Meeting Report: Choosing the Right MR Tools for the Job

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James S. McDonnell Foundation–sponsored workshops discuss issues concerning functional brain imaging techniques and their use in cognitive neuroscience. Reports from workshops on functional neuroenergetics, the use of transcranial magnetic stimulation, and a workshop on the biological correlates of cognitive functions are available (Recommended Reading 1). This report integrates and summarizes the discussions from two workshops with overlapping interests. The first one was concerned with the statistical analysis of functional magnetic resonance imaging (fMRI) data and the second focused on the advantages and disadvantages of functional imaging at different magnetic field strengths.[1]

OVERVIEW

Noninvasive monitoring of metabolic and physiologic indicators of brain activity, particularly by fMRI, is now a standard tool for cognitive neuroscience research. The ready availability of magnetic resonance (MR) scanners, intended primarily for clinical use, coupled with the rapid rate of technical innovations, have resulted in an exponential increase over the past decade in the number of cognitive neuroscience articles that use some application of brain imaging and that present data as visually appealing, multicolored "brain images." The potential of gaining insight into the biological basis of mental processes has encouraged many cognitive neuroscientists to incorporate fMRI into their research. Unfortunately, the ready availability of the technology, the apparent ease of performing fMRI studies, the presentation of the data as visually appealing "brain maps," and the somewhat uncritical enthusiasm for its use has contributed to rather uneven quality in fMRI results. The majority of functional brain imaging data are obtained with unmodified clinical MRI systems and analyzed using statistical packages downloaded from Internet sites (see Recommended Reading 3). These standardized statistical packages are used to convert the data from fMRI studies into 2-D and 3-D "maps" or "images" displaying regional patterns of brain activity. The excitement generated by functional MRI studies and its claims to provide a "window into the mind" have led many researchers to overlook what we can and cannot say in response to the questions: "What does the fMRI signal measure? What can it tell us about neural and mental processes?"

In a typical fMRI experiment, data are acquired from the subject's brain during performance of cognitive tasks and during some reference condition. The "images" obtained, representing the spatial distribution of MR signal intensity changes, are acquired rapidly (on the order of 1 sec each). The large data sets so acquired allow the experimenters to use statistical analysis packages to compare the images obtained during different tasks. The statistical comparison searches for brain regions showing different signal intensities during different tasks. The final presentation, often called the brain activity map, is usually an image of these statistically identified regions, color coded to represent the level of statistical significance, overlaid on an anatomical MR brain image. From these maps, cognitive neuroscientists make inferences about the neural correlates of cognitive processes.

Cognitive neuroscientists, particularly those not actively engaged in fMRI research, when asked the question "what does the fMRI signal measure?," often answer (in decreasing order of frequency and increasing order of accuracy):

- regional neuronal activity
- incremental changes in regional neuronal activity
- incremental changes in regional cerebral blood flow

None of these descriptions are completely accurate. An MR physicist would describe the most popular fMRI method, blood oxygen level-dependent imaging (BOLD), as measuring the change in the intensity of the nuclear MR signal due to changes in the transverse relaxation time of the protons of water molecules in the blood and brain tissue as a result of changes in hemoglobin oxygenation and blood volume. The difference signal is referred to as having BOLD contrast. In this article, when the term "BOLD signal" is used it refers to the difference signal between two measurements.

The basic link between the fMRI signal and neuronal activity is blood oxygenation. Blood oxygenation depends upon physiological parameters related to neuronal activity, including cerebral blood flow, cerebral glucose metabolism, and blood volume. Cerebral glucose metabolism has long been considered a gold standard for indirectly measuring neuronal activity, based upon the energy costs associated with neuronal

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information transfer processes such as action potentials, postsynaptic potentials, and neurotransmitter release and recycling. While considerable evidence supports the hypothesis that metabolic changes are related to changes in neuronal activity, and that the BOLD signal reflects changes in metabolism, the road from the technical MR description to the desired neuronal activity maps is fraught with uncertainties and controversies and remains an area of active research. During 2001, published research findings correlating the percent changes in the BOLD signal with measures of neuronal electrical activity such as spike frequency (see Rees, Friston, & Koch, 2000) or local field potentials (see Logothetis, Paul, Augath, Trinath, & Oeltermann, 2001; Bandettini & Ungerleider, 2001) made important contributions to our understanding of how the BOLD signal acquired in fMRI experiments relates to other measurements of neuronal activity but they do not specifically address the fundamental issues discussed during the JSMF-sponsored workshops. What remains to be defined is how neuronal activity, energy metabolism, regional blood flow, and the BOLD signal are linked (see below for further discussion).

An image analysis expert would also find the more colloquial descriptions of functional brain images oversimplified. Despite the language used to discuss them, the brain images displayed in scientific publications and in the popular press are not representations of changes in brain neuronal activity, or areas of "activation," or even the magnitude of the BOLD signal. Rather, the images are computer-generated, color-coded "maps" of statistically significant comparisons. It is important to stress that the finding of statistically significant differences and a measured change in the actual magnitude of the signal acquired are not necessarily interchangeable. The same BOLD signal may be statistically significant in one subject and not distinguished from noise in another subject. In addition to measurement sensitivity issues, identifying a brain region as having a statistically significant BOLD signal depends on how well the time course of the signal agrees with the assumed time course of the cognitive task. Depending on the nature of the assumptions made in the statistical analysis package, the same data could yield statistical maps identifying different patterns of activation.

