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**Editorial**

# Functional Magnetic Resonance Imaging

## *A new technique with implications for psychology and psychiatry*

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The anatomical resolution of multiplanar magnetic resonance imaging (MRI) is widely known and admired. Since its first clinical application some ten years ago, MRI has become the method of choice for determining the morphology and structure of the brain *in vivo*, and for locating brain lesions. Just as psychiatrists are becoming familiar with conventional MRI, a new development has taken place within the neuroimaging world which has been termed 'functional MRI' (FMRI), and which promises to make an even bigger impact on the neurosciences in general, and, arguably, psychiatry in particular.

The motivation for the development of these methods began with the desire to shorten scanning times from tens of minutes to less than ten minutes. Shortened scan times would improve patient acceptability, especially where psychiatric disorders such as phobias are present, and improve cost-efficiency. The time taken to produce a scan also causes image artefacts produced by both motion of the subject as a whole and by diaphragmatic and peristaltic movement; useful cardiac images would be limited by an image acquisition time of more than a fraction of a second.

Ultra-fast, or functional, MRI has overcome these problems. Small changes in regional cerebral blood flow (rCBF) can be observed that correlate with physiological activity in the cortex, occurring in tens to hundreds of milliseconds.

### How is it done?

Details of the physics in fMRI are well outlined in several recent reviews (Stehling *et al*, 1991; Cohen & Weisskoff, 1991; Heiken & Brown, 1991; Shulman *et al*, 1993). In brief, both conventional and functional MRI produce images derived from radiofrequency (RF) fields emitted by protons, abundant in living tissue, when they are aligned by a magnetic field and resonantly excited by a pulse of RF waves. A gradient is applied to the magnetic field and spatial information may be recorded from the signal emitted. The MR signal gradually decays or 'relaxes' away, with a tissue-specific time constant called the 'transverse relaxation time', denoted $T_2$. Signals from grey and white matter and cerebrospinal fluid decay at different rates, and this generates image contrast.

Following each RF pulse, the protons must be allowed to return to thermal equilibrium, a process which is characterised by the 'longitudinal relaxation time' $T_1$ ($\approx 2$ s) before a new signal can be generated. A conventional image is gradually constructed from a series of repeated excitations and relaxations (one for each line of the image matrix) at intervals constrained by $T_1$. Hence, a reasonably high-resolution image of $256 \times 256$ pixels will take up to $256 \times 2$ seconds. The resulting data are converted into a two-dimensional image by computer using Fourier transformation.

There are two principal methods of obtaining MR images in seconds or fractions of a second. These techniques are known as FLASH (fast low-angle shot) and echo-planar imaging. FLASH is essentially an adaptation of conventional MRI. Here the interval between successive RF pulses, known as the repetition time (TR), is reduced to 5–15 ms, so reducing total scan time. This is made possible by the use of narrow flip angles ($< 90°$), so that the longitudinal relaxation time is shorter. FLASH produces 'free induction decay' images, since only the magnetic gradients are used to rephase the MR signal (as opposed to a 180° refocusing RF pulse to form a 'spin echo' – free-induction image production has also been referred to as the 'gradient echo' technique). The FLASH technique may be used with standard imaging hardware given a magnet of reasonably high field strength, and has a number of variations, such as fast-imaging steady precession (FISP) and gradient-recalled acquisition in the steady state (GRASS).

The other method can be considered the archetype of ultra-fast techniques, and is known as echo-planar imaging (EPI). This was introduced by Sir Peter Mansfield from the University of Nottingham in 1977. The original implementation of EPI involved two-dimensional encoding during free-induction decay following a single RF excitation pulse. A rapidly oscillating readout gradient is then applied which generates a train of closely spaced signals called gradient echoes, analogous to those obtained in conventional MRI. To obtain a resolution great enough for clinical purposes, this rapid switching of the magnetic field gradient requires specially adapted hardware, because of the induction of eddy currents in the magnets, although lower-resolution images

($3 \times 3$ mm) have been obtained on conventional hardware (Blamire *et al*, 1992).

