NEUROSCIENCE FOR NEUROLOGISTS

Functional magnetic resonance imaging

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Blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) is a powerful approach to defining activity in the healthy and diseased human brain. BOLD fMRI detects local increases in relative blood oxygenation that are most probably a direct consequence of neurotransmitter action and thus reflect local neuronal *signalling*. The method allows localisation to volumes of the order of a few to several cubic millimetres and can be used in serial studies of individual subjects. Basic approaches to experimental design and analysis are reviewed briefly, as well as potential clinical applications. The latter include three broad areas: anatomical characterisation of normal or pathological patterns of brain functioning; distinguishing pathological traits; and monitoring treatment responses. New research is emphasising the integration of fMRI with other techniques, particularly electrophysiological. In conjunction with MRI methods for characterising pathological load, fMRI promises a refined understanding of when disease processes begin and how they can be modified by new treatments.

A variety of methods have been developed over the past few decades to allow mapping of the functioning human brain. Two basic classes of mapping technique have evolved: those that map (or localise) the underlying electrical activity of the brain; and those that map local physiological or metabolic consequences of altered brain electrical activity. Among the former are the non-invasive neural electromagnetic techniques of electroencephalography (EEG) and magnetoencephalography (MEG). These methods allow exquisite temporal resolution of neural processes (typically over a 10–100 ms time scale), but suffer from poor spatial resolution (between 1 and several centimetres). Functional MRI (fMRI) methods are in the second category. They can be made sensitive to the changes in regional blood perfusion, blood volume (for example, using injected magnetic resonance contrast agents), or blood oxygenation that accompany neuronal activity. Blood oxygenation level dependent (BOLD) fMRI, which is sensitive primarily to the last of these variables, allows an image spatial resolution that is of the order of a few millimetres, with a temporal resolution of a few seconds (limited by the haemodynamic response itself). An accessible and more detailed introduction to the technique than is possible in this brief review is found in a recent book.[1]

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PRINCIPLES OF FUNCTIONAL MRI

Contrast in a magnetic resonance image

The contrast in a magnetic resonance image (which determines the apparent structure in what we see) depends on how it is acquired. By adding radio frequency or gradient pulses, and by careful choice of their timings, it is possible to highlight different characteristics of the tissue being imaged. While it is generally true that MRI maps the distribution of water in the brain, the useful contrast in MR images comes not just from spatial variations in the density of water but also from differences in fundamental nuclear magnetic processes known as relaxation, which are characterised by distinct rates or ''relaxation times.'' There are three relaxation times that are of primary interest in MRI—T1, T2, and T2*. These describe the time constant for the return of the magnetisation to its equilibrium position aligned along the static magnetic field of the scanner whenever it is disturbed (T1 relaxation) and the time constants associated with loss of signal once the magnetisation has been sampled (T2 and T2* relaxation). T2* is the most relevant relaxation time for understanding contrast in fMRI images.

The physiological basis of BOLD fMRI

Most of the energy used for neuronal activity is expended as a result of the postsynaptic neuronal depolarisation and, to a lesser extent, the action potentials generated.[2] The energy cost therefore arises from information transfer and its integration postsynaptically. Substrate delivery for energy metabolism is increased with increased local blood flow. However, it is not the increased energy use itself that directly drives the increase in blood flow.[3] Instead, increased blood flow appears to be a direct consequence of neurotransmitter action and thus reflects local *signalling*. Electrophysiologically, increases in the BOLD signal are correlated most clearly with the local field potential rather than the neuronal firing rate.[4] Blood flow in fact increases over a wider volume and to a greater extent than is necessary simply to provide oxygen and glucose for the increased energy production, so oxygen extraction decreases with greater neuronal activity.