Efforts to raise concerns about "missing links" in the chain of reasoning from the fMRI signal to neuronal activity are often dismissed as irrelevant, as long as the signal localizes a change in neuronal activity. This objection neglects the obviously strong influence of the data acquisition and data analysis methodologies on the resulting "brain activity map." To the extent that the methodology influences the results, it behooves researchers using fMRI to possess a deeper understanding of the theoretical and practical strengths and limitations of the technique. The conditions of data acquisition and the approaches to image analysis are as integral to the interpretation of the results as the thoughtful design of the cognitive task.

To address the question of what basic knowledge of MR physics (Recommended Reading 2) and statistical analysis (Recommended Reading 3) cognitive neuroscientists need if they are to understand the limitations of interpreting and analyzing the MR signal, as well as surveying new advances in MR technology and signal analysis methods, the James S. McDonnell Foundation sponsored two workshops. The goals of the first workshop were: (1) to identify the core assumptions about the fMRI signal and the neuronal correlates of brain cognitive processes embedded in fMRI statistical analysis packages; (2) to explore the range of validity of these assumptions; and (3) to discuss how the assumptions influence the resultant brain activity map. The second workshop's goals were: (1) to determine the optimum magnetic field strengths for performing fMRI studies based on MR physics; (2) to review the biophysical and metabolic basis of the fMRI signal; and (3) to identify common errors made in the analysis and interpretation of the fMRI signal. In both workshops, the question of what information does cognitive neuroscience need from fMRI physics was addressed. The workshops brought together cognitive neuroscientists, MR scientists, statisticians, and image analysis experts.[2] The main points from each workshop are summarized below.

WHAT IS THE OPTIMUM FIELD STRENGTH FOR fMRI STUDIES?

Douglas Rothman launched the field strength workshop with an historical account of MR and an introduction to the physical principles of the method. He pointed out that the fMRI signal is derived from MR spectroscopy (MRS), which measures the radio frequency (RF) quantum transitions of the proton (^{1}H) nuclei of water in a magnetic field. The transitions are induced by irradiating the proton spins with a pulsed RF field. The transition frequencies are proportional to the strength of the magnetic field. For example, at 1.5 T, ^{1}H nuclei resonate at 60 MHz, while at 3.0 T they resonate at 120 MHz. The spatial location of the spins is encoded through the use of electromagnets called gradients. The magnetic field of the gradient coils varies linearly with position and, as a result, the ^{1}H resonance frequency will also depend upon position. The combination of RF and gradient pulses used to obtain the MRI signal is called a pulse sequence. The RF signal that is emitted from the sample is received by a specialized radio antennae and receiver. The signal is stored in a computer where, using a mathematical method known as the Fourier transform, an image of the spatial distribution of the H_2O spins is calculated. On the basis of physical principles, in the ideal case the MR sensitivity should increase linearly with field strength. In reality, calculation of the actual

gain with field in fMRI is complicated by several factors including:

- hardware limitations at higher fields
- physiological noise
- the intravascular and extravascular components of the BOLD fMRI signal

In addition to these limitations, there are questions about the practicality of higher fields, including:

- safety
- ease and reliability of use

Finally, the higher sensitivity afforded at high fields has the potential of making alternative methods for functional imaging such as sodium and O17 imaging, diffusion imaging, and MRS feasible.

The discussion of each of these factors is summarized in the following sections.

Hardware Limitations

The generation of the fMRI image depends on the same technology as standard MRI and several speakers addressed the limitations these factors impose. At magnetic field strengths up to 4 T, there was general agreement that the theoretically predicted sensitivity enhancement expected from increasing field can be achieved. Peter Van Zijl and Keith Thulborn presented results of direct comparisons of images obtained during identical tasks at 1.5 and 3 T. These comparisons showed the expected two times enhancement in sensitivity with increasing magnetic field strength. Kamil Ugurbil presented data from his laboratory's 7-T instrument that showed a linear increase in the sensitivity of measuring the BOLD signal. Presently at 7 T, there are RF pulse power and gradient stability limitations that must be addressed before the full potential sensitivity enhancement may be routinely achieved. Ugurbil felt that these limitations will be overcome with further technical development and that studies at 7 T have advantages both for sensitivity and for microscopic specificity of the signal to the regions of activity change (see below).

Another technical limitation of higher fields is magnetic field inhomogeneity due to a property of tissue called susceptibility. At interfaces between different materials, such as brain tissue and the skull, the magnetic field will be distorted, resulting in a spatial distortion of the image. Several speakers showed examples of images with large distortions in the frontal lobe near the sinuses and in brain regions near the base of the skull, such as the hippocampus and amygdala. These distortions can be greater in fMRI than standard MRI, which complicates coregistration of the images and may lead to a misindentification of the region of activation. Peter Van Zijl gave examples of how spatial distortion may be reduced by mapping the magnetic field prior to the study and using this information to correct the fMRI.

Douglas Rothman cited ongoing research in several laboratories to develop pulse sequences and hardware magnetic field correction strategies that would reduce spatial distortion during image acquisition. Participants generally agreed that the further development of processing and hardware methods for improving magnetic field inhomogeneity effects is highly desirable.

