The Cognitive MRI Revolution

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No amount of hype is sufficient to convey the impact of magnetic resonance imaging (MRI) on the study of human cognition. Very simply, it is revolutionising psychology. After thousands of years of pondering, and of devising tricks to measure its mechanisms, the scholar can finally peer into the black box and observe it working inside a live human being. And what can the scholar see? How might this new image help him understand the nature of mind? These questions are tough, but we will do our best to sketch some answers below. Part of the excitement is that the answers keep changing. Advancements in MRI methodology are relentless.

Very generally, MRI can examine both structure and function in the brain. It uses very high magnetic fields[1] to ascertain the distribution of a population of atomic nuclei of a given molecule in different types of tissue (see suggested readings for reviews of MRI physics). When one studies nuclei in a highly concentrated and pervasive substance, like the hydrogen atoms in water molecules, it is possible to form a three dimensional picture of the anatomy of the brain. The distribution of water differs considerably between grey matter, white matter, cerebral spinal fluid, bone, skin, etc., leading to corresponding changes in signal intensity within these compartments. The signal intensity also depends on the strength and uniformity (homogeneity) of the applied magnetic field. Disturbances to the homogeneity of the magnetic field lead to decreases in the signal measured. Scientists have capitalised on this property to develop *functional* MRI – with which it is possible to measure local changes in blood circulation associated with neural activity.[1] The theoretical spatial and temporal resolutions of fMRI are excellent. The spatial resolution is hypothetically unlimited. It is possible to image a two-dimensional slice of the brain in tens of milliseconds, which is still within the timeframe of synaptic potentials and of unfolding cognitive functions. However, in practice the spatial and temporal resolution of fMRI are dictated by the proximity of the protons of

[1] Magnetic field strengths of standard scanners for research on humans vary between 1.5-3.0 Tesla. One Tesla is equivalent to 10,000 Gauss. The magnetic field of the earth is approximately 0.3 Gauss.

water molecules in blood to active neurones and by the timecourse of changes in blood circulation that result from neural activity.

MRI can reveal brain structure and function safely and non-invasively. For most scientific applications, there is no need to inject any contrast agent. Results can be analysed on the basis of a single subject or across subject groups, enabling investigations of individual differences as well as of common principles of neural and cognitive organisation . Experiments can be repeated on the same individuals, enabling longitudinal studies. No wonder MRI is becoming the dominant method for investigating human brain and cognition. MRI remains a relatively expensive technology for psychological and medical research.[2] Still, many psychology and medical departments in major American universities are becoming equipped with their own MRI scanners dedicated to research.

The specific applications of (f)MRI to study the relationship between brain and cognition are many and increasing. Structural MRI enables high-resolution studies of brain structures and their connections *in vivo*. Functional MRI enables the investigation of functional specialisation of individual brain areas as well as their interactions in networks that support psychological functions. The role of neurotransmitter and neuromodulatory systems in cognitive functions can also be explored. These strengths of (f)MRI are increasingly being integrated with complementary methods to image or interfere with brain function at high temporal resolutions. MRI hardware and analysis methods continue to advance at an accelerating pace, constantly enhancing our investigative powers.

STRUCTURAL MRI

Imaging anatomical structures

Before MRI, a high fidelity anatomical view of cortical and subcortical structures was only possible through post-mortem or highly invasive analyses. The image quality afforded by structural MRI, often with millimetre resolution or better, can be comparable to that in post-mortem studies. There is also the significant advantage that the image of the brain can be

[2] A state-of-the-art MRI scanner for functional brain studies costs around a couple of million dollars. In addition, MRI scanners are continuously switched on, and require thousands of dollars per day for maintenance.

sliced and re-sliced at any orientation without the destruction of the tissue. Obviously but importantly, structural MRI can be performed in healthy live subjects.

Structural MRI has consequently become the accepted standard for clinical diagnoses of neurological deficits. Brain lesions, such as tumours or strokes, can be clearly visible in structural images. Structural MRI is also sensitive to more subtle or gradual pathological changes. For example, high resolution structural MRI can be used to assess widespread atrophy during degenerative disorders such as Multiple Sclerosis or Alzheimer's Disease, as well as atrophy in specific brain regions during disorders such as epilepsy or Parkinson's Disease (for a review of the application of structural MRI see [2]).

In addition to clinical diagnosis, structural MRI also has basic research applications. For example, it is possible to investigate the effects of genetic disorders on neural organisation. Recently, structural MRI has been applied to assess the consequences of Turner' syndrome[3] on brain anatomy,[3], providing evidence about the neural bases of the disorder's specific cognitive profile, which includes problems in spatial–numerical processing and social cognition. MRI can also chart changes of neural organisation during normal development and aging. For instance, using volumetric MRI measurements, it has been possible to differentiate changes during normal aging from those in Alzheimer's disease and mild cognitive impairment.[4]

Software developments are increasingly providing automated and accurate anatomical measurements that can detect and quantify subtle abnormalities or changes in specific brain structures. One example is segmentation software,[5-7] for demarcating the boundaries between different types of neural tissue and measuring the volumes in different compartments (e.g., grey matter and white matter).

Imaging anatomical connections

One of the most exciting recent developments of MRI is *Diffusion Tensor Imaging* (DTI), which uses the properties of water diffusion to provide information about anatomical connectivity. If unconstrained, water molecules diffuse randomly in all directions. This is called *isotropic* diffusion. If the motion of water molecules is constrained by the structures of

their environment, they diffuse in some directions more than others - *anisotropic* diffusion. Within the brain, axonal fibre tracts constrain diffusion, so that molecules within them move along the primary axis of the tract.