Abbreviations: ASL, arterial spin labelling; BOLD, blood oxygenation level dependent; EPI, echo planar imaging; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; TMS, transcranial magnetic stimulation

The volume over which blood flow increases associated with neuronal activity is found is determined by the level of local control of perfusion, which is thought to be the feeding arterioles.[5] There may be multiple mediators of the arteriolar response, but nitric oxide (NO) and eicosanoids clearly are important under normal circumstances.[6 7] Binding of glutamate to receptors on astrocytes triggers NO release, and glial cells around the synapse may contribute to controlling the vascular response.[8]

Biophysics of BOLD fMRI

Reduced oxygen extraction leads to an increase in the ratio of oxy- to deoxyhaemoglobin in a region of neuronal activation. The origin of the associated BOLD fMRI signal change lies in the different magnetic properties of haemoglobin-carrying oxygen (oxyHb) and deoxygenated haemoglobin (deoxyHb). DeoxyHb is slightly paramagnetic relative to brain tissue, whereas oxyHb is isomagnetic.[9] Vessels containing oxygenated arterial blood thus cause little or no distortion to the magnetic field in the surrounding tissue, while capillaries and veins containing blood that is partially deoxygenated distort the magnetic field in their vicinity[10 11] (fig 1). The microscopic field inhomogeneities associated with the presence of deoxyHb lead to destructive interference from signal within the tissue voxel, a process that tends to shorten the T2* relaxation time. Thus, as oxygen extraction falls with enhanced local blood flow in a region of greater neuronal activity, the T2* becomes longer and the MRI signal intensity increases relative to the baseline state.

The precise amount by which the MRI signal intensity increases depends on several factors. There is a contribution from water molecules in blood (the intravascular compartment) and from water molecules in the tissue space around the vessels (the extravascular compartment). The observed signal is a volume weighted average of signal changes both from intravascular water in local capillaries and veins and water in the immediate extravascular compartment. BOLD signal change increases linearly with the static field strength of the MRI scanner for blood vessels that are of greater radius than approximately 8 μm and quadratically when considering blood vessels that are smaller than this value.[12 13]

Although only 3–5% of the water molecules in grey matter are in the vascular space (in white matter the value is closer to 2%), the contribution of the intravascular contribution to the BOLD signal change can be substantial.[13 14] Because the T2 and T2* relaxation times of blood at 1.5 Tesla are long compared with tissue, and the extravascular water effects are relatively localised around the vessels, signal from the intravascular water pool has a dominant effect (estimated at 60%) on activity related signal intensity changes at 1.5 Tesla.[15] Signal changes with brain activity thus can sometimes be detected in large draining veins that may be some distance from the site of neuronal activity.

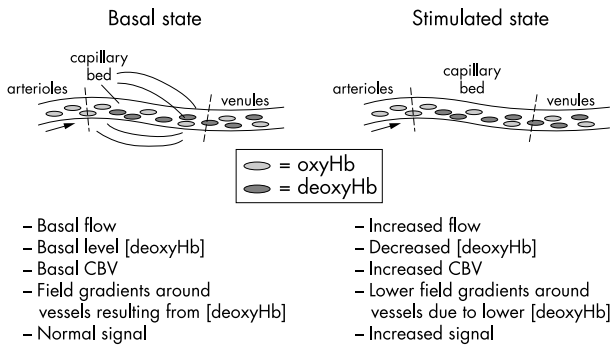

Figure 1 Schematic diagram showing the haemodynamic variables that change during neuronal activity. In the basal state deoxyhaemoglobin in the capillaries and venules causes microscopic field gradients to be established around the blood vessels. This in turn leads to a decreased signal in a gradient echo magnetic resonance imaging sequence. In the activated state there is a significant increase in flow, but only a modest increase in oxygen consumption. This results in a lower concentration of deoxyhaemoglobin in the capillaries and venules and hence in a reduction in the microscopic field gradients and an increase in the signal intensity. CBV, cerebral blood volume; deoxyHb, deoxyhaemoglobin.

In at least some areas of the brain (for example, visual and primary motor cortex), a small transient decrease in the BOLD signal may be observed after onset of activity before the characteristic signal increase.[16] This has been interpreted as reflecting local deoxygenation of blood in the capillary bed preceding the onset of activation associated hyperaemia. This ''initial dip'' may provide a more accurate measure of the localisation of activation.[17] However, the magnitude of the change is several-fold smaller than that of the later BOLD signal increase, so it is unlikely to provide a practical approach for improved functional mapping for clinical applications in the immediate future.