Physiological Noise

The actual sensitivity achieved by fMRI may be constrained by the effects of physiological noise as opposed to physical sensitivity limitations. The term "physiological noise" refers to any source of image intensity variation due to factors other than neuronal activity. These factors include, but are not limited to, respiration, the cardiac cycle, motion of the subject, and possibly low-frequency brain activity, such as measured in EEG. The signal fluctuation from all of these sources increases linearly with field strength, and if not corrected may eliminate any sensitivity increase with field. Physiological noise due to respiratory and cardiac cycles may be distinguished from the functional signal based upon characteristic frequencies. One can compensate for motion by using motion insensitive pulse sequences, navigator pulse sequences that measure motion, and the mathematical manipulations to shape the data after acquisition (termed "postprocessing"). Ravi Menon gave an example in which physiological noise reduction methods improved the sensitivity of the fMRI signal by several-fold.

One Functional Imager's Vein is Another's Venule—The Influence of Field Strength and Imaging on the Microscopic Localization of the fMRI Signal

The beautifully detailed structure depicted in an anatomical MRI is derived from the interactions of the hydrogen atoms of water with its surrounding microenvironment, resulting in contrast between different tissue types. In BOLD fMRI, additional contrast is obtained from the varying transverse relaxation effects from blood. Transverse relaxation is characterized by two time constants, T2 and T2*, which are the durations (typically in milliseconds) for the MRI signal to decay by e^{-1} in spin-echo and gradient-echo pulse sequences, respectively. Based on the physical process of this relaxation, the transverse relaxation constants (including both intravascular and extravascular water) are strongly affected by the local oxygenation level of blood and by the magnetic field strength. BOLD fMRI takes advantage of this relaxation dependence to provide images of the changes in T2 or T2* during brain activity linked to changes in blood oxygenation.

The BOLD fMRI signal may be conceptually viewed as arising from two sources, extravascular and intravascular

water. Typically, neuroscientists need to identify the areas of brain parenchyma (and not their neighboring blood vessels) that are "activated." However, the detected BOLD signal resulting from changes in blood oxygenation may arise from intravascular water in large draining veins, as well as extravascular, parenchymal water in the vicinity of these veins. This lack of distinction may potentially limit the spatial resolution of the method. A major topic of discussion at the meeting was the ability at higher field strengths to enhance the parenchymal extravascular signal in the vicinity of small venules and capillaries. While summarizing the imaging capabilities of the widely available 1.5-T instruments, Peter van Zijl emphasized that cognitive neuroscientists must recognize that at 1.5 T most of the BOLD fMRI signal acquired with gradient-echo sequences is primarily from intravascular water, with the extravascular component also mainly from the parenchyma surrounding large venules. There was general agreement among the physicists that there are limitations on spatial and temporal resolution of signal arising from the venous signal source, but less agreement about the severity of this problem. Van Zijl presented data showing that there was no temporal delay in the BOLD response measured directly within a vein relative to the BOLD signal from the tissue bed it drained. Participants debated the limits imposed by intravascular signal sources at 1.5 T. The influence of larger veins may be eliminated by using angiography to identify them and then discarding the signal from adjacent regions. However, venules in the sub-100-μm-diameter region are too numerous to discard. The competing claims for the delocalization of the signal due to these venules ranged from 1 cm to below 1 mm, largely based on estimates of the size of the tissue bed drained. The contribution from intravascular signal may be reduced by using strong gradient pulses referred to as "diffusion gradients" to suppress most of the signal from flowing water. Several speakers presented results on using diffusion-weighted sequences to determine the fraction of the BOLD signal that arise from brain parenchyma at different field strengths. At fields below 3 T, it was generally agreed that there is not enough signal from parenchymal water to warrant these approaches.

Another approach to improving the localization of the BOLD signal is to use spin-echo sequences. In these sequences, the extravascular signal is primarily obtained in the region of capillaries and small venules. Diffusion gradients may be also added to spin-echo sequences to suppress the signal from intravascular water. In response to questions about the use of spin-echo sequences to reduce the intravascular signal, Van Zijl was quick to point out that at conventional field strength (1.5 T) the loss of sensitivity makes using spin-echo BOLD fMRI disadvantageous (an exception being when it is used to directly measure the oxygenation level of intravascular water as demonstrated by Van Zijl). Keith

Thulborn and other discussants pointed out that higher field magnets allow spin-echo sequences to be used by enhancing the BOLD signal from extravascular water near capillaries by enhancing the size of the BOLD signal. Another advantage of high field is that the size of the intravascular signal decreases due to the very rapid decrease in blood T2 with field. Seong Ji Kim and Kamil Ugurbil showed that at field strengths above 7 T, high sensitivity might be obtained from parenchymal water near capillaries with almost all of the intravascular water eliminated by T2 decay. Ravi Menon presented results obtained at 4 T using a novel method that separated the BOLD signal from veins and tissue based upon differences in signal phase.