All rapid-imaging methods require powerful computers and elegant software to manage and store the data acquired, as well as to reconstruct and display the images. Modifications of the EPI method such as 'Instascan' (Cohen & Weisskoff, 1991) have now been applied by the Massachusetts General Hospital group.

### Use of fMRI in neuroscience

Functional MRI impinges on neuroscience since changes in regional cerebral blood flow (rCBF) in response to sensory stimulation or a cognitive challenge may be 'captured' on successive brain images. The first clear demonstration of this was published by Belliveau *et al* (1991). The study used the Instascan variation of EPI and the paramagnetic contrast agent gadolinium, bound to a chelating agent, DTPA. The presence of Gd-DTPA within the vasculature locally increases the decay rate of the MR signal ($1/T_2$) which in turn changes the image contrast. Serial measurement of image intensity can be converted to regional cerebral blood volume (rCBV). Two bolus injections of Gd-DTPA were given, one at rest in darkness and the other during full-field visual stimulation. A surface coil placed over the occipital pole was used to improve the signal over the area of interest, rather than imaging the whole brain with a more standard 'head coil'. Images were obtained at a rate of 60 per 45 s (i.e., one every 750 ms) in an oblique plane, with each 'snapshot' echo-planar image taking 64 ms. The resulting images were converted to rCBV and the difference taken to reveal stimulation-induced changes which were overlayed onto three-dimensional surface-rendered MR scans to show exquisitely the anatomical localisation. Thanks to the contrast-enhanced signal, mean increases of over 30% across seven subjects were revealed during crude visual photic stimulation, with all subjects showing more than 20% change.

Despite the innovation of this study, many aspects, such as the use of paramagnetic contrast agents, have found limited application. This has been superseded by non-contrast-based techniques developed in several laboratories in the USA. Starting with the work of Thulborn *et al* (1982) on the *in vitro* effect of oxygenation on MRI signal, two groups led by Ogawa and Turner demonstrated that similar changes alter $T_2$-weighted signals *in vivo* in mammals. In parallel with this, Detre *et al* (1992) developed a powerful way of using $T_1$-weighted signals to quantify perfusion. Kwong *et al* (1992) first demonstrated that these two techniques could be modified to image oxygenation and flow changes associated with neuronal activation and, with co-workers, presented the results at the 10th Annual Meeting of the Society of Magnetic Resonance, in August 1991.

The non-contrast technique sensitive to $T_2$*-weighted signal changes relies on the observation that the magnetic properties of haemoglobin change from the oxy- state, which is diamagnetic, to the deoxy- state, which is paramagnetic (Bandettini *et al*, 1992; Kwong *et al*, 1992; Blamire, 1992) and has been called blood oxygen-level-dependent contrast imaging, or BOLD (Ogawa *et al*, 1992). It has long been realised that the distribution of CBF is modulated in response to local increases in cellular activity. In fact rCBF and volume increase with a concomitant increase in oxygen delivery which exceeds oxygen utilisation, so that there is a net decrease in deoxyhaemoglobin. (This is the reverse of the gadolinium experiment, in which the amount of paramagnetic ions is deliberately increased.) The resulting effect on the MR signal is an increase in the relaxation time, known as $T_2$*, or apparent $T_2$, leading to a brightening of the image in active regions.

In the animal models, changes were observed secondary to hypercapnia-induced increases in CBF or levels of anaesthesia. Fortunately, the same effects can be produced by relatively innocuous sensory stimulation in humans.

Functional MRI has also been demonstrated using conventional MRI acquisitions with scan times of about 30 s. These studies show that ultra-fast imaging is not strictly necessary for the observation of functional changes as long as the stimulus (and response) can be sustained throughout the acquisition (Schneider *et al*, 1993).