There are different methods to calculate diffusion anisotropy and, in turn, gain information about the orientation of axonal fibre tracts in the brain. The most widely used anisotropy measure is Fractional Anisotropy (FA*)* – a scalar quantity computed voxel-by-voxel to express the tendency of water to diffuse in either an isotropic or anisotropic manner. By measuring anisotropy, it is possible to estimate the pattern of fibre connectivity in the brain *in vivo*, a method known as tractography (for a review of DTI and tractography see [8, 9]).

There are limits and traps to using tractography based on DTI. It is only possible to define the direction of a fibre track within a voxel when the diffusion anisotropy is high. Problems occur when fibres cross or when more than one fibre passes through a voxel. One consequence is that fibre pathways near the neocortex, where there is considerable fibre divergence, show low anisotropy and are therefore difficult to trace. To overcome these types of limitations, new probabilistic approaches to tractography are being developed.[10-15]

Tractography using DTI will undoubtedly invigorate studies of human functional neuroanatomy. Whereas DTI enables the detection of functional anatomical connections *in vivo*, traditional studies require painstaking anatomical tracing methods of fibres that degenerate after functionally circumscribed focal lesions (e.g., [16]). For example, a comprehensive description of the connections between thalamus and cortex in the human brain *in vivo* has been provided using a probabilistic DTI approach,[10] an endeavour that would have been difficult to achieve over a lifetime of traditional anatomical studies. A better understanding of anatomical connectivity in the human brain is fundamental to understanding the computations of specific brain areas[17] and their organisation into large-scale functional systems.[18]

DTI has a key role to play in clinical research. Some neurological diseases, such as multiple sclerosis and vascular dementia, are characterised by severe white matter pathology.

[3] Turner syndrome is a genetic condition resulting from a partial or complete absence of one of the two

The resulting axonal damage can be identified as decreases in the fractional anisotropy in voxels comprising affected tissue. DTI is also beginning to reveal systematic deficits in anatomical connectivity in psychiatric disorders whose neural bases have remained elusive, such as cognitive developmental disorders. For example, a recent investigation showed decreased diffusion anisotropy bilaterally in the temporoparietal white matter of patients with reading difficulty.[19] Using DTI, it has also been possible to detect characteristic microstructural tissue changes within hippocampal subregions of schizophrenic patients.[20] (for a review of clinical applications of DTI, see [21]).

FUNCTIONAL MRI

But it is the ability of MRI to visualise human brain *function* non-invasively that is most changing the study of human behaviour. The pictures of bright blobs of activation overlaid on the corresponding anatomical image of the brain are familiar to us all. They appear in newspapers, television programs and magazines, as well as in hundreds of scientific articles published each month. Varied psychological functions have been investigated, including those as complex as deception,[22] empathy,[23] and even maternal and romantic love.[24] However, before discussing some of the applications of functional MRI (fMRI), it is important to consider just exactly what kinds of "activity" are measured by those coloured blobs, and what limits this may pose to interpreting the fMRI data.

Source of the signal

Most fMRI experiments measure the blood oxygenation level dependent signal (BOLD signal), which mainly reflects changes in blood flow and blood oxygenation associated with neuronal activity.[1] The deoxygenated form of the haemoglobin molecule in blood is paramagnetic, and therefore causes distortions in the surrounding magnetic field.[25] The resulting loss in field homogeneity leads to an overall loss in the signal generated by local protons in water molecules. The resulting strength of the signal is proportional to the ratio of oxygenated to deoxygenated haemoglobin.[26]

Activation in a brain area follows a BOLD hemodynamic response function (HRF), which is typically characterised by a large rise in relative blood oxygenation, starting around 2 s after stimulus onset and peaking after about 7-10 s, and a return to baseline after 8-11 s.[27,

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X chromosomes in a phenotypic female.

[28] The increase in blood oxygenation is thought to represent mainly an increase in blood flow, which outstrips any increase in oxygen consumption associated with neural activity. It is spread over 3-5 mm and lasts several seconds.[29] Using very high magnetic field strengths (above 4 Tesla), it is sometimes also possible to observe an earlier *initial dip* in the HRF, which is thought to reflect oxygen consumption that is more closely coupled to neuronal activity.[30, 31] Advances in imaging this initial dip will be discussed later, but the large majority of published fMRI studies rely on the sluggish increases in relative blood oxygenation occurring seconds after the relevant neuronal events.

"Activity" as measured in fMRI experiments is therefore not a direct measure of the electrochemical signals in neurones or neuronal populations. Instead, it is a measure of the hemodynamic consequences of neural activity. How neural activity is coupled to these hemodynamic changes is a story in itself, of which not all chapters are fully worked out.