Safety

A common concern expressed about studying human subjects with high magnetic field strength systems is safety. The major safety factors at higher fields are the increases in the RF power, gradient pulse strength and rise time, acoustic noise, and static field effects. Keith Thulborn showed that at 3 T it is possible to perform BOLD fMRI and standard anatomical MRI within FDA safety guidelines. At 4 T and above, some modifications in pulse sequences are needed to avoid tissue heating and excessive gradient strength, but these are not limiting to BOLD fMRI performance. Acoustic noise in high-field systems due to the pulsing of gradient coils can exceed safe levels during fMRI studies. The noise level is reduced experimentally by the using ear protectors and acoustic insulation in the magnet bore. Several discussants cited improvement in noise reduction technology as an important area for development. Safety studies performed at 4 T found the only significant reported effect is dizziness while a subject enters or leaves the bore of the magnet. The dizziness is most likely caused by the magnetic fields effects on the otolymph in the semicircular ear canals. Controlling the speed with which subjects are placed in the bore of the magnet and controlling head movement (required to acquire useable images at any field strength) should eliminate most unpleasant side effects. Kamil Ugurbil reported that there were no negative effects on rat behavior or development following long-term exposure at 9.4 T. The present state of knowledge about safety for human studies at high magnetic fields is summarized in High, Sikora, Ugurbil, and Garwood (2000).

Reliability and Ease of Use

The factors cited throughout the meeting as important criteria for system selection were reliability and optimization of the MRI system. To achieve the advantages of the higher field instruments requires that the electronics and software be optimized to the degree they are presently available in the clinical 1.5-T systems. At

present, this level of system development is only obtainable at 3.0 T and below, due to large investments by clinical imaging manufacturers in the technology. At fields above 3.0 T, where systems are only available from smaller companies specializing in designing research-only systems, it is essential to have the expertise of an MR physics research group to achieve optimized system performance. Even at or below 3.0 T, the participation of an MR physicist was generally agreed to be essential for assuring that the imaging system as provided by the vendor is optimized with respect to both its capabilities and its pulse sequences, hardware, and image processing.

Beyond BOLD, New MR Methods for Mapping Brain Function

The high spatial and temporal resolution of BOLD fMRI compared with other brain imaging tools comes with a cost—the loss of specific knowledge of the neuronal processes contributing to the signal. The BOLD signal is determined by relative changes in metabolism, flow, and blood volume in a region of tissue. The interdependence of these physiological changes may be highly variable in different brain regions and at different levels of activity. An increase in the intensity of the BOLD fMRI signal may not be directly proportional to changes in regional metabolism. Furthermore, although there has been much progress in recent years, there are many uncertainties about the contribution of specific neuronal processes associated with activity to the changes in metabolism. The increased sensitivity available with higher magnetic field strength scanners provides the potential for using MR-based measurements more directly coupled to neuronal activity than BOLD. Seong Ji Kim presented results obtained from cat visual cortex at 4.7 T with perfusion imaging. Perfusion MRI measures the change in the relaxation properties of tissue water due to changes in blood flow. The sensitivity of perfusion MRI increases approximately proportionately with magnetic field. Perfusion MRI may be calibrated to provide a quantitative measure of cerebral blood flow, which has been shown in animal models and humans to track changes in cerebral metabolism. Kim showed perfusion MRI maps of the functional response obtained during stimulation by visual patterns at the level of cortical columns. The degree of spatial localization was superior to images obtained using a standard BOLD fMRI sequence, in which spatial localization was limited by signal arising from draining venules.

The sensitivity possible at higher magnetic fields creates the opportunity to obtain functional brain images using the signal from nuclei other than protons. Kamil Ugurbil's results from rat brains with a 9.4-T system used ^{17}O spectroscopy to track the cerebral utilization of oxygen, a more direct indicator of neuronal activity than BOLD. Keith Thulborn announced that the

University of Illinois-Chicago should soon have a 9.4-T human system available. Thulborn plans to pursue functional imaging of Na$^+$. If it can fulfill its promise, sodium imaging may provide a direct measure of the ion flows associated with action potentials and other electrophysiological phenomenon. Kamil Ugurbil and Doug Rothman described results using ^{13}C MRS, which provides direct information on the rate of excitatory (glutamate) and inhibitory (GABA) neurotransmitter turnover, the trade off being relatively low spatial resolution. The spatial resolution of MRS should be greatly improved at higher field strengths, based upon many years of studies in animals, and is being suggested by the recent studies of Ugurbil et al. on humans at 7 T.

WHAT ARE THE KEY ASSUMPTIONS EMBEDDED IN fMRI STATISTICAL PACKAGES?

The primary goal of the meeting on statistical analysis methods in fMRI was to identify key assumptions in the data analysis and how they influence the brain activity map. Much of the initial discussion focused on the description of the different packages and will not be summarized here (see Recommended Reading 4). A summary of the discussion relevant to the use of statistics for interpreting imaging data is provided below.

Assumptions about the Relationship between the fMRI Signal and Neuronal Activity

Several speakers addressed the issue of the assumptions about the fMRI signal within their analysis packages. There was consensus that due to the time required for the vasculature to respond to an increase in energy demand due to increased neuronal activity, there is a temporal delay in the response of the BOLD signal. A popular method of modeling the relationship between the BOLD response and a change in neuronal activity is as a Volterra kernel, which was described by Rik Henson. Robert Cox presented a similar approach using ANFI. Ted De Yoe showed the results of studies in which the shape of the BOLD response was experimentally measured and incorporated into the ANFI program.

