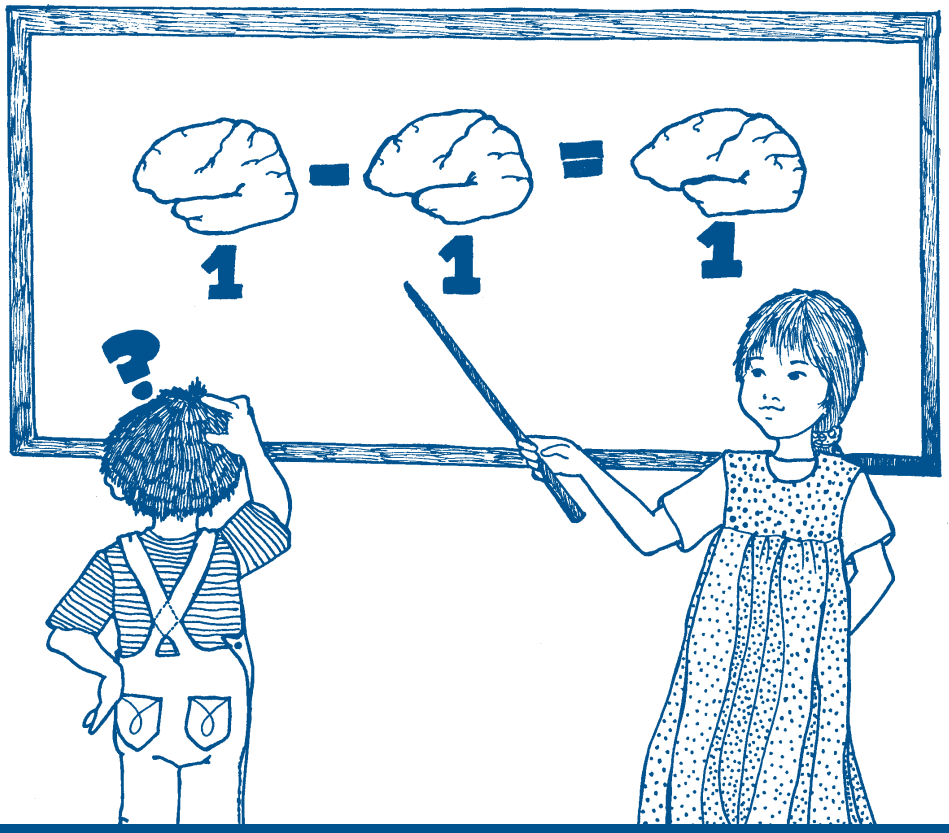
With computer technology, the images obtained by PET and MRI scanners show exactly where the changes in blood flow occur within the brain.

require radioactive substances. This allows people of any age to be scanned. MRI can be used to provide very fine-grained images of brain structure, and a recent development called **diffusion tensor imaging (DTI)** permits detailed images of the white matter tracts of fibres that connect brain regions.

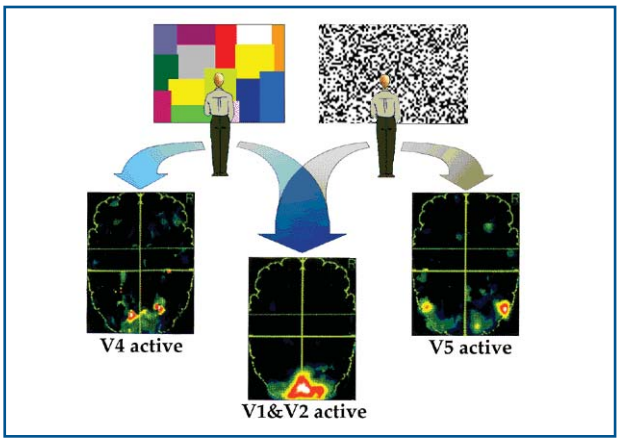
One of the most exciting applications of MRI technology provides images of brain function: this is called **functional Magnetic Resonance Imaging (fMRI)**. This technique is based on the difference in magnetic properties of oxyhaemoglobin and deoxygenated haemoglobin in blood (hence the signal in fMRI is called the **Blood-Oxygenation-Level-Dependent signal – BOLD)**. As increased neuronal activity leads to movements of ions that activate energy-requiring ion pumps, there is an increase in energy metabolism and oxygen consumption. This leads to an increase in deoxygenated haemoglobin and a decrease of the magnetic signal. However increased oxygen consumption is followed within seconds by an increase in local cerebral blood flow. The increase in cerebral blood flow exceeds the increase in oxygen consumption; there is therefore a relative increase in oxyhaemoglobin and the size of the signal. The exact mechanism of the increased cerebral blood flow is still unclear, but neurotransmitter–related signalling is now thought to be responsible.