Practical implementation

Many MRI scanner manufacturers now supply add-on features that allow standard fMRI procedures to be performed easily. These include suitable pulse sequences, peripheral devices for presentation of stimuli to the subjects in the scanner, devices for recording responses from the subject, and even statistical analysis and display packages that allow assessment of the data while the subject remains in the magnet. The most common imaging sequence used is the fast method of echo planar imaging (EPI),[18] which allows collection of whole brain data in a few seconds or less. The spatial resolution is considerably lower (typically $4\times4\times4$ mm^3) than for a conventional MRI scan (fig 2). Image intensity is also reduced in frontal and temporal regions and there is some distortion of the shape of the brain. These problems arise from the sensitivity of the EPI scanning to field gradients caused by magnetic susceptibility differences—for example, at air sinus/tissue interfaces. This problem worsens with increasing field strength.

In an fMRI experiment a large series of images is acquired rapidly while the subject performs a task that shifts brain activity between two or more well defined states. Several hundred such volumes may be collected in a single session while the subject does different tasks. By correlating the signal time course in each volume element (voxel) of the slice stack with the known time course of the task it is possible to identify those voxels in the brain that show changes associated with the brain function under consideration.

Design of fMRI studies

Methods such as positron emission tomography (PET) provide an absolute measure of tissue metabolism. In contrast, BOLD fMRI can at present be used only for determining *relative* signal intensity changes associated with different cognitive states during a single imaging session. The most time efficient approach for comparing brain responses in different states during the imaging experiment is the ''block'' design[19] (fig 3). This design uses relatively long alternating periods (for example, 30 seconds), during each of which a discrete cognitive state is maintained. In the simplest form, there may only be two such states, which are alternated throughout the experiment in order to ensure that variations arising from fluctuations in scanner sensitivity, patient movement, or changes in attention have a similar impact on the signal responses associated with both states.

However, it can become difficult to control a cognitive state precisely for the relatively long periods of each block, or some

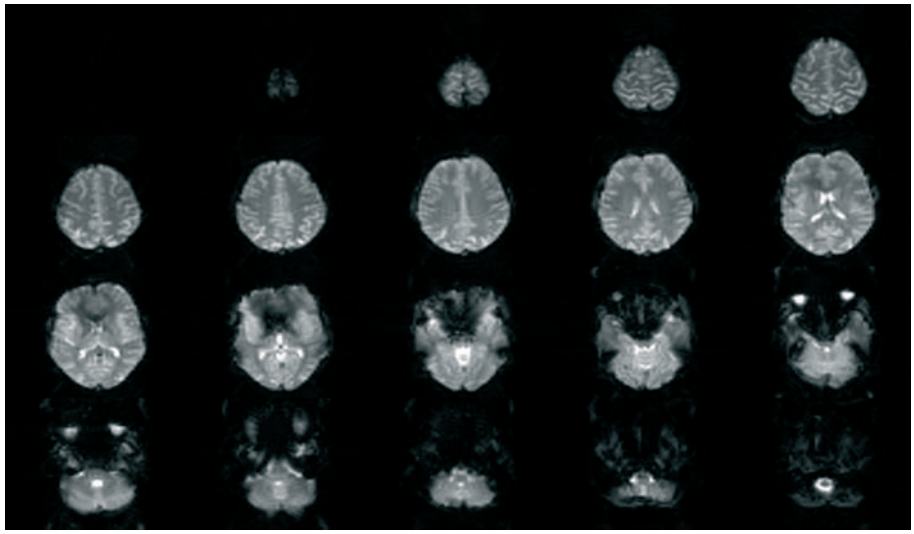

Figure 2 Example of a whole brain echo planar imaging (EPI) dataset collected in three seconds. Note the signal loss in the frontal and temporal lobes of the brain. Note also the lower spatial resolution.

tasks may simply be inappropriate for this design (for example, as in an ''oddball'' paradigm). In such instances an event related design can be used in which data are acquired while discrete stimuli or responses are repeated[20] (fig 3). Results from many trials are then averaged to give a measurable response. Event related fMRI demands longer acquisition times than the block design in order to achieve a sufficient signal to noise ratio. A related approach is to present stimuli in a periodic fashion and then to map responses in terms of their temporal phase relative to that of the stimulus presentation.[21]