Participants also discussed assumptions about the relationship between the intensity of the BOLD signal and the change in neuronal activity. In most of the statistical analysis packages mentioned, this relationship was assumed to be linear with a constant slope throughout the brain (e.g., 1% increase in regional BOLD signal intensity per 9-Hz increase in average neuronal spike frequency). Christoph Koch questioned the validity of the blanket application of this assumption based on fMRI results he and his colleagues obtained recently. In separate studies of monkeys and humans, they measured the relationship between the size of the BOLD signal in human subjects undergoing visual stimulation

at 1.5 T as a function of changes in electrical activity (average spike rate) measured in analogous regions of the visual cortex with single unit electrical recording in monkeys. They found, in accordance with the assumption, a roughly linear relationship in the two regions examined, but a large difference in the slope. This nonconstant relationship between the strength of the BOLD signal and neuronal activity would invalidate comparisons between the levels of brain activity between regions unless calibrations or other compensations are made. John Gabrielli and Mark Desposito both pointed out that a similar alteration in the relationship between BOLD fMRI and neuronal activity may occur in different subject populations who, because of medication or vascular disease, have altered blood flow/metabolism or blood flow/volume coupling. They stressed that this variability must be controlled when these populations are compared with healthy controls in studies to assess impaired cognitive processing in the patients. Steve Hanson added that any comparison between electrical activity and regional BOLD fMRI signal change is affected by the method used to identify the region of interest. For example if a lower threshold value was used more weakly activating pixels would be included and the slope, and possibly functional dependence, would change. Doug Rothman mentioned work being done by several laboratories that promises to allow the BOLD signal to be calibrated in terms of absolute rates of flow and metabolism. Several discussants commented that the availability of calibrated BOLD, which is greatly aided by the ongoing studies with higher field magnets, will be of benefit to the interpretation of fMRI studies.

Steve Hanson raised the possibility that one often-used assumption in analysis of fMRI data, that the noise (fluctuations of signal intensity not due to neuronal activity) is Gaussian, would alter the derived brain activity maps if it were not true. He then alluded to results from his lab that found a non-Gaussian noise distribution that was heavily tailed. Difference maps would therefore be non-Gaussian, in particular also heavy tailed and tend to produce systematically more false negatives in such maps. Several speakers showed graphs of the noise obtained from fMRI data that showed temporal and regional correlations. Much of this noise was ascribable to physiological processes such as heartbeat and respiration, although some findings could not be easily explained. Several speakers presented signal analysis methods for reducing the level of physiological noise.

There were several questions about what specific neuronal processes the BOLD fMRI signal is related to and how answers to these questions affect the calculation of brain activity maps. In many studies that have used EEG to validate fMRI localization, and more recently have used fMRI to better localize the EEG dipoles, there is an implicit assumption that these modalities measure the same underlying phenomena. However, Scott Makeig pointed out that the typical EEG signal

frequencies analyzed in such studies may arise from neuronal circuitry connecting relatively distant regions, as opposed to the neuropil-level activity that is believed to give rise to the fMRI signal. As mentioned above, Koch presented findings supporting a direct relationship between the average firing of pyramidal cells (regionally dependent) and the size of the BOLD response. However, in a recent *Nature* article, Nikos Logothetis et al. questioned this finding in light of the results of studies where he simultaneously measured BOLD fMRI and multiunit electrical activity in monkeys, where he found that the BOLD signal correlated better with lower frequency field potentials than the high pass spiking frequencies (see Logothetis et al., 2001; for a thoughtful analysis of Logothetis et al., see Bandettini & Ungerleider, 2001). It is important to emphasize that studies comparing measures of BOLD with data obtained by techniques monitoring neuronal electrical activity cannot provide a full explanation of how to interpret changes in the BOLD signal. The acquired BOLD signal depends on the ability to detect small differences in the fractional increases of the rates of regional cerebral blood flow, regional cerebral metabolic rate for oxygen, and regional blood volumes. The BOLD signal is also influenced by the brain's vascular geometry and even the 3-D orientation of the brain within the magnetic field of the scanner. Douglas Rothman briefly described studies using MRS at Yale and other laboratories that have found a linkage between brain glucose metabolism, which in animal models has been shown to be measurable using a combination of MRI measurements of the BOLD signal, CBV, CBF, and glutamate release and its recycling by excitatory neurons and glia. Clearly, this is an area of intense interest where further technical advances will be very useful.

Assumptions about the Relationships between Cognitive Processes and Neuronal Activity

In addition to assumptions about the relationship between the fMRI signal and neuronal activity, there are assumptions implicit in some statistical analysis packages about the temporal and spatial relationships between neuronal activity and hypothesized cognitive processes, as well as cognitive processes and the tasks that induce them. In the simplest case of sensory stimulation, the statistical analysis package may include models (often called hypotheses) about the temporal and intensity relationships between the stimulation (e.g., a strobe light) and the induced sensory analysis processes, as well as a model of the relationship between the higher level processes and the neuronal activity that support them. The most common models, including versions of SPM and many other packages, include two assumptions about the linearity of neuronal activity and the fMRI signal in each voxel: (i) the fMRI signal is a linear function of the neuronal activity induced by the task

and (ii) linear addition of the neuronal activity induced by multiple cognitive processes. For example, comparison of the signal in each voxel measured during a hypothetical "task 1" containing cognitive process a ($S(a)$) with "task 2" containing both processes a and b ($S(a,b)$) would reveal the voxels supporting the b process through simple subtraction:

$$S(a,b) - S(a) = S(b)$$

When a hypothesis-based package incorporating these assumptions is used to analyze an fMRI time course, it will test statistically for a linear relationship between the induced neuronal activity (inferred from the fMRI signal as described above) and the hypothesized time course of one or more cognitive processes associated with the task. With SPM, this relationship is referred to as the design matrix. Voxels are identified as "active" during an experimental task if the correlation is significant.