The observation that neural activity is coupled to local circulatory changes is an old one,[32] but the coupling mechanisms are still being investigated (see [33]). There is basic agreement that some part of the neuronal electrochemical signalling process requires energy supplied by glucose. In general, glucose can be delivered through oxidative metabolism (requiring oxygen consumption) or non-oxidative metabolism. It has been found that glucose utilisation is highly correlated with blood flow, but oxygen consumption is not.[34, 35] Possible interpretations are that at least some energy is supplied by non-oxidative metabolism in highly active neurons, or that oxygen is extracted less efficiently when blood flow is fast.[36] It is still not entirely clear what the metabolically costly aspects of electrochemical signalling are. A large proportion of the energy may be spent reversing changes in intracellular ion concentrations caused by action potentials and post synaptic potentials.[37] The recycling of extracellular neurotransmitter into precursor molecules by astrocytes through glycolysis has also been proposed to require significant energy.[38] Future research is still required to identify all the relevant metabolically costly steps and the mechanisms coupling these to changes in circulation. A further complication is that, whilst increased blood flow provides necessary supplies of oxygen and glucose, the haemodynamic response may be triggered in parallel to these requirements, as a response to increased neurotransmitter cycling (see [39] for review).

An alternative, perhaps more pragmatic, approach to determining what aspect of brain activity the BOLD signal reflects is to compare the BOLD response to electrophysiological

responses evoked by the same stimulus (see [40]). This was first done directly in monkeys by Logothetis,[41, 42] who compared the BOLD signal with simultaneously recorded activity from an electrode in the monkey's visual cortex. Electrical activity was subdivided into action potentials (spikes) and postsynaptic potentials (local field potentials, LFPs) by using the different temporal profiles of these two types of activity. Spikes last on the order of 1-3 ms whereas synaptic potentials last for tens or hundreds of ms. High-pass and low-pass filtering can therefore be used to isolate spikes and local field potentials respectively. The studies showed that BOLD was better correlated with local field potentials than multi-unit spike activity. This means that the fMRI signal reflects mainly inputs to brain areas and integration of activity within brain areas. Under most circumstances, these activities also correlate with the output of a brain area (the spikes), but this need not always be the case. In areas where strong neuronal input leads to neuronal inhibition, the BOLD signal will correlate with the synaptic input but not with neuronal output (see [39]). So far neural activity and BOLD have only been compared directly in visual cortex. It is likely that our understanding about the neuronal correlates of the BOLD response will increase in sophistication with ongoing research.

The nature of the BOLD signal constrains interpretations about the implications of activations in cognitive studies. For example, we cannot assume that an activated area produces an output. Furthermore, the activations could be biased measures of synaptic activity. Electrochemical signalling along some neurotransmitter pathways could be more metabolically costly than along others. It is also necessary to bear in mind the nature of the BOLD response when considering the contribution of multiple methodologies to a problem (see below). Results from fMRI experiments and electrophysiological studies need not be qualitatively equivalent.

Applications of fMRI

With all these caveats in mind, it is still possible to address several interesting and important questions regarding the neural basis of human behaviour using fMRI. The applications of fMRI have continually broadened with the advances in hardware and data analysis. So far, fMRI has been used effectively to reveal differences in functional specialisation between brain areas, within brain areas, and between large-scale neural systems; to explore the functional relationships between brain regions; and to investigate the role of different neurotransmitters on neural activity.

Experimental designs

Early fMRI experiments used very simple experimental designs, where two or more task conditions alternated in a regular cycle. These blocked designs used long cycles (usually 20-50 s) to separate the hemodynamic responses in different conditions. Data analysis relied on comparisons or subtractions between activations in the different conditions, following the assumption that the elemental psychological functions and their neural correlates summed linearly in a task.[4] Activation maps were influenced by neural processes evoked by the events in the task as well as by tonic processes associated with the psychological state of the participant over block of trials.

Today the experimenter is no longer confined to blocked designs or subtraction approaches. Blocked designs continue to be used, since they are a statistically powerful way to compare activations in two conditions in a short period of time. But the experimental arsenal for fMRI studies is almost as varied as that for the normal behavioural laboratory. Hemodynamic response functions have been shown to sum sufficiently linearly to separate activations associated with different events.[44] Using varied intervals between events of interest (stimuli or responses) it is possible to separate HRF functions associated with brief transient events, even when these are presented at a relatively rapid pace (e.g., every 2-4 s).[45-48] Several types of events can be intermixed in an experimental run. Interpretations of signal modulations in event-related designs can be more straightforward than those in blocked designs.

Data analysis and processing

Experimental variables in blocked or event-related designs can be manipulated in any number of ways (e.g., factorially or parametrically) and analysed accordingly. It is possible to analyse results using general linear models or non-parametric statistics applied to the magnitude or extent of activated voxels. Statistical tools for evaluating image data are well tailored for their task. Analysis of fMRI data typically takes into account errors introduced by multiple comparisons and non-sphericity of data, and can use variance variables to evaluate results using fixed- or random-effects models (see suggested readings for reviews of fMRI data analysis). There are still several difficult issues regarding experimental design and

[4] This is sometimes referred to as the principle of pure insertion Donders, 1868, reprinted in 43. F. C. Donders, *Acta Psychol (Amst)*. **30**: p. 412-31.(1969).S

analysis, but these are not only specific to fMRI studies. Choosing the right condition as a reference for a comparison, or predicting how the putative psychological factors may interact between conditions, is a challenge for any psychological experiment.

Preparing fMRI data for analysis requires handling several possible sources of artefact. Fortunately, there are many excellent research groups dedicated to developing software for processing and analysing fMRI data. The tools are becoming increasingly sophisticated and well-validated. There are reliable off-the-shelf algorithms to correct for the effects of head motion, remove temporal autocorrelations between successive images, filter away slow drifts in signal caused by hardware instability, co-register functional and structural images, and transform images into standardised anatomical frameworks (see suggested readings for reviews of fMRI data processing). Web sites for the major software packages for processing and analysing fMRI are listed at the end of this article.