### Neuropsychological studies

The studies using fMRI published at the time of writing are summarised in Table 1. As can be seen, most have concentrated on the visual system (and to a lesser extent the sensory motor cortex), since other functional imaging methods, most notably positron emission tomography (PET), have shown robust activation using simple photic stimulation. Furthermore, there is a wealth of information on the neurophysiology of the visual cortex derived from primate studies (Zeki *et al*, 1991). Activation, as measured by an increase in intrinsic signal, is relatively small ($< 5\%$) when the deoxyhaemoglobin method is used at 1.5 Tesla.

Generally the sites of increased blood flow are entirely as predicted from clinical neuropsychology – the effects of brain lesions; classic brain stimulation studies, and PET, etc. A notable exception was the

Table 1
Summary of published functional MRI studies on human subjects

| Authors | Tesla | No. of subjects | Method | Experiment | Signal change | Region of action |
|---|---|---|---|---|---|---|
| Belliveau *et al* (1991) | 1.5 | 7 | EPI with Gd | Photo stimulation at 7.8 Hz with LED goggles | 32 ± 10% | Calcarine cortex |
| Belliveau *et al* (1992) | 1.5 | 7 | EPI with Gd | Black/white hemifield checkerboard at 8 Hz | | Contralateral calcarine cortex (+extrastriate cortex?) |
| Kwong *et al* (1992) | 1.5 | 7 | EPI with deoxy Hb | Photic stimulation at 8 Hz with LED goggles | 1.8 ± 0.8% | Calcarine cortex, precentral gyrus |
| | | 2 | | Motor (hand squeezing) | ≈ 2% (from Fig. 5) | |
| Ogawa *et al* (1992) | 4 | 6 | FISP; acquisition time ≈ 10 s (i.e. not snapshot) | Photic stimulation with LED goggles, and hemifield stimulation with red/green checkerboard | 8.2 ± 3.3% | Calcarine cortex: contralateral occipital lobe activity (except 'macular cortex' region) |
| Menon *et al* (1992) | 4 | 6 | ≈ 5 s between scans | Hemifield stimulation with red/green checkerboard - intra-subject comparison | 8.2 ± 3.3% | Occipital activity grey matter only<br>High intra-subject test-retest reliability |
| Bandettini *et al* (1992) | 1.5 | 1 | EPI | Right-hand: touching fingers to thumb<br>Both hands: fingers to thumb | 4.3 ± 0.3% | Contralateral sensory and motor cortices<br>Bilateral sensory and motor cortices |
| Blamire *et al* (1992) | 2.1 | 7 | EPI | Photic stimulation at 8 Hz with LED goggles | 9.7 ± 2.8% | Calcarine cortex (grey) |
| Frahm *et al* (1993) | 2 | 5 | FLASH; time resolution 3,6 and 12 s | Photic stimulation at 8 Hz with red checkerboard | Depends on voxel size and echo time<br>17-43% in 1 subject | Calcarine cortex (grey) |
| Kim *et al* (1993) | 4 | 6 | FLASH; image acquisition time 10.8 s | Touching fingers to thumb; right, left and bilateral | Ranges: right ipsilateral, 2.8-8.9%; left contralateral 4.1-21.6%; bilateral 4.9-14.0% | Right precentral gyrus, mean 3.55 cm from midline mean surface area: left ipsilateral 1.2; right contralateral 0.06; bilateral 1.3 $cm^2$ |
| Turner *et al* (1993) | 1.5 and 4 | 6<br>4 | EPI | Photic stimulation at 16 Hz with LED goggles | 4.7 ± 2.0%<br>15.1 ± 6.0% | Calcarine cortex |
| McCarthy *et al* (1993) | 2.1 | 7 | EPI | Repetition of common nouns<br>Generate verbs from nouns<br>Control conditions: mouth movements, listening and covert speech | 8-9%<br>12-13% | Brodmann areas 47, 10 plus anterior insula and right inferior frontal for generate condition |

greater than expected activation of ipsilateral motor cortex during a finger–thumb opposition task, although this was restricted to a very small area of cortex (Kim *et al*, 1993).