An extended discussion took place on the effects of violations of the standard assumptions of linearity on the identification of active regions. Several discussants referred to studies by Friston et al., and similar studies by Desimone and Ungeleider, in which the intensity of the BOLD fMRI signal induced by visual stimulation in the visual cortex is modulated by the degree of attention given to the stimulus. The assumption of linearity was violated in these studies because the BOLD fMRI signal induced by visual stimulation and attention simultaneously was different than the sum of the signals induced by either task on its own [$S(a, b) = S(a) + S(b)$]. If this nonlinearity was not taken into account, the regions identified as active would have been altered. Randy McIntosh gave examples of how linear and nonlinear interactions between regions may be taken into account using connectivity theory, which uses a matrix approach to assess the strength and functionality of co-interactions between neuronal activity in different regions in the brain. Scott Makeig and Mauritzio Corbetta each presented results using independent components analysis (ICA), which tests for the significance of an fMRI signal based upon pure signal analysis criteria without including hypotheses about the time and amplitude relationship between the signal intensity and the underlying cognitive response to the task. Their results showed that ICA found several significant regions of activation in tasks that were judged insignificant by hypothesis-based methods. The additional regions exhibited signal time courses that were not in phase with the postulated cognitive responses to the task or stimulus, including regions of negative signal (some of the implications of the negative signal were discussed in the first JSMF workshop, see Fitzpatrick & Rothman, 1999).

During the discussion, several participants raised questions about appropriate criteria for choosing a particular signal analysis package. Although no consensus was achieved, there was general agreement that under conditions of low sensitivity (due to small signal changes or poor subject compliance) the hypothesis-based methods such as standard SPM are more reliable for detecting regions of activation. However, Ben Bly pointed out that special care must be taken not to interpret the failure of a region to be deemed significant by the statistical analysis package as proving that the region was not involved in performing the task. At minimum, he felt that other statistical approaches should be examined and issues of relative signal to noise be taken into account to avoid false negatives.

Thinking Out of the Box—Is Modularity Implicit in fMRI Data Analysis Packages?

Ben Bly presented a general criticism of the way in which many cognitive neuroscientists use statistical analysis packages, that is using packages to force the production of brain maps that support hypotheses of modular activity. He defined modular activity as the localization of functions to discrete anatomic brain regions. He believes the approach used in most statistical analysis packages to compare activations arising from different tasks is intrinsically biased to support modularity, because these packages throw away areas common to both tasks. As an example, he showed a recent article that presented brain activity maps of a bilingual subject speaking two languages. The brain activity maps showed different and discrete areas of activation, which were interpreted as supporting the claim that different regions of the brain were recruited for each language. However, the brain activity maps obtained from the two languages relative to not speaking or speaking nonsense languages showed extensive regions of overlap. He interpreted the differences as a small shift in the same cognitive processes involved in generating language, rather than as the development of a new language module for the second language as the authors of the article argued. Another example he gave of how analysis methods may lead to false modularity claims, was the commonly used practice of averaging the brain activation maps of several subjects. In addition to issues of improper anatomic registration due to warping of images (see the discussion of the question "What is the optimum field strength for fMRI studies?"), the method is vulnerable to false conclusions, if subjects use different strategies to perform the same task. In this case, the average map may only yield a few small discrete regions of activation, which corresponded to the region of overlap, as opposed to identifying all regions necessary and sufficient to perform the task.

Steve Petersen vigorously criticized Bly's attack on pure modularity as being unsubstantiated. He claimed that in every case properly studied, there was a discrete brain region associated with a process, which was

invariant between subjects. Any variation between subjects, Petersen argued, was due to disease or poor study design. Petersen's rebuttal was criticized on the basis of results presented by other speakers that showed that in some cases different statistical analysis packages identified different regions of activation. Some felt these results brought into question the strength of the findings on which Petersen based his assertion for consistent localization. A lively discussion ensued with no general conclusion reached.

Pet Peeves: What Technical and Experimental Information Must Be Included in Manuscripts so Readers Can Better Evaluate the Validity of an fMRI Study?

In both meetings, the participants were asked to identify critical information about the MR acquisition and statistical analysis that should be included in publications. In the meeting on field strength, Elizabeth Phelps addressed this issue by asking her fellow participants to list their pet peeves about fMRI and cognitive neuroscience. Peter Van Zijl was concerned about the coregistration of the BOLD fMRI and standard anatomical MRI without correcting for spatial distortions in the BOLD image due to field inhomogeneity. Even at 1.5 T, these distortions can shift the apparent location of a BOLD activation by up to 1 cm. Furthermore, the degree of distortion varies between subjects that complicates subject averaging unless adequately corrected. As Ben Bly pointed out, because the distortion varies regionally, improper correction may lead to false negatives, that is, to improper conclusions that a region was not involved in a task because it was not present on the brain activity map.