Imaging functions of brain areas

Functional specialisation is one of the major principles of neural organisation. Far from being a mass of equipotential tissue, the brain is separated into numerous cortical and subcortical structures with unique patterns of inputs and outputs and profiles of sensitivity to stimulus parameters. The high spatial resolution and non-invasive nature of fMRI make it an ideal methodology for identifying and characterising these functional areas in the human brain. Functional brain areas can vary substantially relative to sulcal and gyral anatomy between people, and therefore the ability to analyse data at the single-subject level is also key. Mapping functional brain areas in the human brain provides a starting point for understanding general principles of organisation of functional neural systems.

Mapping the functions of brain areas is probably the most common application of fMRI. Elegant studies have defined functional areas within perceptual (e.g., [49, 50]) and motor systems (e.g., [51, 52]). For example, visual areas have been characterised in terms of their retinotopic organisation and modulation by simple visual features – luminance, location, colour, motion, disparity, visual shape.[53, 54] The sensitivity to higher level "features" has also differentiated between visual recognition areas, such as areas activated preferentially by face stimuli[55, 56] or by letter strings.[57, 58] Using fMRI it is also possible to test the modulation of activity by cognitive factors, such as selective attention[59, 60] or memory.[61] Characterising the functional profiles of brain areas provides an important bridge to experiments on other

animals, where more detailed investigations of neuronal mechanisms and computations are possible.

Of course it is also possible to use fMRI to investigate specialisations of brain areas for functions that cannot be easily measured or may not be well developed in other animals. Language functions provide a good illustration. Two critical language areas were discovered by investigations of brain-lesions patients in the late 1800's.[62, 63] These formed the core of models of language processing in the brain (see review by [64]), but their specific anatomical locations and functional roles remained difficult to pinpoint. Studies using fMRI have advanced greatly our understanding of the brain areas involved in language processing. For example, a variety of symptoms have been associated with lesions to the posterior inferior frontal cortex – the general region associated with Broca's area. Such patients can have difficulties with speech articulation,[65] grammatical comprehension,[66] or semantic analysis.[67] Imaging experiments are beginning to revise the concept of this traditional language area. Instead of being one unitary area with a restricted language-specific function, Broca's area may contain a mosaic of functionally specialised regions with different sensitivities to linguistic factors. More posterior portions of inferior frontal cortex around the pars opercularis are modulated by phonological and articulatory factors, whereas more anterior portions around pars triangularis and pars orbitalis are sensitive to semantic factors.[68-70] Furthermore, functional imaging studies have challenged the language-specificity of Broca's region,[71-73] and have raised the possibility that it is a premotor area involved in selecting and executing specific motor acts as well as in perceiving the same acts performed by others.[74] Some believe that this premotor view of Broca's area may help explain the evolution of language communication[75] (for reviews of the application of fMRI to the investigation of language see [76, 77]).

When functional areas are small and anatomically variable, it may be tricky to map them reliably over a group of subjects. To draw correspondences between function and structure, it is necessary to locate functional areas relative to individual anatomical landmarks (i.e., sulci and gyri). However, most approaches for standardising results over groups of subjects do not take into account variations in individual sulcal and gyral anatomy, which can vary considerably, leading to possible errors in localisation. Alternative coordinate systems that use flattened maps of cortical tissue and preserve relative gyral and sulcal anatomy have been developed, but are not yet used routinely.[78, 79]

One major problem with fMRI data is that there is just too much of it around. It can become overwhelming to distil sense out of reports of activation in a given brain region over numerous experiments with different experimental designs and manipulations, and analysed with different statistical approaches. The need for pooling data in centralised databases is increasingly recognised, enabling meta-analyses and validation of results (see [35, 80-83]). However, several thorny issues remain to be resolved before scientists agree on the structure and management of a fair and effective brain-imaging database, such as confidentiality, ownership and access to data (see [84]; NIH data sharing policy (http://datasharing.net/). At the moment, several databases are running in parallel, competing for the endorsement of the brain-imaging community. Their web sites are listed at the end of this article.

Imaging functions within brain areas

Functional specialisation also occurs within brain areas. The primary visual cortex provides a textbook example. Cell populations are subdivided in columns according to which eye's input prevails in driving the neuron's activity (ocular dominance columns), and the preferred orientation of the input stimulus (orientation columns). Cells are also clustered according to their sensitivity to colour versus shape and motion parameters (blobs and interblobs). Some have suggested that cortical hypercolumns, such as those in primary visual cortex, form the key units of neural functional specialisation in the brain (for a recent outlook, see [85]). Ideally, we would like to visualise differences in brain activity at the columnar level of neural organisation. Routine fMRI studies do not have sufficient spatial fidelity to resolve activity at the columnar level. However, using a high magnetic field (4 Tesla) coupled with a surface head coil placed over occipital cortex to measure signals with higher spatial resolution, it has been possible to image ocular dominance columns in the human primary visual cortex.[86]

Imaging networks of brain areas

The high spatial resolution of fMRI, however, is only one side of the coin. The other major advantage of fMRI is its ability to measure activity over several brain areas nearly simultaneously. Though there is unquestionable functional specialisation of brain areas, it is through the interaction of multiple brain areas that cognitive functions are achieved. For example, no visual brain area in isolation can 'see' anything.