Analysis of fMRI studies

The raw BOLD fMRI data can be acquired over periods as short as a few minutes. For simple analyses, near ''real-time'' viewing of final statistical maps of activation is possible (although—at least in a research environment—full analysis may demand extensive computation and much more substantial analysis times). The basic objective in the analysis of functional imaging experiments is to identify voxels that show signal changes that vary with the changing brain states of interest across the serially acquired images. This is a challenging problem for fMRI data because the signal

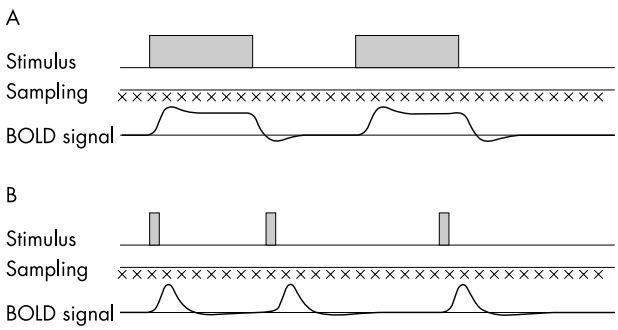

Figure 3 Schematic representation of a block design functional magnetic resonance imaging (fMRI) paradigm (A) and an event related fMRI paradigm (B). For the block design a relatively long (30 second) stimulation period is alternated with a control period. For the event related design a brief stimulus period is used, which can either be periodic or randomised. In both cases volumes of data (indicated by the crosses) are collected continuously, typically with a repeat time of three to five seconds.

changes are small (0.5% to 5%) (leading to potential false negative results or type II error) and the number of voxels simultaneously interrogated across the imaged volume is very large (potentially giving potential false positive results or type I error). One approach to enhancing the sensitivity is to undertake studies of groups of individuals: even if the changes are small, consistently activated regions may then be identified.

Different types of statistical analyses can be done. A ''fixed effects'' analysis gives an expression of changes in the group mean signal relative to the group pooled within-subject variance. This provides a sensitive measure of whether the group is activating on average, but does not look at subject to subject variability and therefore cannot be used to make generalisations about the larger population from which the group was drawn. To do this one would use a ''random'' or ''mixed'' effects model. Such models take into account not only the variance in a measurement for an individual subject, but also the variance in measurements between individuals.

The signal changes observed are small, and interpretation of results for single individuals (for example, in a clinical study) demands an appreciation of the reproducibility of a study. The exact volume of significant activation may show considerable variation between sessions, as the low signal to noise voxels on the edge of the activation volume will be included variably, depending on noise fluctuations.[22] Nonetheless, test–retest correlations of activation extent for typical cognitive tasks are good (for example, $r = 0.69$).[23 24] Meta-analyses have confirmed consistent localisations.[25] Specific BOLD signal characteristics (such as the maximum signal change or timing relative to a stimulus) also can be highly reproducible.[26]

The accuracy of localisations must be quantified only with respect to other techniques. This is complicated by uncertainties as to how data from different modalities (or brains of different sizes and shapes) are best aligned (or registered).[27] Comparisons with invasive electrophysiology in non-human primates suggest that the correspondence between direct recordings of local field potentials and fMRI changes may be high.[4] Good agreement has been found between functional localisations based on EEG and fMRI in humans.[28]

One of the most significant confounding factors in fMRI is the extreme sensitivity to *motion*, either of the whole head or even the brain alone (for example, pulsations associated with the respiratory or cardiac cycles). A first step in analysis

therefore is post hoc realignment of the brain volumes using automated algorithms that minimise the difference between subsequent images. Following motion correction of the data, spatial smoothing and temporal filtering of the data are often applied, primarily to reduce noise in the data. A variety of statistical tests can then be done to identify voxels in which the signal changes correlate over time with switching between the applied "control" and "stimulus" states. The simplest approach is to generate a map of the *t* statistic for signal changes on a voxel by voxel basis. A related approach is to correlate the time course of signal change in each voxel with a model time course based on the expected neural response (suitably convolved with a model of the haemodynamic response), which can also be used to generate a *t* statistic map. The significance threshold in all cases must be made more stringent in proportion to the number of independent comparisons (although, because of spatial correlations in the data, this is smaller than the total number of voxels).