Several discussants stated their pet peeves about false negatives not being discussed in articles. As described above, several speakers presented results that showed that false negatives may derive from a variety of sources because the statistical analysis packages test for the reliability, as opposed to the absolute value, of the signal. Among these sources, as described above, are loss of BOLD signal due to poor blood oxygen homogeneity (such as around the sinuses), inaccurate coregistration between images, varying relationships between the intensity of the BOLD signal and neuronal activity within brain regions and between subject groups. It was suggested that when these possibilities are present, efforts should be taken to evaluate or correct them.

Regarding statistical analysis packages, there was little consensus among the discussants about what information should be provided in a article, or for that matter in the description of the statistical analysis package available to the end user. Several discussants complained that there is little academic reward for people who maintain these packages for general usage. However,

there was general agreement that cognitive neuroscientists using statistical analysis packages should become familiar with the assumptions the packages make about the relationships among the fMRI signal, neuronal activity, and cognitive processes, as well as publications that look at the effect of these assumptions on the derived brain activation maps. Jullie Pan suggested an approach to normalize fMRI studies between different groups by incorporating standard (simple) activation paradigms into all studies, so as to potentially allow (a) a uniform task for comparisons between different MR facilities and studies and (b) a means of normalizing any given subject and task.

WHAT DOES THE AVAILABILITY OF HIGH-FIELD IMAGING SYSTEMS MEAN FOR COGNITIVE NEUROSCIENCE?

In both meetings following the topical presentations, there was lively discussion on whether the sensitivity and spatial resolution available from fMRI and further enhancements from higher B_o fields would significantly benefit cognitive neuroscience. One obvious benefit is the refined ability to localize specialized regions engaged in mental processing. Ugurbil presented human functional images showing that what appears as a single area of increased BOLD signal at 1.5 T resolves into three distinct regions at 7 T. Ravi Menon, Seong Ji Kim, and Kamil Ugurbil all presented results showing functional images of discrete cortical columns at fields of 4 T and above. Marcia Johnson expressed concern that at higher field strengths, important regions for studying memory, such as the hippocampus, would be lost due to the increase in the strength of B_o homogeneity effects and the decreased efficiency of RF coils for providing coverage of the whole brain. Several discussants pointed out that considerable progress was being made in addressing these limitations.

THE DEAN'S DILEMMA

There are currently many fewer 3.0-T than 1.5-T scanners. In 1998, it was estimated there were 2200 systems operating at 1.5 T, 16 systems at 3-T, and fewer than 10 systems at 4 T or higher (personal communication). These numbers are gradually changing as more 3.0-T scanners are adopted clinically (see below). For scanners operating at 4.0 T and the ultrahigh-field human scanners of 7.0 T or higher, the capabilities increase but so do the complexities of data acquisition and analysis. Is the higher cost and investment in personnel required to install and operate a high-field system worthwhile for an institution interested in adding the capability of fMRI to a cognitive neuroscience program?

One way to evaluate the costs/benefits of investing in the various imaging systems available for research is by

working through what could be called "The Dean's Dilemma." On the one hand, deans must be responsive to the research needs of the faculty, while on the other hand, they must consider practical and fiscal questions. In addition to the system purchase price, there are real costs associated with space requirements, maintenance contracts, staffing, and the recurrent costs of equipment upgrades. There are also issues of reliability and ease of use that must be considered in terms of the real costs associated with lost time and productivity. How then does a dean evaluate the request for the purchase of a high-field imaging system made by a cognitive neuroscience group? Keith Thulborn suggested that developing a business plan is a useful way of working through the dilemma. There was general consensus among the workshop participants that for most cognitive neuroscience applications, keeping all the various caveats in mind, 1.5-T scanners are adequate. Although much concern has been raised about the etiology of signal (intravascular, parenchymal), data analysis, and interpretation, nonetheless many neuroscientists essentially require information as to general region of activation (e.g., superior parietal lobule), rather than highly localized cellular or laminar activity. There was also general consensus that 3.0-T scanners will gradually replace 1.5-T magnets mainly because the instrument manufacturers are targeting 3.0-T scanners for clinical use and they already have demonstrated clear sensitivity advantages over 1.5 T for fMRI. The reality of the marketplace dictates that MRI systems and technical support be responsive to clinical, not research, needs. Because it is also likely that most MR scanners will be housed in radiology departments and subsidized by clinical revenues, deans must consider the clinical requirements for turn-key, reliable, workhorse systems. Eventually, the Dean's Dilemma regarding 1.5-T systems versus 3.0-T systems will be minimized as manufactures ramp up and refine production of 3.0-T scanners. The new 3.0-T imaging systems occupy the same footprint as the 1.5-T machines and the hardware and software are designed as turn-key operations. MR scanners that operate at magnetic field strengths greater than 3.0 T, still demand major resource commitments from institutions. The main justifications for acquiring scanners with magnets greater than 3 T are the demands of research programs requiring the enhanced sensitivity. Examples are research programs involving the use of MRS or fMRI studies requiring resolution at the submillimeter level. For BOLD fMRI, there appears to be little advantage of 4 over 3 T, with real gains only coming at 7 T and above.

Regardless of field strength selection, successful centers, which emphasize accuracy and innovation, will require the creation of the faculty and support staff positions and continued investment in the high-field instruments needed to sustain an MR science research program. The quality of the functional imaging program and the integrity of the data are dependent upon meaningful involvement by MR scientists. Since institutions without the necessary infrastructure will not recruit and retain the very best MR scientists, the wise dean will carefully consider investing in MR research.