Putting it to use

You're probably pretty good at subtracting numbers. But have you ever tried subtracting brains? No wonder the boy looks confused (cartoon). Subtracting brain images in 2- and 3 - dimensions turns out to be critical for the data analysis. Most fMRI studies involve measuring the BOLD signal while people are engaged in carefully controlled tasks. During a scan, subjects lie within the bore of a magnet, and their behavioural responses to stimuli are monitored. A wide range of stimuli can be presented, either visually, projected onto a screen for the subject to view, or in the auditory domain via headphones. It is possible to examine covert phenomena



such as perception, learning, remembering, thinking or planning. Often two very similar tasks are designed with one to be done immediately after the other. The idea is that the first task should involve the brain process an experimenter is interested in whereas the other should not. The succession of brain images obtained are then subtracted from each other to yield a pixellated 2D image of what changes in activity are specifically associated with performing the critical brain process. These images are stacked up by the computer to yield an effective subtraction of the image in 3 dimensions (see cartoon previous page). Recent developments mean that even very brief thoughts or brain events (as little as one or two seconds in duration) can be measured. This is known as event-related fMRI. Sophisticated methods of data analysis are used to test whether changes in the signal during performance of a task are statistically reliable. One widely-used analysis package

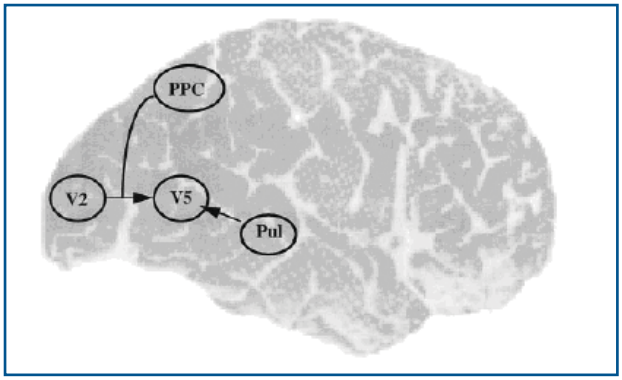


A person in the scanner might be shown a variety of visual images. All of these would 'light up' the primary areas of the visual cortex, V1 and V2. Use of clever subtraction techniques has revealed that colour processing (left) is in area V4, while motion processing (of random dots moving about on a screen – right) activates V5.

that has standardized the processing of imaging data is called statistical parametric mapping (SPM). SPM maps are often given colours, with a fiery yellow used for the 'hottest' areas of activity through to blue and black for 'cooler' areas.

Brain imaging scientists speak of areas 'lighting up' when certain functions are carried out. If a person watches a constantly changing checkerboard pattern, substantial activation is observed in the primary visual cortex. The use of moving and coloured colour patterns and other clever stimuli designed to activate different areas of the visual system has given us a great deal of new information about the organisation of the human visual system. Similar studies have been conducted for other sensory modalities. This localisational way of thinking has also helped to identify the brain areas involved in distinct components of reading – such as transforming visual words into a phonological code, the grouping of phonemes into whole words, the process of extracting the meaning of words, and so on. Learning tasks have also been studied, including work dissociating the brain areas involved in anticipating and perceiving pain.

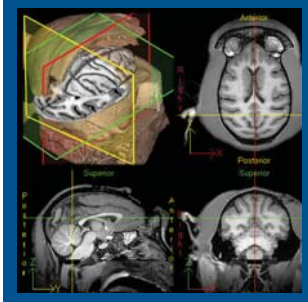
However, as research has proceeded, various surprises have emerged. One early example was the unexpected failure to



Activation of area V5 reflects the perception of motion. This area's inputs come from V2 of the cortex and the pulvinar (Pul) that is deeper in the brain. The posterior parietal cortex (PPC) controls the flow of information. Effective connectivity analyses enable the relative contributions of these to be worked out.

see the medial temporal lobe lighting up routinely in long term memory tasks. However, newer testing paradigms – some including virtual reality - are now revealing its activity in memory processing along with other areas such as the prefrontal cortex and precuneous. Coupled with new neuropsycholgical and other imaging findings, this diversity of brain areas involved has led to a revision of our understanding of the memory systems of the brain.
New mathematical techniques are also being developed to look at how the neural activity of different brain regions interacts and correlates during complex tasks - known as **effective connectivity**). This measure allows us to appreciate how brain areas work as a team and not merely as isolated functional hot spots. The hope is that these new techniques, with magnets of high field strength providing even more precise images, will tell us about the dynamics of networks of neurons talking to each other in the seamless control of perception, thought and action.

Research Frontiers



Nikos Logothetis is a young researcher making a major contribution to understanding the relationship between the activity of neurons in the brain and the signals seen in brain-imaging experiments.

Recent experiments in which electrical recording is combined with fMRI have shown a much closer correlation between synaptic activity and the BOLD signal than action potential discharge. The BOLD signal is therefore a more reliable index of synaptic processing within a brain region than its action-potential output. This has important implications for the interpretation of the BOLD signal in terms of localisation of function.