There are now several software packages produced by academic centres that include a full set of tools for analysis of fMRI data and that are distributed at no cost. Examples of these are FSL (www.fmrib.ox.ac.uk/fsl), SPM (www.fil.ion.ucl.ac.uk/spm), and AFNI (afni.nimh.nih.gov/afni).

CLINICAL APPLICATIONS OF fMRI

Localisation of brain functions

Lateralisation of language functions in the surgical treatment of epilepsy

Surgery offers the possibility of improved seizure control or cure, especially for patients with temporal lobe epilepsy, but demands an understanding of language lateralisation for surgical planning. However, current clinical methods for language lateralisation (for example, the Wada test) are highly invasive. fMRI offers a promising alternative approach[24] (fig 4). While there is good agreement between conventional invasive Wada testing and fMRI results, fMRI is more sensitive to involvement of the non-dominant hemisphere. fMRI also provides more specific anatomical information. The reproducibility of distinct patterns of activation in individual subjects is good, potentially allowing clinical decisions to be made on the basis of results.[24]

Localisation of eloquent cortex before surgery

A general issue in presurgical planning for excisions near regions of eloquent cortex is precise localisation of essential functions. fMRI is an attractive strategy for this functional mapping because of its potentially wide availability in clinical centres and relatively low cost.[29] However, because the fMRI BOLD response is sensitive to signal changes in draining veins, there is potential for mislocalisation of major brain activity. The true correspondence between the BOLD fMRI and electrocortical localisations is difficult to define exactly because of difficulties in accurately registering (that is, aligning) the fMRI data with brain structural images. As described earlier, aberrations in brain geometry are induced by distortions of the magnetic field in the functional images which are not found in the conventional structural images. The brain also may shift position in complex ways when exposed for surgery.

These issues were recently reinvestigated.[30] Distances between the centres of the MEG and fMRI activation regions were measured, and consistent differences (of the order of 10 mm) were identified. For example, localisation of the primary motor cortex from the fMRI data was consistently more posterior than for the MEG localisation. For somatosensory responses, the localisation of the fMRI activation was inferior and lateral to that of the MEG. Thus, while the MEG dipole and the BOLD fMRI response maximum are in *similar* regions, the different physiological responses are slightly displaced.

Considering the possible causes for these localisation discrepancies is informative. Fundamentally different information is provided by the two techniques, not just with respect to the basis of signal change (for example, the potential sensitivity of fMRI to the "draining vein"), but also to the time period over which the response is averaged. The MEG "window" is short (tens of milliseconds). In contrast, the fMRI response is averaged over a much broader time period (seconds). The fMRI response may therefore reflect contributions from more than a single electrophysiologically defined dipole in the region of interest. For example, in the somatosensory cortex the early MEG response is localised in Brodman's area 3b, while later responses may be found in areas 1 and 2. The shift in the fMRI response relative to the

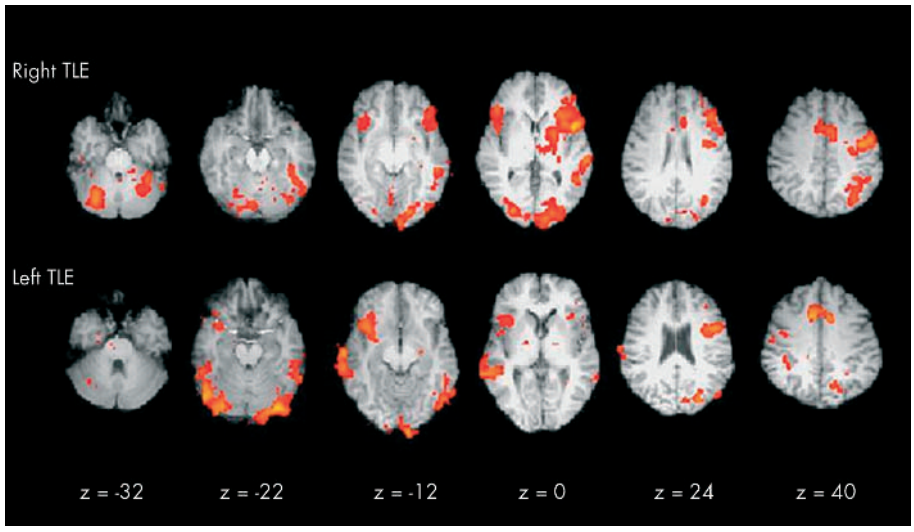

Figure 4 Differences in relative language lateralisation for a verbal fluency functional magnetic resonance imaging (fMRI) task can be found between patients with right or left temporal lobe epilepsy (TLE). Illustrative activation maps are shown here, coregistered with individual high resolution structural MRI. Cluster detection was done on all voxels above $z=2.3$ to determine clusters significantly activated (corrected $p<0.01$) in the experimental task condition. The right TLE patient has predominantly left hemisphere activation. In contrast, the activation map for a patient with left TLE shows bihemispheric activations.