Beyond these perceptual and motor studies using fMRI, it is the applications which examine language and higher cognitive processing which will be of most interest to psychiatrists and neuropsychologists. The study by McCarthy *et al* (1993) is of particular interest since it recorded substantial levels of activation during a linguistic task, namely generating verbs from nouns (e.g. 'erupt' from 'volcano'). This is essentially a replication of the PET study by Petersen *et al* (1988), and the results largely concur.

Numerous other studies of neuropsychological interest have been presented in abstract form, and their full publication is awaited eagerly. However, four will be mentioned briefly. The first is by Stern *et al* (1993) at the Massachusetts General Hospital which has shown, using a picture recognition memory test, distributed patterns of changing signal intensity within medial temporal and frontal lobes. The second is by Rao *et al* (1992) in Wisconsin, which showed activation of the superior temporal gyrus (left greater than right) in response to passive word listening. This confirms that auditory stimulation, presumably via magnet-free sound tubes, is feasible despite the ambient noise produced by fast MRI. The third is by Le Bihan *et al* (1992), from the National Institute of Mental Health, which suggests that activation of the visual cortex can be achieved by merely imagining photic stimulation, at almost the same intensity as during actual stimulation. Finally, the first psychiatric application of fMRI involved the study of symptom provocation in patients with obsessive–compulsive disorder, and disgust reactions in normal controls, respectively. Activation was seen in the orbital gyri and dorsolateral prefrontal cortex in patients only (Breiter *et al*, 1993).

It would be unfair to ask whether any genuinely novel discoveries have been made in neuropsychology using fMRI, since the technique is so new. So far, most studies have been rightly concerned with demonstrating the validity of the method by showing increases in rCBF in response to relatively crude stimuli. However, the time delay between stimulation and haemodynamic response and of 3–8 s plus an overshoot or transient hypoperfusion following cessation of stimulation have rarely been observed so clearly and consistently, and this may lead to renewed investigation into just how mental activity marshals changes in blood flow.

## Comparison with PET

Initially, fMRI was proclaimed by its practitioners to have several advantages over PET. These have been consolidated into four categories.

(a) In comparison to PET, fMRI offers a high resolution, *in-vivo* method for studying human cerebral anatomy and functional neurophysiology. In the same imaging session, functional activity can be mapped onto the actual contours of an individual brain (e.g. Menon *et al*, 1992), since high-definition structural images can be obtained from the same subject in the same plane of orientation.

(b) Functional MRI has an in-plane spatial resolution which can be in the millimetre range, vastly exceeding any other tomographic technique. This is bound to improve further with the use of stronger magnets (Turner *et al*, 1993) and other technical advances. A related issue is signal-to-noise ratio (SNR). There are trade-offs between resolution (both spatial and temporal) and SNR, but manipulations in the image-acquisition parameters and reductions in slice thickness can improve SNR by reducing partial-volume artefacts.

(c) The temporal resolution exceeds that of other tomographic methods. With fMRI this is limited in practice by the physiological basis of the functional contrast, namely the blood flow response. Functional MRI is able to track cortical responses in as little as one second but these may have spectral components in the 10–50 ms range.

(d) The non-invasiveness of fMRI gives it an indisputable advantage over PET. With the blood-oxygenation contrast methods now generally used, there is no need for any intravenous injections or infusions, and this will improve the compliance of psychiatric patients. More importantly, with fMRI there is no need for concerns over exposure to radioactive substances, so there is potentially no limit to the number of scans an individual may undergo: temporal averaging can be maintained until a predetermined degree of statistical significance is achieved in a single subject. This repeatability allows quantification of individual variations in location and extent of activation for tasks too subtle to be studied in an isolated experiment.

Some of these 'advantages' may not be evident in practice. For instance, it must be noted that PET researchers have made use of MRI and clever image-analysis software, so that 'coregistration' of PET and MRI images can be obtained (e.g. Watson *et al*, 1993). Furthermore, improvements have also taken place in PET gamma cameras, which are now sensitive enough to detect significant changes over noise in single subjects. Turning to temporal resolution, the only true real-time method for studying cognitive processing remains with event-related potentials, which we can expect to be allied with PET or fMRI in future studies.