Activation studies

Some may fear that fMRI has endorsed a phrenological view of brain organisation.[87] On the contrary, we believe fMRI has promoted a systems-view of brain function, and is beginning to expose principles of organisation of cognitive neural systems. Neural systems involved in major cognitive domains are increasingly well understood. Two concepts are emerging: (1) purely cognitive functions can 'borrow' specialisations of brain areas in related sensorimotor functions to achieve behavioural goals and (2) individual brain areas can contribute to networks in different cognitive domains.

We have already mentioned the possibility that areas that contribute core functions to language may not be language-specific.[88] Another example is the parietal-frontal system for the orienting of spatial attention (see [60, 89, 57]). Brain areas in the posterior parietal cortex and superior premotor and dorsal prefrontal cortices that shift the focus of spatial attention overlap extensively with brain areas that control saccadic eye movements toward stimuli.[90-92]. Attentional orienting seems to capitalise on the specialisations of the oculomotor system to map, predict and update spatial positions of events at high speeds taking into account several spatial frameworks (retinal position, head position, etc, see [89]).

Connectivity studies

In parallel with the increasing emphasis on imaging functional circuits, analysis techniques are being developed to investigate dynamic interactions between different brain regions. Relationships between activity in different brain areas have been divided into two types - functional connectivity and effective connectivity.[93-95] Functional connectivity is defined as the simple correlations of activity between different brain areas, and does not necessarily represent meaningful interactions. Effective connectivity is defined as the influence that one region exerts over another, usually reflecting meaningful interactions within an established neural model. Revealing patterns of effective connectivity and their modulation by cognitive factors is of primary interest in current studies of cognitive neural systems. Analyses of effective connectivity have yielded an exciting range of results relating to modulatory roles between discrete brain areas, which would not otherwise have been discovered using conventional fMRI techniques.

Effective connectivity can be estimated using different approaches. Structural equation modelling[5] was the first step to look at brain connectivity.[96, 44] This method works out connectivity based on the covariance structure of activity in a predefined anatomical model. It does not accommodate explicit inclusion of the experimentally manipulated factors within the model, but modulatory influences can be inferred by comparing connectivity values in different task conditions. For example, in an fMRI study on attention to visual motion,[96, 44] a significant increase in the connectivity between V5 and posterior parietal cortex occurred in attention conditions, suggesting that attention modulates neural connectivity along this pathway. As with all modelling techniques, there are disadvantages to structural equation modelling. The number of areas that can be included in the model is limited[96, 44] and their choice can be difficult.[97] Furthermore, it assumes interactions between brain areas are linear and instantaneous.

Dynamic causal modelling is a new approach being developed to estimate effective connectivity under different experimental contexts.[98, 99] Like structural equation modelling, a pre-defined network of brain areas is required. The technique is based on a Bayesian framework. The model can accommodate non-linear interactions between brain areas and considers the temporal evolution of the fMRI signal. There is also no theoretical limit on the number of connections that can be modelled.[99] With this new method, it is possible to estimate the impact that an experimental manipulation has on pathways or connections within the brain. For example, [100] used dynamic causal modelling to investigate the interaction between association areas and category-selective visual areas (i.e., those showing strong preferences for face, house, or chair stimuli) during visual perception versus visual imagery. The modelling results suggested that during visual perception, patterns of activation in category-selective extrastriate cortex are modulated by content-sensitive forward connections from early visual areas. During visual imagery however, the category-selective visual activations were mediated by content-sensitive backward connections from prefrontal cortex. These results suggest that there is a dynamic interaction within this network of brain areas involving bottom-up influences from striate visual areas during visual perception, and top-down influences of prefrontal regions during visual imagery.

[5] Structural equation modelling, or path analysis, was first developed in economics, psychology and the social sciences.

Measuring the modulation of effective connectivity in neural systems during cognitive tasks is clearly important for deriving organisational principles of cognitive neural systems. This type of measure requires both the high spatial resolution to individuate functional brain regions and the global view of activity in several brain regions simultaneously, making fMRI particularly suitable to this task. At present, there are still several difficulties with estimating and interpreting the psychophysiological interactions[101] between task conditions and brain areas with connectivity models. Predefined anatomical models are usually oversimplifications based on animal research, but the increasing knowledge of human anatomical connectivity yielded by methods such as diffusion tensor imaging should help. As discussed above, interpretation of BOLD results can be difficult. However, as the connectivity methods mature, fMRI is replacing the phrenological view of the brain with a dynamic systems view.[102]

Imaging pharmacology

Neurotransmitters, such as glutamate, acetylcholine or dopamine, provide the main currency for the integration and modulation of activity in neural systems. With standard fMRI methods, it is still not possible to visualise specific neurochemicals (but see [103] for review of MR spectroscopy). This remains the domain of Positron Emission Tomography (PET), where specific radioligands can be used to reveal the distribution, density and uptake of neurotransmitter receptors in both normal and diseased brains (for a review see [104]). However, it is possible to combine fMRI with pharmacological manipulations, in order to test how changes in neuromodulators affect the functioning of brain areas and systems.