Notes

1. The authors take full responsibility for the information provided. This summary is not a consensus document approved by all workshop participants.
2. The participant lists are available on the McDonnell Foundation website (www.jsmf.org).

RECOMMENDED READINGS

For summaries of other McDonnell Foundation–sponsored workshops relevant to the topics presented in this meeting report see:

Fitzpatrick, S. M., & Rothman, D. L. (1999). New approaches to functional neuroenergetics. *Journal of Cognitive Neuroscience, 11,* 467–471.

Fitzpatrick, S. M., & Rothman, D. L. (2000). Meeting report: Transcranial magnetic stimulation and studies of human cognition. *Journal of Cognitive Neuroscience, 12,* 704–709.

McIntosh, A. R., Fitzpatrick, S. M., & Friston, K. J. (2001). Meeting report and commentary: On the marriage of cognition and neuroscience. *Neuroimage, 14,* 1231–1237.

Readers seeking more detailed information about the physics, biophysics, implementation, and safety of MRI and MRS beyond that provided in the meeting report are encouraged to read the articles referenced below:

High, W. B., Sikora, J., Ugurbil, K., & Garwood, M. (2000, July). Subchronic in vivo effects of a high static magnetic field (9.4 T) in rats. *Journal of Magnetic Resonance Imaging, 12,* 122–139 [special journal issue devoted to articles on MR safety].

Ogawa, S., Menon R. S., Kim, S. G., & Ugurbil, K. (1998). On the characteristics of functional magnetic resonance imaging of the brain. *Annual Review of Biophysics and Biomolecular Structure, 27,* 447–474.

Thulborn, K. R. (1999). Why neuroradiologists should consider very-high-field magnets for clinical applications of functional magnetic resonance imaging. *Topics in Magnetic Resonance Imaging, 10,* 1–2.

Rothman, D. L., Hyder, F., Sibson, N., Behar, K. L.,

Mason, G. F., Shen. J., Petroff, O. A. C., Shulman, R. G. (2002). In vivo magnetic resonance spectroscopy studies of the glutamate and GABA neurotransmitter cycles and functional neuroenergetics. In K. L. Davis, D. Charney, J. T. Coyle, & C. Nemeroff (Eds.), *Neuropsychopharmacology: The fifth generation of progress* (pp. 315–342). Philadelphia: Lippincott Williams & Wilkins.

Stieltjes, B., Kaufmann, W. E., van Zijl, P. C., Fredericksen, K., Pearlson, G. D., Solaiyappan, M., & Mori S. (2001). Diffusion tensor imaging and axonal tracking in the human brainstem. *Neuroimage, 14,* 723–735.

Buxton, R. B., Wong, E. C., & Frank, L. R. (1998). Dynamics of blood flow and oxygenation changes during brain activation: The balloon model. *Magnetic Resonance in Medicine, 39,* 855–864.

Friston, K. J., Mechelli, A., Turner, R., & Price, C. J. (2000). Nonlinear responses in fMRI: The balloon model, Volterra kernels, and other hemodynamics. *Neuroimage, 12,* 466–477.

Hanson, S. J., & Martin Bly, B. (2001). The distribution of BOLD susceptibility effects in the brain is non-Gaussian. *NeuroReport, 12,* 959–966.

Details on the statistical analysis packages discussed in the meeting report can be downloaded from the web site address below:

The Brain Imaging Software Toolbox. Montreal Neurological Institute, McGill University. http://www.bic.mni.mcgill.ca/software/.

SPM99. Wellcome Department of Cognitive Neurology, University College London. http://www.fil.ion.ucl.ac.uk/spm99.html.

Dartmouth Brain Imaging Center, Dartmouth College. http://dbic.dartmouth.edu/~inati/spm/analysis/php.

AFNI Information Central. http://afni.nimh.gov/afni.

Independent Components Analysis (ICA). www.cnl.salk.edu/~scott/pdf/IEEEProc01.pdf.

Latent Structure Analysis. http://psychology.rutgers.edu/RUMBA/.

Articles on the relationship between electrical activity and fMRI:

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature, 412,* 150–157.

Rees, G., Friston, K., & Koch, C. (2000). A direct quantitative relationship between the functional properties of human and macaque V5. *Nature Neuroscience, 3,* 716–723.

Bandettini, P. A., & Ungerleider, L. G. (2001). From neurons to BOLD: New connections. *Nature Neuroscience, 4,* 864–866.

Articles on connectivity and violations of assumptions about linearity of cognitive processes (see also the references in McIntosh et al., 2001):

McIntosh, A. R. (1999). Mapping cognition to the brain through neural interactions. *Memory, 7,* 523–548.

Kastner, S., & Ungerleider, L. G. (2000). Mechanisms of visual attention in the human cortex. *Annual Review of Neuroscience, 23,* 315–341.

Friston, K. J., & Price, C. J. (2001). Dynamic representations and generative models of brain function. *Brain Research Bulletin, 54,* 275–285.

This article has been cited by:

1. E. M. Robertson, H. Théoret, A. Pascual-Leone. 2003. Studies in Cognition: The Problems Solved and Created by Transcranial Magnetic StimulationStudies in Cognition: The Problems Solved and Created by Transcranial Magnetic Stimulation. *Journal of Cognitive Neuroscience* **15**:7, 948-960. [Abstract] [PDF] [PDF Plus]