MEG response may reflect the fact that fMRI is measuring an *average* localisation across these multiple regions. It is intriguing to consider whether shifts in the relative timing of activation from adjacent regions might contribute to apparent changes in functional localisation with brain injury.[31 32]

Localising spontaneous brain activity: the ictal focus

It is not only induced brain activity (that is, associated with task performance) that is associated with increased local blood flow. The spontaneous electrical discharges of an epileptic focus are also accompanied by increased tissue metabolism, oxygen utilisation, and blood flow. In the absence of information on the phase of the haemodynamic signal change with respect to the scanning acquisition, it is not possible readily to identify such foci using conventional methods (although see Matthews *et al* [33]), but a model for the time course of the expected signal change can be developed *after* the imaging data are acquired.

Electroencephalography provides a measure of locally coherent cortical field potentials and can give precise information on the timing of ictal spiking activity to inform such a model if EEG and fMRI data are acquired simultaneously. Indeed, with simultaneous EEG and fMRI it has been possible to identify ictal foci in patients with subclinical seizures.[34 35] Direct comparisons between dipole localisation using a simple EEG dipole based model and fMRI showed fair correspondence between the centres of activation for the two subjects, or revealed major foci within a few centimetres of each other but clearly in the same regions of the brain. However, potential applications still may be limited. This approach is time consuming even with an active subclinical ictal focus, and motion from a clinical seizure would probably introduce artefacts that would make the fMRI signals irrecoverable.

Brain plasticity with injury or disease

A direct extension of work for localisation of brain functions is to try to define explicitly ways in which these localisations may change with brain injury or disease. Such changes may be a consequence of so called ''adaptive plasticity'' (that is, induced changes in functional organisation in the brain), or of recruitment of intact brain regions in compensation for functional deficits arising from disease.

It has long been thought that the younger or developing brain has greater inherent plasticity, but there have been few direct tests of this notion. From an fMRI study of children with hemiplegia acquired either in utero or after birth, Gadian and his colleagues came to the unexpected conclusion that factors *other* than age must dominate the potential for adaptive changes.[36] Perhaps not surprisingly then, even the adult brain shows considerable potential for adaptive plasticity or compensatory recruitment of new brain regions. Several studies of patients after strokes[32 37–40] have confirmed earlier PET observations[41] suggesting that new regions of intact brain are recruited in the motor cortex ipsilateral to the hand moved. A key question has been whether such changes are adaptive or whether they represent either epiphenomena or even maladaptive responses. Increased activation in primary sensorimotor cortex relative to premotor cortical areas has been identified in dystonic musicians, for example, emphasising that ''greater'' activation is not necessarily ''better.''[42]

To test for a functional role of ipsilateral motor cortex recruitment, Johansen-Berg and colleagues studied a group of healthy controls and patients after stroke using both fMRI and transcranial magnetic stimulation (TMS).[43] TMS transiently interferes with any ongoing brain activity below the stimulation coil. There was a significant slowing of movement reaction time with TMS over ipsilateral premotor cortex with movements of the paretic hand for patients, but no significant effect of TMS applied in the same way in the healthy controls. Thus the greater ipsilateral motor cortex activity shown by fMRI in patients must contribute to function in a unique way after corticospinal tract injury.

fMRI studies are showing that functional reorganisation is a general response to brain injury.[41 44] A wide range of regions within the spatially distributed cortical motor network may contribute to this.[45] Adaptive changes may in fact contribute to maintaining subclinical the expression of pathology in early stages of the disease.[44 46]

fMRI studies of learning in healthy subjects show that changes in functional brain organisation also may be induced.[47] An exciting clinical extension of this concept is to defining functional changes in the brain with neurorehabilitation.[48] Specific regions of the brain change activity with clinical improvements after treatment. With definition of the functional anatomy and mechanisms responsible for recovery, it may be possible to provide improved prognostic markers for better identification of patients who will benefit from a treatment or better tailoring of treatment to individual needs.