Initially, pharmacological fMRI methods were mainly applied to patients suffering from disorders such as schizophrenia,[105] depression[106] or from drug addiction,[107] but more recently, with the development of new neurochemical ligands, pharmacological fMRI studies are being used to tackle questions about neurotransmitter involvement in several cognitive domains. Studies are addressing longstanding and important questions, such as the role of acetylcholine in memory,[108] the role of noradrenaline in selective attention,[109] the roles of GABA and acetylcholine in working memory,[110, 111] the role of dopamine in evaluating rewards,[112] and the role of serotonin in impulsivity.[113] Most pharmacological experiments at the moment focus on how drug compounds act on specific brain areas. However, another fruitful area for study is the analysis of how pharmacological manipulations modulate effective connectivity (e.g., [114]).

However, despite these advantages, there are several important methodological considerations about using pharmacological agents with fMRI. The drug agonists or antagonists used can themselves cause vascular changes (e.g. on blood pressure, blood flow) and therefore directly induce changes in the BOLD response that are independent of their neuromodulatory action. It is important therefore to determine the extent to which changes in signal reflect neuronal activation versus vascular effects (e.g. [115, 116]; for a review see [117]). Other methodological difficulties come from systemic drug administration, which does not always provide the targeted effects of interest. Furthermore, currently there are only a select number of available drugs licensed for use in humans.

Combining fMRI and other Imaging Methods

Though there are many fMRI praises to sing, every method has its limitations. Functional MRI is a correlational method, and it is often difficult to test whether activated areas play critical or even active roles in the tasks at hand. The temporal resolution is limited by the sluggish hemodynamic response. When the experimental question requires assessing the critical role of brain functions or calls for real-time temporal resolution, then other complementary techniques can be employed, such as transcranial magnetic stimulation (TMS) and event-related potentials (ERPs). Current technological developments have been providing for the *simultaneous* use of such very different methodologies. The advantages of doing this are far beyond simply doing two experiments at once.

TMS-fMRI

TMS is an "interference" technique – its use involves changing brain activity and observing the consequences upon behaviour or neural processing. Brief transcranial magnetic pulses induce voltage changes that stimulate populations of neurons within focal brain regions. The induced synchronous stimulation of large neuronal pools normally interferes with ongoing neural processing in the region, and TMS therefore has an effect similar to a virtual and reversible lesion.[118] Data recorded in TMS experiments are usually either disruptions to behavioural performance of alterations of responses to further TMS pulses. The latter is thought to index changes in neural excitability. TMS has been integrated with imaging techniques (apart from fMRI) for nearly a decade.[119] TMS studies have often incorporated MRI studies by using a structural MRI image to co-register the site of stimulation. But now there is a steadily growing body of studies that have combined the two techniques simultaneously.

There are two main obstacles to combining fMRI and TMS: ensuring that TMS hardware can be placed safely within a high magnetic field, and eliminating the interference of the strong magnetic pulses delivered by TMS to the fMRI signal. For safety reasons, experiments need to use TMS equipment made of nonferromagnetic materials. To eliminate signal interference, long shielded cables that fit inside the magnetic coil can be used (and may restrict which brain areas can be stimulated). The feasibility of TMS-fMRI has now been demonstrated using an event-related fMRI design[120] and using a field strength of 3 Tesla.[121] One key application of concurrent TMS/fMRI is to examine exactly what effect TMS has on the brain, and in particular, to what extent the effects of the electrical noise that TMS inserts spread to other regions. Understanding this would help interpret the results from TMS-only experiments, and may also illuminate the connectivity of the regions stimulated. Recently, several experiments have contrasted the BOLD responses elicited when TMS has been applied at strengths above and below the motor threshold.[122, 123] The difference is in the strength and not the pattern of activation: subthreshold TMS has been found to elicit a BOLD response in many of the same areas as superthreshold TMS, but to a lesser extent. One surprising finding of a number of studies is that during subthreshold TMS there is no detectable BOLD response in the area directly stimulated, although there is activation in the areas connected to it. It is not currently clear why the effect of TMS should be able to spread – and be detectable with BOLD – to other regions without being present in the area stimulated. This finding has been demonstrated with stimulation over primary motor and sensory cortices[121] and lateral premotor cortex,[123] and suggests there is a real need for future experiments to integrate TMS with fMRI to describe TMS' effect on the brain, as well as investigating the functional connectivity using the causal (rather than plain correlational) power of TMS.

fMRI-EEG

Whereas fMRI is slow because it relies on the hemodynamic response, electrophysiological methods that measure directly voltage changes or their associated magnetic fields have real-time resolution. The voltage changes that can be recorded at the scalp reflect summation of synaptic potentials as well as some slow currents associated with the action potentials over large populations of neurones (for reviews of EEG/MEG see [124, 125]). There are many research questions that require the high temporal resolution of methods

based on electroencephalography (EEG) or its magnetic counterpart magnetoencephalography (MEG).

MEG cannot currently be combined with fMRI because it relies on delicate superconductor technology that is not easily transportable into an MRI scanner environment. However, EEG-related methods have been successfully integrated with fMRI.[126] Again, one major consideration is ensuring safety. It is imperative to use MRI-compatible materials and to isolate the subjects from possible stimulation by the radiofrequency pulses through the EEG electrodes.[127] The principle technical problem is removing the fMRI artefact from the EEG data. MRI scanning requires changes in the magnetic field gradient, which, unchecked, mask all EEG data. Another problem arises from the ballistocardiogram – the prominent artefact created when the subject's pulse causes slight movements of the EEG electrodes. These movements induce large currents when in the strong magnetic field within the MRI bore. The ERP-fMRI artefacts comprise frequencies within the whole EEG range, which rules out the use of a simple filter. Many different signal processing techniques have been developed, e.g. frequency domain processing,[128] spatial filtering,[129] average waveform subtraction[130] and great improvements in artefact removal have now been made (e.g. [131]).