### Artefacts and other problems

While the speed and repeatability of image acquisition of fMRI are its prime attributes, precise localisation is prone to error, caused by movement during the scanning procedure, especially where the intention is to subtract the cognitive component of one, baseline task from another, higher-order task (Posner *et al* 1990), a common paradigm in this field. For instance, nodding movements of the head by just a few degrees will result in large displacements of key frontal lobe structures. This concern is not restricted to MRI studies but must affect PET images. However, the subtraction artefacts produced by head movement are likely to be greater with fMRI because of the relative size of the movement to the pixel dimensions. Full three-dimensional scans with external fiducial markers on the scalp could be used to correct for such movements. This superficially trivial problem is rather difficult to overcome without restricting patients excessively, so reducing their ability to carry out naturalistic tasks – already severely limited by their situation within the coil of a magnet. Such confinement will limit the application of fMRI (as well as PET) to investigate restless and anxious clinical groups.

Early fMRI work was hampered by technical difficulties caused by macroscopic field inhomogeneities. This is caused by the proximity of different kinds of matter with very different magnetic properties, for example air and brain. Thus regions such as the frontal lobes, of interest to psychiatrists, are prone to artefact from the neighbouring frontal sinuses. This is dealt with by a procedure known as 'shimming', which reduces these problems such that the frontal lobes, basal ganglia, and brainstem may be readily imaged.

Although there are no known complications of MRI in subjects fulfilling the usual inclusion criteria (e.g. no implanted metal objects) there is some uncertainty as to the effects of very high magnetic fields. Some volunteers undergoing echo-planar imaging have reported 'tickling' and even painful sensations when the rapidly switched magnetic field approaches 60 T/s (Cohen *et al*, 1989, quoted in Stehling *et al*, 1991) and dangerous currents in cardiac conduction may be induced at this range.

In summary, fMRI has already proved itself to be a robust technique. Many problems will need to be solved, such as the reliable distinction between brain and vein activation, and the choice of optimal methods for data analysis, to pick two current preoccupations.

### The possibilities

Zeki (1991) posed the provocative question as to whether PET was a method capable of generating and testing new hypotheses or merely of confirming old ones. His answer was in the affirmative, but tentatively so. As the psychological experiments adapted for functional imaging encompass the higher functions, including language, the relevance of animal models becomes less, and human *in vivo* functional imaging correspondingly more so. A caveat should be inserted here. A psychological explanation of cognition and psychopathology can only be achieved through psychological methods, which may gain little from cerebral localisation *per se* (see David, 1993). But as both PET and fMRI research has shown, sophistication in both realms can be complementary and mutually beneficial (Joyce, 1992). This applies especially to psychiatric research, where crude localisation has failed to advance understanding (David, 1992).

Nevertheless, fMRI holds particular promise for psychiatric research for the following reasons. Firstly, the ability to repeat investigations allows researchers to explore topics such as cognitive development and long-term learning and memory. These may be studied over days, weeks, or even years. The Minnesota group (Menon *et al*, 1992) has shown that the precise areas of the visual cortex activated by photic stimulation, which may themselves differ somewhat from patient to patient and hemisphere to hemisphere in the same patient, remain constant over testing sessions some months apart. Such phenomena as habituation, belief formation and 'working through' may, for the first time, be mapped onto a cerebral substrate. Secondly, and in contrast to the above, fMRI may be the only technique able to capture fleeting events such as hallucinations, thought disorder, sudden affective responses, and even dreams, during a long sequence of repeat scans (e.g., every few seconds for 60 minutes). The brief report on voluntary visual imagery is encouraging in this regard (Le Bihan *et al*, 1992), if replicated.

Finally, one major ambition in neuroimaging research in schizophrenia is to resolve the structural changes observed with conventional MRI in regions of the temporal lobes (Weinberger *et al*, 1992) with functional deficits which seem to gravitate towards the frontal and prefrontal regions. A single investigative tool which will integrate structure with function has the best chance solving these and other riddles.

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