fMRI as a marker of pathological state: Identifying preclinical expression of disease

fMRI can be sensitive to early (and even preclinical) stages of brain pathology. A pioneering illustration of this approach was an fMRI based memory study of a group of apparently healthy subjects at risk of developing earlier onset Alzheimer's disease.[49] One year after fMRI scanning, those who were beginning to develop memory problems in early clinical expression of presumed Alzheimer's disease were identified. A significant difference in the pattern and volume of activated cortex with the memory task was found in these subjects relative to those who did not develop memory impairment.

A related application is the use of fMRI to identify patients with a disease trait. Subjects who have recovered from depression have a substantial risk for recurrence of depression, suggesting that there are persistent abnormalities in brain function associated with vulnerability to depression. Because of the potential interaction between depression and stimuli associated with aversive emotional conditioning, Smith *et al* applied a pain conditioning paradigm to study a group of patients who had recovered from depression and who were not on drug treatment, but were at risk of recurrence of depression.[50] While the direct response to pain itself was similar between healthy control subjects and the previously depressed patients, and there were no differences in ratings of mood or affective response, the responses to anticipation of painful stimuli were different between the two groups. The recovered depressed patients showed an altered fMRI response in the cerebellum relative to healthy controls. This provides a link between theories of depression and a growing body of work showing that the cerebellum plays a role in conditioning, cognition, and emotional responses. Antidepressant treatment has also been associated with increased cerebellar metabolism in other work. In principle, this type of study might be used to distinguish between different types of depression or to identify healthy subjects at risk of depression.

fMRI in the development of new treatments

Using fMRI to guide therapeutic development is clearly one of the most exciting prospects for the technique. Initial work has not just been for drug development and response monitoring. The greatest impact may be on areas in which sensitive and objective end points were previously difficult to define—for example, neurorehabilitation.[48]

A similar example is the assessment of outcomes using behavioural therapy, such as for the control of pain. Distinct

mechanisms contribute to the perception of pain, including attention.[49] Bantick and her colleagues reported how the patterns of the fMRI brain response may change with self induced distraction from a thermal pain stimulus. When attention is distracted, the overall brain activation is reduced substantially. There is a particular reduction in regions of limbic cortex associated with emotional response to pain. ''Gating'' of pain signals to the brain as a result of higher cortical processes may occur through several areas. fMRI studies of brain stem changes associated with pain suggest that the periaquaductal grey matter is an important locus for such action.[51] Similar mechanisms may contribute to the placebo effect.[52]

Identification of the biological basis for cognitive and behavioural changes offers insights into mechanisms of vulnerability and variability of responses to treatments for neurological and psychiatric diseases. The recent evidence that functional neuroimaging methods such as fMRI may have relative sensitivity to systems level brain changes suggests that the method also may provide a powerful strategy for identifying specific genetic factors that may play dominant roles in cognitive processes. A ''candidate gene'' approach, which investigates the relation between a brain functional phenotype defined by imaging and a specific allele, is one example. Egan and his colleagues have recently shown that the met allele of brain derived neurotrophic factor (BDNF) is associated with poorer episodic memory and abnormal hippocampal activation by fMRI.[53]

LINKING fMRI TO OTHER MRI TECHNIQUES FOR CHARACTERISING PATHOLOGY AND OTHER DIRECTIONS FOR THE FUTURE

fMRI can localise brain functions well, allowing eloquent brain areas to be defined, characterising the reorganisation of patterns of brain activation as a consequence of disease or injury, and potentially identifying differences in brain function between subjects associated with disease susceptibility or other factors causing variation. There are limitations of the technique that remain important to overcome. The specificity of the information provided could be improved, as the BOLD signal includes contributions from multiple factors. It is also a *relative* measure of activity. The genesis of differences between groups of subjects may thus be complex to interpret.