The most commonly used EEG-related method in cognitive studies involves averaging the signals that are time-locked to sensory or motor events in order to extract consistent patterns of voltage changes. Event-related potentials (ERPs) contain identifiable peaks and troughs (known as "components") that vary according to the perceptual, cognitive and motor demands in tasks. Some ERP components, especially in the early phases of the ERP waveform, have well defined sources. For example, the C1 component evoked by visual stimuli reflects early activation of primary visual cortex.[132] Other components, especially in later phases of the ERP waveform, probably reflect summation of activity in several brain regions that vary in spatial location as well as precise timecourse. For example, there are books about the possible brain areas and cognitive factors that contribute to the generation of the P300 component.[133] The main advantage of ERPs is that they provide very sensitive measures of transient modulation of information processing in the brain. These measures are temporally specific and can be obtained without the requirement for overt behavioural responses. The main problem is that the lack of knowledge about the brain areas contributing to the ERP components can make the results difficult to interpret.

One reason to combine ERP and fMRI is to help constrain source-localisation analyses to define the brain areas contributing to ERP components (e.g., [134]). The ERP-fMRI combination generates a dynamic view of the network of brain areas that support behavioural tasks.[135] Another reason is to disambiguate interpretation of fMRI results. For example, while activity in primary visual cortex shows modulation by selective attention in fMRI tasks, there is no modulation of the early C1 component of the ERP (see [136]). Findings from non-human primate studies have also questioned the ability of selective attention to modulate activity in primary visual cortex (e.g., [137]). Modulation of primary cortex in fMRI studies therefore appears to reflect modulation of later re-entrant pathways, and source localisation in ERP experiments has supported this interpretation.[138] Whether modulation in V1 occurs early or late has significant impact on theoretical models of visual selective attention.

One might argue that it is sufficient to run parallel fMRI and ERP experiments for these purposes, not justifying the technical challenge of combining the methods simultaneously. Simultaneous methods become necessary, however, when it is not possible to repeat the same experiment on a subject without this changing the nature of the task. For example, drug or patient studies might need to examine transient 'one-off' changes in neural activity at particular times (e.g. post-administration/post-operation). Another situation is when the analysis of neural data requires correlation with subjective judgments by participants, for example when comparing brain activity related to subsequently remembered versus forgotten items, or when correlating brain activity with emotional ratings of different stimuli. Furthermore, there is potential for EEG measures to be used as regressors in BOLD-signal analysis, to find if the trial-by-trial variation in a particular waveform – for instance the enhancement of a visual component by selective spatial attention – correlates with the variation in the BOLD signal from a particular neural region. In this vein, [126] found a negative correlation between the power of the EEG alpha rhythm (present when an awake subject closes their eyes) and the BOLD response, in a set of areas that concur with results from animal experiments investigating the location of alpha-band activity. The use of EEG and ERPs may therefore extend the analyses of effective connectivity, introducing greater temporal accuracy.

However, the difference between the bases of the signals measured by fMRI and ERP prevent these techniques from aligning perfectly. Even though the BOLD signal has been shown to correlate with synaptic activity in local field potentials[41, 42] (see above), the

macroscopic behaviour of EEG and BOLD signals can differ in some important respects. For example, the alignment of the orientation of neurons within a brain region is critical to the generation of macroscopic voltage changes that can be recorded with EEG[139] but it is unlikely to have a significant effect upon the BOLD response in a brain region. Voltage decays exponentially with distance, and therefore the EEG is biased toward populations of aligned neurones that are close to the scalp, whereas he BOLD signal samples brain activity more homogeneously within the brain. Finally, EEG methods can detect very brief transient modulations in neural processing, whereas the sensitivity of BOLD to changes in brain activity may depend on the duration of modulation.[140, 48] In integrating these highly complementary methods, it is essential to keep these factors in mind, and not simply merge the data sets blindly.

ERP-fMRI example

New developments of MRI

As indicated by previous sections, (fMRI offers intriguing advantages over other brain imaging techniques, but it also suffers from some limitations, e.g. the rather coarse temporal resolution, or the potential discrepancy between the actual measured signal and the assumed underlying neuronal processes. Since its relatively recent initial applications,[141-143] technical advances in fMRI technology have been unrelenting. Over the last few years significant progress has been made in overcoming some of the method's limitations. Given the pace of developments, much more is certain to come.

Over the past decade, hardware improvements have significantly increased the strength of the gradient magnetic fields. The signal intensity in MRI is proportional to the magnetic field. Increasing the magnetic field sufficiently makes it possible to image signals from nuclei in less densely distributed molecules. Recently, a 9.4 Tesla scanner for humans was unveiled, which should enable studies not only to image the anatomy and blood-related changes, but metabolic processes, by capturing signal from molecular building blocks such as sodium, phosphorus, carbon, nitrogen & oxygen atoms (Nature-News, 09/21/2004). In addition, such high field-strengths also offer advantages for functional imaging in providing higher spatial resolution and signal-to-noise ratios.