There are several ways in which the technique is currently being advanced. More quantitative approaches to functional mapping are being applied. One promising area is the development of non-invasive methods for direct perfusion measurement, such as arterial spin labelling (ASL).[54] While the sensitivity of these techniques remains low relative to BOLD imaging, in some applications ASL may provide critical adjunctive information—for example, by providing an *absolute* measure baseline blow flow changes against which the task associated changes of BOLD imaging can be calibrated. An entirely different strategy that relies on detecting perturbations of the MRI signal by the very tiny magnetic fields generated by oriented coherently depolarising neuronal aggregates is being explored.[55]

A broader range of methods for characterisation of brain pathology can be combined with fMRI in order to interpret the heterogeneity in responses across patient populations. The importance of this has already been emphasised by various studies[31 44–46] in which differences in brain activation have been demonstrated with variations in the extent of pathological changes, rather than simply in association with a disease (fig 5).

New techniques may allow much more precise characterisation of neuroanatomical relations with functional changes. The potentially important distinction between adaptive

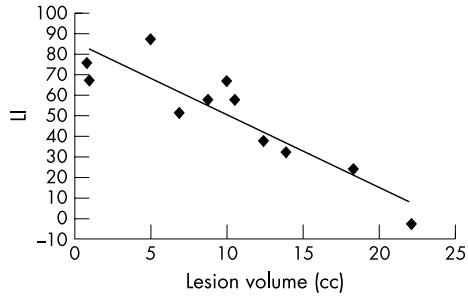

Figure 5 Patients with multiple sclerosis show greater activation in the motor cortex ipsilateral to the hand moved than do healthy controls. Here activation in the contralateral relative to the ipsilateral hemisphere is expressed as a lateralisation index (LI). LI decreases (that is, activation becomes more bihemispheric) as the lesion load increases.

reorganisation and compensatory recruitment could be addressed by defining whether brain regions previously uninvolved in a process are recruited. This ideally would demand cytoarchitectonic characterisation of associated grey matter regions. Recent advances in diffusion tractography have allowed regional connectivity patterns to be used to map local cortical or local grey matter structures.[56] These correspond closely to conventional cytoarchitonic maps, but are obtained entirely non-invasively. Diffusion tractography also provides direct information on axon tracts, constraining solutions to problems of functional connectivities between brain areas (fig 6). The approaches available are thus continuing to evolve.

For the clinician, the accessibility of MRI promises the freedom to exploit these new methods rapidly. Already many centres are using fMRI as an adjunct to neurosurgical planning. Functional measures may ultimately be incorporated as surrogate markers of responses in drug trials,[57] in triage for selection or assessment of neurorehabilitation procedures,[48] or used to complement neuropsychological measures in cases of suspected early cognitive impairment.[49] First steps towards understanding how fMRI might be used to define the prognosis for recovery after stroke or other brain injury at an early stage have already been taken.[58] Brain functional characterisation of non-organic impairments may make more confident diagnosis possible.[59] Recent work has shown how vulnerability traits for mental illness or atypical responses to psychoactive drugs can be identified.[50 60] The scope of possibilities is as broad as the range of questions that can be asked. It is a field that will deserve watching for some time to come!

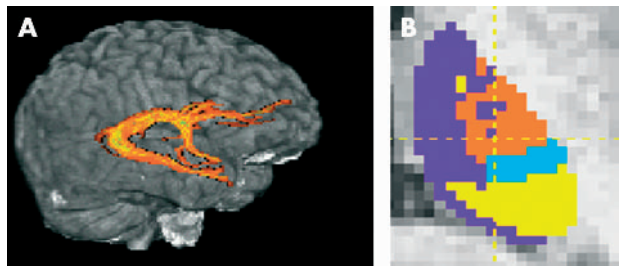

Figure 6 (A) A probabilistic diffusion tractography path is defined between a voxel in the medial dorsal thalamus and prefrontal and temporal cortex. (B) Local patterns of connectivity in the thalamus can be used to define structures corresponding well to cytoarchitectonically defined nuclei. The axial view of the thalamus shows clusters of common projections to prefrontal (purple), motor, and premotor (orange), somatosensory (blue), and occipital/parietal cortex (yellow) that correspond well with medial dorsal and anterior, ventral lateral, ventral posterolateral nuclei, and the pulvinar, respectively.

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