A separate development has focused on bridging the knowledge gap between the measured fMRI BOLD response and the underlying neuronal events, i.e. to characterise more precisely where and when the neural activity happened, which elicited the measured hemodynamic response. One method, which could improve the BOLD contrast, is diffusion-weighted imaging. This method adjusts the contribution of single voxels according to the mobility of protons they contain. For example, protons in blood in large blood vessels move more quickly and uniformly than those within small capillaries. The BOLD contributions from large vessels might skew the functional map of activity, since the true neural activity is more tightly coupled with the smaller vessels. Diffusion weighting aims at selectively reducing such contributions, leading to a higher spatial resolution.[144, 145]

Another method for improving spatial and temporal resolution of fMRI is to measure the initial dip of the hemodynamic response.[30, 31] The initial dip is believed to result from early increases in oxygen consumption coupled to metabolic demands of neuronal signalling that precede the over-compensation by blood flow (see above). As mentioned earlier, it has been possible to image ocular dominance columns in the human brain. This was achieved by imaging the early hypoxic response resulting from brief eye-specific stimulation using high magnetic field strength and a surface head coil overlying the occipital scalp.[86] Researchers using high-field fMRI have also been able to identify separate orientation columns in the visual cortex in animals using the initial dip, whereas the later positive BOLD response was blurred over columns.[146, 147] Despite these exciting results, the use of the initial dip remains a controversial topic (see [148, 149]). Most of the convincing results rely on animal research, whereas the initial dip is not observed in most human fMRI experiments. With the advances in hardware, it may become possible to use the initial dip as a marker of neuronal activity with much greater spatial and temporal resolution than is currently standard.

A more daring approach is to overcome the need to rely on indirect hemodynamic measures altogether, and to measure the activity of neurons directly using fMRI. In theory this should be possible, since the magnetic transients induced by voltage changes in neurons should also create inhomogeneities in the magnetic field. However, because electrical signals in neurons are relatively weak, transient and spatially inhomogeneous, these measurements are very challenging. The results have not been altogether disappointing, and different lines of research are being pursued. One line aims at measuring Lorentz forces, which arise from charged particles moving through a magnetic field (Lorentz-effect imaging: [150]). Since

neurons contain moving electrical charges (e.g. within active axons) these should be detectable. Another line of research focuses on the temporal profiles of magnetic transients induced by neuronal activity. Electrical signals in action potentials are very fast. It may therefore be possible to identify neuronal spikes by suppressing concurrent slow magnetic changes to emphasise the rapid changes.[151] The ability to visualise neuronal activity directly, and to ignore the hemodynamic response altogether would greatly enhance the spatial and temporal resolution of fMRI. The spatial resolution would climb to its full potential and enable imaging of small clusters or even individual neurons. The temporal resolution would be limited only by the radiofrequency pulses used to excite and measure the signal, which would be within the temporal framework of the evolving cognitive and neural functions.

Don't be surprised if much more than that unfolds in the MRI world over the next decade.

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J. Culham, *fMRI for Dummies: defiant.ssc.uwo.ca/Jody_web/fmri4dummies.htm.*

fMRI databases

- BrainMap (Fox et al 2002): www.brainmapdbj.org.
- Neurogenerator (Roland et al, 2001): www.neurogenerator.org.
- Human Brain Project: www.nimh.nih.gov/neuroinformatics/index.cfm.
- International Consortium for Brain Mapping: www.loni.ucla.edu/ICBM/ICBM_About.html.
- Surface Management Systems DataBase: sumsdb.wustl.edu:8081/sums/index.jsp.
- FMRI Data Centre (Van Horn et al., 2004): http://www.fmridc.org/.

fMRI methods for data processing and analysis

- http://www.fil.ion.ucl.ac.uk/spm/course/notes02/overview/Refs.htm, Welcome Department of Imaging Neuroscience.

- http://www.fmrib.ox.ac.uk/fslcourse/lectures/fmri/, Oxford Centre for Functional Magnetic Resonance Imaging of the Brain.
- http://www.mrc-cbu.cam.ac.uk/Imaging/Common/fmridefaults.shtml, Cognition and Brain Sciences Unit, Cambridge University.
- http://www.radiology.northwestern.edu/research/neuro/, Northwestern Cognitive Brain Mapping Group.

fMRI software for data processing, analysis & visualisation

- http://afni.nimh.nih.gov/old/afni/index.shtml, AFNI (National Institute of Mental Health, Bethesda).
- http://airto.bmap.ucla.edu/BMCweb/SharedCode/SharedSoftware.html, software from UCLA Brain Mapping Center.
- http://brainmap.wustl.edu/caret/, Caret (Washington University, St Louis).
- http://brainmap.wustl.edu/resources/surefitnew.html/, SureFit (Washington University, St Louis).
- http://surfer.nmr.mgh.harvard.edu/, Free Surfer (CorTechs).
- http://white.stanford.edu/software/, Vista Software (Stanford Vision and Imaging Science and Technology, Heeger and Wandell labs).
- http://www.bic.mni.mcgill.ca/software/, software from BIC (McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University).
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- http://www.fil.ion.ucl.ac.uk/spm/, SPM (Wellcome Department of Imaging Neuroscience).
- http://www.fmrib.ox.ac.uk/, FEAT (Oxford Centre for Functional Magnetic resonance imaging of the brain).
- http://www.mrc-cbu.cam.ac.uk/Imaging/, software from CBU (Cognition and Brain Sciences Unit, Cambridge University).
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